**Sequential drug decision problems in long-term medical conditions:**

**A Case Study of Primary Hypertension**

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# Abstract

**Background**: Sequential drug decision problems (SDDP) occur when assigning drugs sequentially in long-term medical conditions. SDDPs are important for both clinical decision-making and resource allocation. They can be large and complex because of the considerable number of drug sequences and disease pathways and the interdependence between them over time. Where classic mathematical programming has a limited capacity for dealing with the complexities of a sequential decision problem, approximate optimisation methods have been widely used to solve the problem more efficiently using simulation.

**Objective**: This thesis aims to set down the definitions of SDDPs mathematically to understand the nature of SDDPs, to examine the potential methods to identify optimal or near-optimal sequential treatment strategies in a long-term SDDP; and to discuss the performance of the proposed methods using a case study of primary hypertension.

**Methods**: A mathematical description of SDDPs was developed to gain an understanding of the nature of SDDPs. A systematic review was conducted to examine potential optimisation methods for solving large and complex SDDPs. A hypothetical simple SDDP was used to test the feasibility of incorporating the promising methods into an economic evaluation model. A de novo hypertension cost-effectiveness model estimating blood pressure lowering effects of sequential use of antihypertensive drugs was developed. Enumeration, simulated annealing (SA), genetic algorithm (GA) and reinforcement learning (RL) were used to solve the SDDP in primary hypertension. Their performance was tested in terms of computational time and the quality of solution, which is defined by the closeness of the final objective function values and the real global optimum are obtained from enumeration.

**Results**: The computational complexity of SDDPs comes from a range of factors, which are: 1) the number of relevant health states, 2) the number of potential drug treatment options, 3) the number of times that a treatment change may occur, 4) whether the transition probability between health states depends on historic health states and drug uses and 5) relevant clinical-based rules that need to be incorporated. Various trade-offs, such as the trade-off between the computational complexity and model validity, the trade-off between the research effort and time required to develop the optimisation model and the underlying evaluation model, and the trade-off between the amount of search time and the quality of the solution, are fundamental features of SDDP modelling. These trade-offs are all interrelated with each other rather than existing separately. In the case study of primary hypertension, the optimal solution identified by enumeration was to start with an angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker (ACEI/ARB), followed by the combination of thiazide-type diuretic (D) and ACEI/ARB, the combination of D, ACEI/ARB and calcium channel blocker (CCB) and the combination of D, ACEI/ARB and beta-blocker (BB) as second, third and fourth-line treatments. The total expected net benefit for this optimal sequential treatment policy was £330,080 (95% CI £330,013-£330,147). SA and GA found the same (or statistically indifferent) solution(s) identified by enumeration with shorter search time and smaller iteration number. The computational time was 4.1-4.6 hours in SA or GA whereas enumeration took 12.20 hours. The performance depended on some key parameters of the methods: cooling rate and the maximum number of iterations within the same temperature for SA and the number of generation, population size, crossover rate and mutation rate for GA. The performance of RL was relatively less favourable. This may be because of the structure of the hypertension SDDP model, whose total net benefit is mostly affected by the add-on Markov model after the drug switching period than the short-term drug switching model.

**Conclusion**: SA and GA can be used to solve a large and complex SDDP as demonstrated in the primary hypertension case study. They can find the optimal or near optimal solutions efficiently where the key parameters are properly set. The optimal parameter setting is problem specific and requires a tuning procedure considering various scenarios with different sets of parameters. RL needs further investigation to improve the performance possibly by using more complicated RL methods or in a different structure of the underlying evaluation model. This study can be extended to construct the underlying evaluation model using a DES and to technically improve the optimisation methods. Producing the data relevant to SDDPs will also help to make better informed decisions for SDDPs in health technology appraisal.

# Table of contents

[**Chapter 1. Introduction 1**](#_Toc426018018)

[1.1 Chapter overview 1](#_Toc426018019)

[1.2 Introduction to sequential drug decision problems 1](#_Toc426018020)

[1.3 General optimisation approaches to solve sequential decision problems 7](#_Toc426018021)

[1.4 Motivations and research objectives 11](#_Toc426018022)

[1.5 Thesis structure 12](#_Toc426018023)

[**Chapter 2. Problem specification for sequential drug decision problems 14**](#_Toc426018024)

[2.1 Chapter overview 14](#_Toc426018025)

[2.2 Classification of evaluation models for sequential drug decision problems 14](#_Toc426018026)

[2.3 Comparison between sequential drug decision problems and representative combinatorial optimisation problems 20](#_Toc426018027)

[2.4 Mathematical description of sequential drug decision problems 24](#_Toc426018028)

[2.5 Computational complexity of sequential drug decision problems 27](#_Toc426018029)

[**Chapter 3. Potential optimisation methods for sequential drug decision problems 31**](#_Toc426018030)

[3.1 Chapter overview 31](#_Toc426018031)

[3.2 Systematic review on approximate optimisation methods 31](#_Toc426018032)

[3.3 Simulated annealing 47](#_Toc426018033)

[3.4 Genetic algorithm 49](#_Toc426018034)

[3.5 Reinforcement learning 51](#_Toc426018035)

[3.6 Application of the key optimisation methods on a hypothetical case 59](#_Toc426018036)

[**Chapter 4. Modelling sequential drug decision problem for hypertension: Overview 73**](#_Toc426018037)

[4.1 Chapter overview 73](#_Toc426018038)

[4.2 Hypertension and pharmacologic management 73](#_Toc426018039)

[4.3 Previous economic evaluations in primary hypertension 83](#_Toc426018040)

[4.4 Conceptual framework of the hypertension sequential drug decision problem 86](#_Toc426018041)

[4.5 Implication for the hypertension SDDP modelling 95](#_Toc426018042)

[**Chapter 5. Modelling sequential drug decision problem for primary hypertension: evaluation model 98**](#_Toc426018043)

[5.1 Chapter overview 98](#_Toc426018044)

[5.2 Population 98](#_Toc426018045)

[5.3 Time 99](#_Toc426018046)

[5.4 The structure of the short-term drug switching model 100](#_Toc426018047)

[5.5 The structure of the long-term CVD model 105](#_Toc426018048)

[5.6 Treatment effectiveness and costs 109](#_Toc426018049)

[**Chapter 6. Modelling sequential drug decision problem for hypertension: Implementation 130**](#_Toc426018050)

[6.1 Chapter overview 130](#_Toc426018051)

[6.2 Overview of the hypertension SDDP optimisation model 130](#_Toc426018052)

[6.3 Enumeration 142](#_Toc426018053)

[6.4 Simulated annealing 153](#_Toc426018054)

[6.5 Genetic algorithm 156](#_Toc426018055)

[6.6 Reinforcement learning: Q-learning 160](#_Toc426018057)

[**Chapter 7. Modelling sequential drug decision problem for hypertension: Results 167**](#_Toc426018058)

[7.1 Chapter overview 167](#_Toc426018059)

[7.2 Model validity 167](#_Toc426018060)

[7.3 Markov model-based optimisation: Enumeration 178](#_Toc426018061)

[7.4 Simulated annealing 204](#_Toc426018062)

[7.5 Genetic algorithm 210](#_Toc426018063)

[7.6 Reinforcement learning: Q-learning 218](#_Toc426018064)

[7.7 Summary of the case study of primary hypertension 224](#_Toc426018065)

[**Chapter 8. Discussion 230**](#_Toc426018066)

[8.1 Chapter overview 230](#_Toc426018067)

[8.2 Summary of research 230](#_Toc426018068)

[8.3 Future research 241](#_Toc426018069)

[**Chapter 9. Conclusion 248**](#_Toc426018070)

[**Reference 254**](#_Toc426018071)

[**Appendices. 288**](#_Toc426018072)

# List of tables

[Table ‎2.1. Classification of evaluation models for SDDPs 15](#_Toc426018622)

[Table ‎2.2. Comparison between SDDPs and the representative combinatorial optimisation problems: traveling salesman problems and job-shop scheduling problems 21](#_Toc426018623)

[Table ‎3.1. The number of papers retrieved from four electronic databases by search strategy 35](#_Toc426018624)

[Table ‎3.2. The characteristics of each category 37](#_Toc426018625)

[Table ‎3.3. Potential heuristic and optimisation methods for sequential decision problems 38](#_Toc426018626)

[Table ‎3.4. Comparison of different optimisation approaches proposed in the classification 71](#_Toc426018627)

[Table ‎3.5. Optimal treatment pathway obtained from the different optimisation approaches 72](#_Toc426018628)

[Table ‎4.1. Blood pressure classification from the NICE guideline 74](#_Toc426018629)

[Table ‎4.2. Recommendations from major clinical guidelines of primary hypertension 81](#_Toc426018630)

[Table ‎4.3. Recommended drugs for cardiovascular diseases and diabetes 83](#_Toc426018631)

[Table ‎5.1. The mean TC, HDL, BMI of the hypertensive patients in the UK 99](#_Toc426018632)

[Table ‎5.2. Age and gender-specific proportions of first-onset CVD 102](#_Toc426018633)

[Table ‎5.3. All-cause mortality between 2008 and 2010 in England and Wales 102](#_Toc426018634)

[Table ‎5.4. Age and gender-specific non-circulatory deaths as a proportion of all deaths 103](#_Toc426018635)

[Table ‎5.5. Incidence per 100,000 of HF in the UK 103](#_Toc426018636)

[Table ‎5.6. Type 2 DM annual risk per 100,000 population in the UK 104](#_Toc426018637)

[Table ‎5.7. Risk of type 2 DM according to category of antihypertensive drug 104](#_Toc426018638)

[Table ‎5.8. Health states and possible transitions in the long-term CVD model 106](#_Toc426018639)

[Table ‎5.9. Annual baseline risks of primary and secondary CV events 108](#_Toc426018640)

[Table ‎5.10. Comparison between Framingham models and QRISK2 111](#_Toc426018641)

[Table ‎5.11. Comparison between systematic reviews on SBP lowering effect of antihypertensive drugs 113](#_Toc426018642)

[Table ‎5.12. Absolute SBP lowering effects accumulated over one year 114](#_Toc426018643)

[Table ‎5.13. Relative SBP lowering effects (%) accumulated over one year 117](#_Toc426018644)

[Table ‎5.14. Relative risks to CVDs, DM and death depending on antihypertensive drug 118](#_Toc426018645)

[Table ‎5.15. Comparison between Ross et al’s and Law et al’s systematic reviews 120](#_Toc426018646)

[Table ‎5.16. Annual costs and utility weights by CVD and DM 122](#_Toc426018647)

[Table ‎5.17. Antihypertensive drug costs per year 123](#_Toc426018648)

[Table ‎5.18. Parameters of key variables for PSA 125](#_Toc426018649)

[Table ‎5.19. Comparison between the SDDP hypertension model and the NICE hypertension model 129](#_Toc426018650)

[Table ‎6.1. Summary of the functions included in the hypertension SDDP model 131](#_Toc426018651)

[Table ‎6.2. Scenario selection to implement the hypertension SDDP model 134](#_Toc426018652)

[Table ‎6.3. Matrix of the decision tree generated by ‘TreeGenerator’ 135](#_Toc426018653)

[Table ‎6.4. Matrix of the search space generated by ‘PolicyGenerator’ 136](#_Toc426018654)

[Table ‎6.5. Matrix of the actual drug use generated by ‘VasGenerator’ 137](#_Toc426018655)

[Table ‎6.6. Matrix of the maintenance therapy generated by ‘MTGenerator’ 138](#_Toc426018656)

[Table ‎7.1. Treatment effectiveness predicted from the validation scenarios where the same treatment is applied in the follow-up period 171](#_Toc426018657)

[Table ‎7.2. Comparison of the CE results from the hypertension SDDP and the NICE hypertension models in men 176](#_Toc426018658)

[Table ‎7.3. Breakdown of the costs and QALYs of the hypertension SDDP model in men 176](#_Toc426018659)

[Table ‎7.4. Comparison of the CE results from the hypertension SDDP and the NICE hypertension models in women 177](#_Toc426018660)

[Table ‎7.5. Breakdown of the costs and QALYs of the hypertension SDDP model in women 177](#_Toc426018661)

[Table ‎7.6. Optimal solutions using enumeration in the base-case 179](#_Toc426018662)

[Table ‎7.7. The list of tested groups divided by the combination of initial and second-line drugs 190](#_Toc426018663)

[Table ‎7.8. Optimal treatment sequences and total net benefit depending on gender and initial age 197](#_Toc426018664)

[Table ‎7.9. Optimal solutions and total net benefits depending on the change in key parameters 201](#_Toc426018665)

[Table ‎7.10. Computational results from SA depending on cooling rate and the maximum number of iterations within the same temperature 206](#_Toc426018666)

[Table ‎7.11. The average performance of SA from 20 repeated runs 207](#_Toc426018667)

[Table ‎7.12. Computational results by the number of generations and population size from GA 212](#_Toc426018668)

[Table ‎7.13. The average performance of GA from 20 repeated runs, depending on the generation number and the population size 213](#_Toc426018669)

[Table ‎7.14. Computational results by crossover and mutation rates from GA 215](#_Toc426018670)

[Table ‎7.15. The average performance of GA from 20 repeated runs, depending on the crossover rate and the mutation rate 216](#_Toc426018671)

[Table ‎7.16. Results from RL depending on the number of iterations where the feedback is from one-step future reward 220](#_Toc426018672)

[Table ‎7.17. Results from RL depending on the number of iterations where the feedback is from two-step future reward 221](#_Toc426018673)

[Table ‎7.18. Results from RL depending on the number of iterations where the feedback is from three-step future reward 222](#_Toc426018674)

[Table ‎7.19. Comparison of the optimisation results in the case study of primary hypertension 227](#_Toc426018675)

# List of figures

[Figure ‎1.1. Long-term continuation rates of antihypertensive drugs 2](#_Toc426019119)

[Figure ‎1.2. Simulation-based optimisation model 9](#_Toc426019120)

[Figure ‎2.1. An example successive decision tree model for SDDPs 17](#_Toc426019121)

[Figure ‎2.2. An example Markov model of SDDPs 18](#_Toc426019122)

[Figure ‎2.3. An example IBM model of SDDPs 20](#_Toc426019123)

[Figure ‎2.4. Graphical presentation of an SDDP with the Markovian assumption 27](#_Toc426019124)

[Figure ‎3.1. The process of refining the search strategy 34](#_Toc426019125)

[Figure ‎3.2. Flow-chart of study selection 36](#_Toc426019126)

[Figure ‎3.3. A decision algorithm to select the optimisation method for SDDPs 44](#_Toc426019127)

[Figure ‎3.4. Pseudo-code of SA 49](#_Toc426019128)

[Figure ‎3.5. Pseudo-code of GA 51](#_Toc426019129)

[Figure ‎3.6. Value iteration algorithm 53](#_Toc426019130)

[Figure ‎3.7. Policy iteration algorithm 54](#_Toc426019131)

[Figure ‎3.8. Q-learning algorithm 58](#_Toc426019132)

[Figure ‎3.9. Decision-tree of the hypothetical simple SDDP 59](#_Toc426019133)

[Figure ‎3.10. Pseudo-code of the enumeration used for the simple hypothetical case 62](#_Toc426019134)

[Figure ‎3.11. Pseudo-code of the DP used for the simple hypothetical case 64](#_Toc426019135)

[Figure ‎3.12. Pseudo-code of the SA used for the simple hypothetical case 66](#_Toc426019136)

[Figure ‎3.13. Pseudo-code for the Q-learning used for the simple hypothetical case 69](#_Toc426019137)

[Figure ‎4.1. The prevalence of hypertension in 2011, by age and gender 74](#_Toc426019138)

[Figure ‎4.2. Mean SBP in 2011, by age and gender in England 75](#_Toc426019139)

[Figure ‎4.3. Mean DBP in 2011, by age and gender in England 75](#_Toc426019140)

[Figure ‎4.4. Possible combinations of antihypertensive drug classes 82](#_Toc426019141)

[Figure ‎4.5. Graphical display of the sequential drug decision process in primary hypertension 87](#_Toc426019142)

[Figure ‎4.6. Potential treatment pathways and treatment assignment in the short-term drug switching model 92](#_Toc426019143)

[Figure ‎5.1. The absolute SBP lowering effect of single drugs and two or three drug combinations over time 116](#_Toc426019144)

[Figure ‎6.1. The structure of the hypertension SDDP model built by m-files 141](#_Toc426019145)

[Figure ‎6.2. Pseudo-code of the enumeration used for the hypertension SDDP model 142](#_Toc426019146)

[Figure ‎6.3. Pseudo-code of the function ‘EvModel’ included in the hypertension SDDP model 147](#_Toc426019147)

[Figure ‎6.4. Pseudo-code of the function ‘SBP modelling’ included in the hypertension SDDP model 149](#_Toc426019148)

[Figure ‎6.5. Pseudo-code of the function ‘CVD modelling’ included in the hypertension SDDP model 152](#_Toc426019149)

[Figure ‎6.6. Pseudo-code of the SA used for the hypertension SDDP model 155](#_Toc426019150)

[Figure ‎6.7. Roulette wheel selection operator applied to the GA 157](#_Toc426019151)

[Figure ‎6.8. Double-point crossover operator applied to the GA 157](#_Toc426019152)

[Figure ‎6.9. Mutation operator applied to the GA 158](#_Toc426019153)

[Figure ‎6.10. Pseudo-code of the GA used for the hypertension SDDP model 159](#_Toc426019154)

[Figure ‎6.11. Possible health states and treatment options, where the decision space is decomposed 163](#_Toc426019155)

[Figure ‎6.12. Pseudo-code of the Q-learning used for the hypertension SDDP model 166](#_Toc426019156)

[Figure ‎7.1. The percentage of patients without either CVD or DM history by age 172](#_Toc426019157)

[Figure ‎7.2. The percentage of death by age 172](#_Toc426019158)

[Figure ‎7.3. The percentage of patients in a CVD state by age 173](#_Toc426019159)

[Figure ‎7.4. The percentage of patients in the DM state by age 173](#_Toc426019160)

[Figure ‎7.5. Total net benefit of 4,128 policies where enumeration was used 181](#_Toc426019161)

[Figure ‎7.6. Total net benefits of 4,128 sequential treatment policies depending on the initial drug 182](#_Toc426019162)

[Figure ‎7.7. The percentage of the patients who were using first, second, third or fourth-line drug at the end of the drug switching period 183](#_Toc426019163)

[Figure ‎7.8. Graphical summary of the mean and CIs for each group classified by initial drug 184](#_Toc426019164)

[Figure ‎7.9. Graphical summary of the mean and comparison intervals for each group classified by second-line drug 186](#_Toc426019165)

[Figure ‎7.10. Graphical summary of the mean and comparison intervals for each group classified by third-line drug 187](#_Toc426019166)

[Figure ‎7.11. Graphical summary of the mean and comparison intervals for each group classified by fourth-line drug 188](#_Toc426019167)

[Figure ‎7.12. Graphical summary of the mean and comparison intervals for each cluster classified by the combination of initial and second drugs 191](#_Toc426019168)

[Figure ‎7.13. Distribution of the drugs included in the top 10% policies 192](#_Toc426019169)

[Figure ‎7.14. Distribution of the drugs included in the top 10% policies, where Ds are used initially 193](#_Toc426019170)

[Figure ‎7.15. Distribution of the drugs included in the top 10% policies, where BBs are used initially 193](#_Toc426019171)

[Figure ‎7.16. Distribution of the drugs included in the top 10% policies, where CCBs are used initially 194](#_Toc426019172)

[Figure ‎7.17. Distribution of the drugs included in the top 10% policies, where ACEIs/ARBs are used initially 194](#_Toc426019173)

[Figure ‎7.18. SBP lowering effect calculated based on ALLHAT and Dutch-TIA 198](#_Toc426019174)

[Figure ‎7.19. Proportion of patients who used four lines of treatments depending on the modelled drug switching period 202](#_Toc426019175)

[Figure ‎7.20. Total net benefit depending on the modelled drug switching period 203](#_Toc426019176)

[Figure ‎7.21. Maximum total net benefit depending on the cooling rate and the number of iterations within a temperature 205](#_Toc426019177)

[Figure ‎7.22. Convergence of SA depending on the cooling rate and the maximum number of iterations 208](#_Toc426019178)

[Figure ‎7.23. Search rate of SA depending on the cooling rate and the maximum number of iterations 209](#_Toc426019179)

[Figure ‎7.24. Convergence of GA depending on the number of generation and population 214](#_Toc426019180)

[Figure ‎7.25. Search rate of GA depending on the crossover and mutation rates 217](#_Toc426019181)

[Figure ‎7.26. Convergence of the discrepancy in the Q-values from RL 223](#_Toc426019182)

[Figure ‎7.27. Comparison of the size of decision space between the simple hypothetical model and the hypertension SDDP model 228](#_Toc426019183)

[Figure ‎7.28. Comparison of the computational time, search rate and iteration number between the simple hypothetical model and the hypertension SDDP model 229](#_Toc426019184)

# Abbreviations

|  |  |
| --- | --- |
| **ABS** | Agent-based simulation |
| **ACEI(s)** | Angiotensin converting enzyme inhibitor(s) |
| **ADP** | Approximate dynamic programming |
| **AE(s)** | Adverse effect(s)/event(s) |
| **AF** | Atrial fibrillation |
| **ARB(s)** | Angiotensin II receptor blocker(s) |
| **BB(s)** | Beta-blocker(s) |
| **BMI** | Body mass index |
| **CCB(s)** | Calcium channel blocker(s) |
| **CEA(s)** | Cost effectiveness analysis/analyses |
| **CHD(s)** | Coronary heart disease(s) |
| **CI(s)** | Confidence interval(s) |
| **CKD(s)** | Chronic kidney disease(s) |
| **CMA(s)** | Cost minimisation analysis/analyses |
| **CRD(s)** | Chronic renal disease(s) |
| **CUA(s)** | Cost utility analysis/analyses |
| **CVD(s)** | Cardiovascular disease(s) |
| **D(s)** | Thiazide-type diuretic(s) |
| **DAE(s)** | Discontinuation(s) due to AEs |
| **DMARD(s)** | Disease-modifying anti-rheumatic drug(s) |
| **DAS** | Disease activity score |
| **DBP** | Diastolic blood pressure |
| **DES** | Discrete-event simulation |
| **DM** | Diabetes |
| **DP** | Dynamic programming |
| **ESH/ESC** | European Society of Hypertension-European Society of Cardiology |
| **GA** | Genetic algorithm |
| **HbA1C** | Glycated haemoglobin |
| **HDL** | High-density lipoprotein cholesterol |
| **HF** | Heart failure |
| **HR(s)** | Hazard ratio(s) |
| **HSE** | Health Survey England |
| **HTA** | Health technology assessment/appraisal |
| **IBM(s)** | Individual-based model(s) |
| **ICER(s)** | Incremental cost-effectiveness ratio(s) |
| **ITT** | Intention-to-treat |
| **JNC** | The Joint National Committee on Prevention, Detection, Evaluation,  and Treatment of High Blood Pressure |
| **LDL** | Low-density lipoprotein cholesterol |
| **MDP** | Markov decision process |
| **MI** | Myocardial infarction |
| **NDP** | Neuro-dynamic programming |
| **NHS** | National Health Service |
| **NICE** | National Institute for Health and Clinical Excellence |
| **NP-hard** | Non-deterministic polynomial-time hard |
| **PSA** | Probabilistic sensitivity analysis |
| **QALY(s)** | Quality-adjusted life year(s) |
| **QoL** | Quality of life |
| **RA** | Rheumatoid arthritis |
| **RAS** | Renin-angiotensin system |
| **RCT(s)** | Randomised-controlled trial(s) |
| **RD** | Renal disease |
| **RL** | Reinforcement learning |
| **RR(s)** | Relative risk(s) |
| **SA** | Simulated annealing |
| **SBP** | Systolic blood pressure |
| **SD** | Standard deviation |
| **SDDP(s)** | Sequential drug decision problem(s) |
| **SE** | Standard error |
| **SLE(s)** | SBP lowering effect(s) |
| **SMDP(s)** | Semi-Markov decision process(es) |
| **SPLDT** | Simulated patient-level decision-tree |
| **SPLMM** | Simulated patient-level Markov model |
| **TC** | Total cholesterol |
| **TD** | Temporal difference |
| **TNB** | Total net benefit |
| **TNFb** | Tumour necrosis factor-blocking agents |
| **UA** | Unstable angina |

# Introduction

## Chapter overview

This study aims to set down the definitions of sequential drug decision problems (SDDPs) mathematically, to examine potential methods to identify optimal or near-optimal sequential treatment strategies in the context of a multiple drugs, multiple switches and multiple health states decision space problem and to discuss the performance of the proposed methods using a case study of primary hypertension. In the first chapter, SDDPs and the practical and methodological issues related to SDDPs are introduced. The optimisation methods used for sequential decision problems in other research areas are also introduced. These methods motivated this thesis and the research questions provided at the end of this chapter.

## Introduction to sequential drug decision problems

In the healthcare sector, selecting drug(s) among competing alternatives has been a key interest of decision-makers not just for clinical decisions but also for resource allocation policy[1]. Existing economic evaluations are normally concerned with evaluating drug alternatives at a specific point in a disease pathway, which could be first, second or third-line drugs. However, decision-makers are also interested in which subsequent drug(s) should be used when the current drug needs to be replaced or complemented due to inefficacy, diminishing efficacy or AEs. These questions represent an SDDP that aims to identify a sequence of drugs along the disease pathway of a health condition with the objective of maximising the overall net benefits of treatment. A sequential decision process consists of a series of states and actions. In a dynamic system, which moves a sequence of states *h1, h2, h3,…* at the times *t = 1, 2, 3,…,* a sequential decision consists of a sequence of actions *a1, a2, a3,…*. The essential features of the sequential decision problem are that, given *ht* at time *t*, the action *at* decides the subsequent state *ht+1* and the cost *ct* and/or effectiveness *et* for the time spent in the state *ht*. The action *at* could be a dose titration, replacing the current drug with a new drug or adding a new drug to the current drug. The overall treatment net benefit is defined as total health benefits expressed in the monetary units minus the total costs associated with sequential treatment.

The SDDP is most relevant for long-term health conditions where drug switching commonly happens. Taking the example of hypertension, 25.9-32.6% of participants in a major clinical trial took an additional open-label drug in one year due to lack of efficiency and safety concerns[2]. In real practice, 50-60% of patients with hypertension experience some alteration of treatment regimen including a dose titration, drug switching or adding another drug to their initial prescription in the initial six months[3]. In the longer term, the high drug discontinuation rate levelled off after one year regardless of the type of drugs (see Figure ‎1.1)[2, 4]. The main reasons for drug switches were either poor efficacy or adverse effects (AEs)[3-6].[Hughes, 1998 #228]

1) Ds, BBs, CCBs, ACEIs and ARBs refer to different types of antihypertensive drug more fully defined in Chapter 4. The graph for "Others" was presented in the source from which this figure came from[4]

Figure .. Long-term continuation rates of antihypertensive drugs

Although major clinical guidelines have recommended the pharmacological treatment algorithms for the subsequent treatments, the variation in their recommendations implies that there is no established standard of evidence-based optimal treatment sequence (see section 4.2.3 for details)[7-10]. In addition, the recommendations from clinical guidelines are based on the piece-wise evidence but have not been tested in clinical trials or in economic evaluations. In the absence of robust evidence after initial treatment, the choice of the second or third-line drug among competitive drugs has been largely empirical and showed a random pattern[3, 4]. Such non evidence-based decisions may reduce the net benefits of treatment and cause the inefficient use of constrained resources.

Several studies have been performed to compare the cost-effectiveness of a limited number of pre-defined drug sequences, particularly, where drug switching is commonly recommended because of the chronic and progressive features and concerns about potential resistance, tolerability and AEs (see Appendix 1 for the summary of an exploratory literature review, which was conducted to understand how sequential treatment policies for long-term medical conditions were modelled in health economic evaluation). These disease areas include rheumatoid arthritis (RA)[11-21], cancer[22-27], schizophrenia[28, 29], glaucoma[30], and diabetes (DM)[31-33]. The model structures were constructed to reflect the disease pathway or its pre-defined treatment pathway. In order to allow drug switching, most studies modelled a key drug switching point defined by non-response to treatment, the occurrence of AEs or other progressive events. When the drug switching point was reached, the next drug was given followed by the pre-defined treatment strategies. For example;

Welsing et al compared the 5-year cost-effectiveness of five sequential treatment policies including Tumour Necrosis Factor-Blocking agents (TNFb) and/or leflunomide (LEF) in the usual treatment for RA patients in the Netherlands[12]. A Markov model was constructed with four health states defined by the Disease Activity Score (DAS). Patients with a high DAS score initially moved to another state depending on the results of a response assessment every three months. The patients, who did not respond to the initial treatment, switched to LEF for the patients who took usual treatment initially, or to usual treatment for the patients who took LEF or TNFb initially.

Cameron et al and Lux et al constructed a Markov model with four different treatment sequences of hormone-receptor-positive (HR+) advanced breast cancer, which included or excluded fulvestrant as either a second or third-line therapy[24, 26]. Once patients experienced a progressive event, they moved to another treatment option up to five including best supportive care.

Bobes et al analysed the economic impact of most commonly used antipsychotic drugs - ziprasidone, olanzapine, risperidone and haloperidol - in schizophrenic patients[28]. A Markov model was developed to simulate the AEs seen in the EIRE study (that is, Estudio de Investigacio´n de Resultados en Esquizofrenia; Outcomes Research Study in Schizophrenia)[34]. Treatment started with one of four antipsychotic drugs. Depending on the type of AE, treatment was modified (i.e., decreasing dose or switching drug) as obtained from a local cross-sectional study and clinical trials previously published.

Payet et al defined the Markov states by alternative treatment options for glaucoma. Travoprost or latanoprosat were given to patients initially. If a patient failed to respond at the end of each cycle, the patient could 1) continue with the initial drug; 2) receive an additional glaucoma treatment; 3) switch to a new treatment; 4) undergo laser therapy or surgery; or 5) die. Treatment success rate and transition probability to alternative options were estimated from an observational study conducted to record the ophthalmologist's therapeutic decision within four weeks[30].

To overcome the structural limitations of cohort-based models to consider patients’ time-dependent risk factors, some Markov models made attempts to add time-dependent variables and the interrelationship with health states and treatment decisions over time, using individual sampling and mathematical equations. For example, Brennan et al compared the cost-effectiveness of including or excluding etanercept to the most commonly used sequential treatment strategies of disease modifying ant rheumatic drugs (DMARDs) for the patients who failed with two DMARDs[13]. The sequential use of DMARDs following disease progression was determined based on time-dependent variables such as response rates, mortality rates and Health Assessment Questionnaire (HAQ) score changes. In particular, modelling of HAQ score progression following initial response, non-response, ongoing success or withdrawal made it possible to present a patient’s medical history and the impact on costs and quality-adjusted life year (QALYs) over time.

Individual-based models (IBM) such as discrete-event simulation (DES) were employed for better description of the dynamic relationship between the disease pathway and individual patients’ time-dependent variables. Barton et al developed the Birmingham Rheumatoid Arthritis Model (BRAM) to compare the cost-effectiveness of different DMARDs sequences for the patients starting a DMARD[35]. The most representative DMARD sequence, which was selected in a survey conducted in UK rheumatologists, was compared with two other strategies including etanercept or infliximab in the representative strategy. Each patient was assigned age, gender and initial HAQ score at the beginning of the simulation, and a drug was switched to the next drug in the case of HAQ increase, joint replacement or discontinuing the drug. The risk of joint replacement or death was dependent on HAQ, which was varied according to treatment. Time to competing events was calculated by the probabilities that each event occurs in an assumed constant time interval.

The Januvia Diabetes Economic (JADE) Model was designed to project the impact of different Glycated Haemoglobin (HbA1c) thresholds on long-term health outcomes for type 2 DM patients who have failed with metformin[32]. The baseline profile included time-dependent risk factors, medical history and current treatment regimen. The first occurrence of DM-related complications was projected using equations of the UK Prospective Diabetes Study (UKPDS). Once a drug failed to reduce HbA1c below the threshold, the patient moved to the next treatment regimen. The model allowed up to six drug switches over a lifetime. Different sequential treatment regimens were used according to the patient’s HbA1c response, toleration and contraindications.

The main objective of these studies was to evaluate the overall cost and effectiveness of 1) including or excluding a specific new drug in/from routinely used treatment in practice, as a second or third-line therapy or 2) representative sequential treatment strategies selected based on survey or interview of expert groups[11, 24, 36]; a separate micro-simulation generating the probability of treatment sequences[29]; or clinical trials and retrospective observational studies[28, 30]. Therefore these studies could show the improvement in the cost-effectiveness ratio across the competing sequential treatment strategies (i.e., local optimality), but do not present whether the strategy is the optimal strategy to reach a treatment goal. To the author’s knowledge, there has been no economic evaluation to address the global optimality of SDDPs in a long-term health condition.

The reason that the economic evaluation addressing the global optimality of an SDDP is rarely found is partially associated with the main interest of health technology appraisal (HTA). Due to the scarcity of resources in healthcare, economic evaluation was introduced as a means of promoting the efficient use of available resources. In the case of pharmaceuticals, particularly, economic evaluation has become a core procedure for pricing and reimbursement in many countries. The primary goal of economic evaluation is to help decision makers arrive at the best choices among competing claims on resources[37, 38]. Therefore the cost-effectiveness evidence has been generated following the current guideline published by the HTA body, which limits the alternative treatments (sometimes treatment sequences) to the current best practice for a restricted population because of resource requirement, time to develop the model and to make a decision[7, 39].

From a methodological perspective, it has been argued that a methodological shift in economic evaluation is required from a static to a dynamic perspective to identify the optimal treatment sequence in long-term medical conditions[40, 41]. However, studying the dynamic nature of SDDPs can be challenging because of the computational complexity caused by a potentially large number of drug sequences and disease pathways (i.e., the sequences of health states) and the interdependence between the drug sequences and the disease pathways over time[42]. Another challenge is how to model SDDPs when experimental or observational longitudinal data of sequential drug use are not available. While data on the clinical effectiveness of first line drugs is relatively abundant, data on the effectiveness of subsequent treatment(s) after an initial drug fails and any potential interaction with concurrent drugs is scarce for many health conditions.

Several studies have developed a comprehensive policy model, which can simultaneously evaluate the cost and benefit associated with the prevention and therapeutic interventions across the entire disease pathway. Weinstein et al developed the coronary heart disease (CHD) policy model, which consists of the demographic-epidemiologic model for persons free of CHD, the bridge model for persons with new CHD and the disease history model for persons with a CHD history, to forecast the CHD incidence, mortality and cost of alternative preventive and therapeutic interventions[43]. Recently, Tappenden et al proposed a methodological framework of “Whole Disease Modelling” in cancer treatment and prevention that covers the costs and effectiveness occurring in pre-clinical disease state, diagnosis and referral, treatment for early disease, follow-up for surveillance and treatment for metastases, using a case study of colorectal cancer[39, 44, 45]. However, the comprehensive disease pathway model is a simulation model but not an optimisation model. It can provide the cost-effectiveness estimates for a larger part of complicated disease pathway but does not include a solution procedure, which finds the best solution to maximise the overall treatment net benefit. In particular, solving SDDPs involves testing a considerable number of possible treatment pathways to identify the optimal or near optimal solution. This means that an SDDP model will need to be incorporated with an optimisation technique, which could search the large decision space more efficiently. Hence this thesis tried to identify the potential optimisation methods to solve SDDPs efficiently and to discuss about the applicability of the key optimisation methods using a case study of primary hypertension.

## General optimisation approaches to solve sequential decision problems

Optimisation is the process of finding the conditions that give the maximum or minimum value of an objective function under given circumstances[46]. Classic optimisation technique is mathematical programming, which finds the global optimal solution where the objective function and constraints are described as the functions of certain decision variables. Linear programming (LP) can be applicable for a problem whose objective function and the constraints appear as linear function of the decision variables. Key assumptions of LP are 1) proportionality of the value of the objective function and constraints to the level of the input parameters, 2) additivity of the individual components of the objective function and constraints, 3) divisibility of the decision variables into non-integer values and 4) certainty of all model parameter values[47]. Any problem, which satisfies the four assumptions, can be solved using the simplex method[48]. However, it is common in real applications that some or all of the four assumptions do not hold. In this case a number of useful alternative models are available. If the proportionality assumption is violated (e.g., due to an increasing marginal return) or the additivity assumption is violated (e.g., due to interaction between the individual components of the objective function and constraints), nonlinear programming can be used[49]. Integer programming can be used if the divisibility assumption does not hold[50]. If the parameter values used involves some degree of uncertainty, a simulation model can be incorporated into the optimisation procedure[51].

Sequential decision problems involve the extension of conventional optimisation problems to determine the best order of the decision variables given a set of circumstances. In operational research, such a problem belongs to combinatorial optimisation problems, which find a set, or a sequence, of discrete decision variables to achieve the stated objective[52]. Most of the early attempts to solve sequential decision problems (i.e., combinatorial optimisation problems) used variants of LP methods, generally by taking the values 0 or 1, in order to produce an LP formulation[53]. However, such LP formulations often involve very large numbers of variables and constraints for large and complex sequential decision problems. As the alternative, dynamic programming (DP) was introduced for sequential or multi-stage decision problems[54]. It reduces multistate problems to a set of smaller problems defined by the decision period and solves them using a backward induction considering the future expected reward. DP is still widely used as an efficient optimisation technique for solving many problems involving a sequence of interrelated decisions and has been a theoretical basis of many approximate optimisation methods. This will be further discussed in section 3.5.

Stochastic sequential decision problems are often formulated as a Markov Decision Process (MDP), which is a controlled Markov chain allowing actions in each state to maximise the decision maker’s goal[55]. The elements of MDP *P(T,S,A,p,r)* include the set of time *T*; the set of possible discrete states *S*; the set of allowable actions *A*; the set of transition matrices *p* where *a∊A* is used at *t*; and the set of immediate rewards *r* where *a∊A* is used for *s∊S* at *t*[55-57]. In MDPs, the decision maker selects a particular action *x∊A* for *h∊S* at *t*, and this leads to an immediate reward and specifies a transition probability where *x∊A* and *h∊S.* In most cases, the transition probability follows Markovian assumption whose transition probabilities to a subsequent state depend only on the current state and action selected. This Markovian property can be relaxed by varying the transition probabilities or the timing of events based on the given information to a limited extent, which is called a semi-Markov decision process (SMDP). The global reward for a sequence of decision (i.e., the value of the objective function) is estimated by DP: therefore MDP is also called stochastic DP[51]. The difference between stochastic DP and deterministic DP is that the next state *ht+1* is not completely determined by the current state *ht* and action *xt*. Rather, stochastic DP uses a probability distribution dependent on the conditional expectation of the previous state(s) and action(s).

As MDP has the form of a successive decision tree, it may suffer the curse of dimensionality in large and complex sequential decision problems. Where a SMDP is used, in particular, considering the previous states and actions inevitably increase the computational complexity: therefore some studies tried to alleviate the computational complexity using the state aggregation[58], partial-observability[59] or limited-memory[60]. State aggregation reduces the number of potential states by combining several similar states with respect to transition probabilities or reward to an aggregated state. Partial-observability and limited-memory assumptions reduce the amount of memory used for each decision by relaxing the no forgetting rule, which uses all information known for those previous decisions.

An alternative stochastic optimisation method is simulation-based optimisation, which uses a simulation model to evaluate the objective function[61](see Figure ‎1.2). The problem formulation is identical with MDP; however, the problem solving procedures can differ. Whereas mathematical programming and MDP inherently integrate the evaluation process and the optimisation process, simulation-based optimisation is constructed with two key components; an optimisation model and an evaluation model. The optimisation model includes the overall process of guiding the search procedure, generating candidate solutions and determining the optimality of the candidate solutions based on the expected value provided by the evaluation model. The underlying evaluation model is not restricted to individual-based models (IBMs) such as DES, but may include any decision analytic models such decision-tree and Markov models. The problem solving procedure can work forward or backward depending on the optimisation algorithm used.



Figure .. Simulation-based optimisation model

Many search algorithms have been developed. The simplest search method is enumeration, which examines all possible candidate solutions and ranks them based on the results obtained from the simulation model[51]. If the solution space is small, enumeration will guarantee the global optimal solution in a reasonable amount of time. However, sequential decision problems often have an enormous number of possible solutions. In this case, enumeration is not practical or efficient. The alternative is using a local search method, which is one of the fundamental elements of heuristic methods. Rather than examining all possible solutions to the problem, local search methods focus on searching a neighbourhood of particular solutions by introducing certain pre-set subjective factors (more details are described in section 3.2.8). They would not guarantee an optimal solution, but can be attractive because it provides ‘near-optimal’ solutions in a reasonable amount of time by reducing the risk of spending too much time solving the problems[62]. Therefore, the term ‘heuristic’ is often used equivalently with approximate optimisation methods, as a contrast to mathematical programming (or exact algorithm).

These stochastic optimisation methods introduced above have been widely used to solve sequential decision problems in computer science, applied mathematics, artificial intelligence, engineering and operational research. Some of them also have been introduced for healthcare-related sequential decision problems. For example;

Hauskrecht and Fraser introduced a framework to use a partially observable MDP (i.e., MDP assuming the partial observability) for the management of patients with ischemic heart disease[59]. The set of actions included no treatment, pharmacological treatment, surgical procedure such as angioplasty (PTCA) and coronary artery bypass surgery (CABG), and investigative actions such as coronary angiogram and stress test. The set of patient’s states included coronary artery disease, ischemia level, acute myocardial infarction (MI), decreased ventricular function, history of CABG and PTCA, chest pain, resting electrocardiogram ischemia, catheter coronary artery result and stress test result. Some of them were assumed to be observable, whereas the others were assumed to be hidden. The objective was to minimise the expected cumulative cost of the treatment.

Van Gerven et al used a dynamic limited-memory influence diagram (i.e., successive influence diagram assuming a limited memory) for the underlying evaluation model to identify the optimal permutation of different levels of chemotherapy for high-grade tumour patients[60]. The decision problem was whether to administer chemotherapy or not at each decision moment in cancer population. The set of the patient’s health states includes normal, mild complaints, ambulatory, nursing care, intensive care and death, which were assumed to depend on the patient’s age, gender, tumour mass and the treatment strategy. Effectiveness is tumour progression depending on tumour response. The objective was to maximise the global utility, which was the quality of life (QoL) minus cost of chemotherapy. Experimental results from single policy updating, single rule updating and simulated annealing (SA) showed that the framework was applicable to find reasonable treatment strategies for complex dynamic decision problems in medicine.

Although many optimisation algorithms have been developed, there is no single method, which is generally known to be consistently better than the others in the context of sequential decision problems. The performance is problem-specific and varies depending on the way that the problem is constructed and the applied problem solving procedure. Therefore this thesis tries to identify the key approximate optimisation methods, which are applicable to SDDPs, and to discuss about the feasibility and the performance of the proposed methods using a case study of primary hypertension. The key criterion to decide the performance is the quality of solution, which shows how close the final objective function values and the real global optimum are, where the real global optimum is known; or how good the objective function values of the finally generated solution are, where the real global optimum is unknown. Computational efficiency, which means finding a good solution in a reasonable amount of computation time, is also an important criterion to compare the performance of approximate optimisation methods.

## Motivations and research objectives

This study was motivated by the clinical reality that drug switching commonly happens in long-term medical conditions, but there is limited evidence and research about the optimal treatment pathway. Clinical guidelines in the treatment of primary hypertension are an example, with recommended treatment algorithms being based on piece-wise evidence, resulting in lack of clear consensus and differences between guidelines[8-10, 63]. Furthermore those recommended clinical guidelines have not been tested in clinical trials or in economic evaluations.

From a methodological perspective, conventional economic evaluations have been interested in evaluating the cost-effectiveness of a drug at a specific point in the disease pathway: however, the most cost-effective drugs can be different as the patient’s health state changes over time. Although there were some studies, which considered the treatment sequences in a broader disease pathway, there has been no economic evaluation to address the global optimality of SDDPs in a long-term health condition.

Due to the practical importance of stochastic sequential decision problem, many approximate optimisation methods have been developed. None of those optimisation algorithms works consistently better than others. The performance can be different depending on the type of optimisation problems: therefore, this study aims to set down the definitions of SDDPs mathematically to understand the nature of SDDPs, to examine the potential methods to identify optimal or near-optimal sequential treatment strategies in the context of a multiple drugs, multiple switches and multiple health states decision space problem; and to discuss the performance of the proposed methods using a case study of primary hypertension.

The objectives of this study are:

1. To develop the formal definitions of SDDPs using the framework of MDP.
2. To review approximate optimisation methods to identify the set of methods appropriate for SDDPs.
3. To develop a de novo hypertension cost-effectiveness model considering blood pressure lowering effects of sequential use of antihypertensive drugs.
4. To test the feasibility and performance of selected approximate optimisation methods using the developed hypertension model.

## Thesis structure

The rest of the thesis is organised as follows. In the following chapter, a mathematical description of SDDPs is developed to gain an understanding of the nature of SDDPs. As the mathematical definition of SDDPs can be structured in different ways depending on the structure of underlying evaluation model, key cost-effectiveness modelling techniques are introduced first, followed by their advantages and disadvantages in using for the underlying evaluation model of SDDPs. Other issues, which need to be considered to structure SDDPs, are also discussed with the comparison between SDDPs and representative combinatorial optimisation problems. Potential sources of computational complexity of SDDPs are explained based on the mathematical description of SDDPs.

In Chapter 3, a systematic review is presented to identify approximate optimisation methods to solve an SDDP. The theoretical background and methodological application of the potential optimisation methods, which were identified in the systematic review, are explained. A simplified SDDP case-study is used to test the feasibility of the selected methods within the context of SDDPs.

Chapter 4 is the overview of modelling an SDDP for primary hypertension. Hypertension and the pharmacologic management are explained based on the clinical guidelines and textbooks. A literature review on previous cost-effectiveness modelling studies in primary hypertension is summarised. A conceptual framework of the hypertension SDDP model is detailed based on the elements used for the mathematical definition of SDDPs.

The hypertension SDDP model consists of two closely linked models - an evaluation model and an optimisation model. Chapter 5 describes the population characteristics, model structure, data used and key assumptions to populate the underlying evaluation model. Chapter 6 explains how the suggested optimisation methods - enumeration, SA, genetic algorithm (GA) and reinforcement learning (RL) – works with the underlying evaluation model using the pseudo-codes.

Chapter 7 presents how the hypertension SDDP model was validated internally and externally. The experimental results obtained from different approximate optimisation methods in various settings of key parameters are investigated regarding the quality of solution and computational efficiency.

Chapter 8 summarises what this study achieved and discusses the applicability of the proposed methods. This chapter also lists the limitations of the hypertension SDDP model and suggests the direction of future research.

Chapter 9 is the conclusion of this study.

# Problem specification for sequential drug decision problems

## Chapter overview

Chapter 2 classifies the cost-effectiveness modelling techniques by the key issues, which should be considered for SDDP modelling, and discusses the potential strengths and weakness of each technique when they are used as the underlying evaluation model in SDDPs. Various ways to define SDDPs are also introduced with the comparison between SDDPs and representative combinatorial optimisation problems. A mathematical definition of SDDPs is presented using the framework of MDP, assuming the underlying evaluation model follows the structure of a discrete time Markov model. The potential computational complexity is discussed based on the mathematical definition of SDDPs.

## Classification of evaluation models for sequential drug decision problems

Several studies have categorised modelling techniques by the key issues, which should be considered to select an appropriate method in economic evaluation in healthcare[14, 64-66]. Brennan et al developed guidance on choosing a modelling technique using a range of model structure criteria, which include time and interaction between individuals, the heterogeneity of entities, the role of expected values, randomness and the degree of non-Markovian structure[64]. This thesis uses the taxonomy proposed by Brennan et al as the basis to develop a specific classification for economic evaluation of SDDPs (see Table ‎2.1).

Firstly, similar to the taxonomy proposed by Brennan et al[64], the models are classified according to whether it is cohort/aggregate level (column A and B) or individual level (column C and D), and then by whether the model is Markovian (column A and C), semi-Markovian (column B and C) or non-Markovian (column D). From another perspective, the models are classified as decision-tree (row 1), Markov models (row 2), and non-Markovian IBMs (row 3) according to the underlying type of models commonly known in the discipline of healthcare modelling and operational research. Regarding the specific models included in the proposed classification for SDDPs, decision-tree models, where the Markovian assumption is difficult to be relaxed, are classified as classic cohort-level decision-tree models (column A, row 1) and simulated patient-level decision-tree (SPLDT) (column C, row 1). Markov models are classified as classic cohort-level Markov models where the Markovian assumption is strictly applied (column A, row 1), and cohort-level semi-Markov models (column B, row 1) and simulated patient-level Markov model (SPLMM) (column C, row 1) where the Markovian assumption is relaxed. This study broadly defines non-Markovian IBMs as individual level models where the changes of individual states do not necessarily need to follow the Markovian assumption. According to this definition, non-Markovian IBMs include individual event history model (IEH) (column C and D, row 3), which includes two commonly known specific IBMs: DES and agent-based simulation (ABS).

Table .. Classification of evaluation models for SDDPs

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | | A | B | C | D |
| Cohort/aggregate level | | Individual level | |
| Markov | Semi-Markov | Markov or semi-Markov | Non-Markov |
| 1 | Decision-tree | Decision-tree | n/a | Simulated patient-level decision-tree (SPLDT) | n/a |
| 2 | Markov models | Markov model | Semi-Markov model | Simulated patient-level Markov model (SPLMM) | n/a |
| 3 | Non-Markov individual-based models (IBM) | n/a | n/a | Individual event history model (IEH), including discrete event simulation (DES), agent-based simulation (ABS) | |

Compared to the taxonomy proposed by Brennan et al, the classification proposed for SDDPs makes no distinction between timed vs. untimed models and between continuous vs. discrete state models, because considering time is essential for modelling SDDPs (i.e., all timed) and in most cases, discrete, rather than continuous, health states would be used for SDDPs. No distinction between discrete vs. continuous time was made in the proposed classification because Markov-based models and various non-Markovian IBMs could potentially handle both discrete and continuous time (this feature is less relevant to decision-tree models). There is also no distinction between deterministic vs. stochastic models, because all the models within the proposed classification could be evaluated both deterministically and stochastically. Finally, the proposed classification makes no distinction between models allowing or not allowing for interaction, because interactions among patient cohorts or individual patients are not necessary for SDDPs, especially in long-term medical conditions assuming unconstrained-resource.

In practice, SPLDT and SPLMM are not as common as the classic cohort-level decision-tree and Markov models. It is also straightforward to adapt IEH models such as DES or ABS to develop SPLDT or SPLMM models. Therefore, this study will focus on three types of models for the evaluation of SDDPs: cohort-level decision-tree models, cohort-level Markov models (Markovian or semi-Markovian) and IEH including DES and ABS. These models are simply referred to as decision-tree, Markov models and IBMs hereafter.

### Decision-trees

Decision-trees are simple directed graphs consisting of branches showing a clinical problem, decision nodes presenting a decision maker’s choice between competing strategies, chance nodes determining the consequences of treatment probabilistically and terminal nodes denoting the final outcome state associated with each possible pathway[67]. The object that is usually modelled is a hypothetical homogeneous cohort. The parameters of the tree have either the average or probability distributions, which are generally constant over time.

If the given SDDP is simple enough to be presented diagrammatically as a successive decision-tree, a decision-tree can be used to solve the SDDP[36, 68-70]. The successive decision-tree consists of 1) branches showing the disease pathway or the treatment pathway, 2) chance nodes determining the probability of treatment success or failure and 3) decision nodes allowing sequential treatment decisions. The main assumption is that a drug is continuously used if it is effective for the previous period and switched if it is not effective (see Figure ‎2.1). However, the decision-tree would quickly become unmanageable where there are more time periods, more health states or more drug alternatives. Moreover, decision-trees may be of limited value to represent real world SDDPs, which inevitably involve the functionalities to memorise current and previous information and to carry information over time, and to perform logical evaluations based on this information.



Figure .. An example successive decision tree model for SDDPs

### Markov models

Markov models are partially cyclic directed graphs, which describe the transition of a homogeneous cohort of patients from the current state to the next state over time according to the specified transition probabilities[71]. In cohort simulations, which assume a Markov state-transition model, a proportion of patients in each state transfers from one state to another state every cycle depending on the current health state. The model runs until all the patients in the cohort are in the absorbing state or until the time horizon assumed in the model is reached. The results are presented in a chart showing what proportion or cumulative proportion of the cohort is in which state at a given time. The costs and effectiveness incurred by patients across the different health states are added up every cycle. The final outcome is the average costs and effectiveness of the patients in the original cohort for the follow-up period. In order to provide probabilistic results, Monte Carlo simulation can be incorporated into the model.

Under the Markovian assumption the transition probability to a subsequent state of a cohort solely depends on the current state of the cohort. Thus, no information on the past is used to determine the subsequent transition of state at the current time. Some researchers have tried to relax the Markovian assumption by using time-dependent (or age- or time-in-state dependent) transition matrices[72, 73]. The structure of these models is similar to the standard Markov model. However, the difference is that the transition probabilities in the modified Markov models can be time-dependent (or age or time-in-state dependent) or varied according to the level of patients’ risk factors. Such models have been referred to as semi-Markov models[65, 66, 74].

Compared to the successive decision-tree, the Markov model has a simpler model structure because the time dimension is not explicitly shown (see Figure ‎2.2). If an SDDP generally satisfies the Markovian assumption (i.e., previous drug uses or health states have no or limited impact on the drug decision and health state transition at the current time), then, Markov models may be appropriate to build the evaluation model for the SDDP. In practice, the memoryless assumption would be restrictive for most real SDDPs because previous drug uses or health states may have a substantial impact on the subsequent drug decision and health state transitions. Therefore, either a suitable semi-Markov model or more flexible model methods, such as IBMs, need to be considered. Note that the ability of semi-Markov models to represent complicated systems, where more detailed heterogeneity of population needs to be considered, may be still restricted by the curse of dimensionality as a result of the fundamental choice of the cohort model structure[64].



Figure .. An example Markov model of SDDPs

### Individual-based models

Rather than a cohort of patients moving through the model simultaneously, a large number of individual patients can move through the model consecutively in IBMs. In the context of healthcare modelling, IBMs, such as DES, explicitly model the disease progression and other relevant characteristics (either static such as gender or dynamic such as age and drug uses) of sampled individual patients over time. Entities represent patients assigned with attributes such as age, gender and other risk factors. These attributes are updated while the patients go through the events that can happen to an entity during simulation. The updated information is stored in a variable and used to determine the transition to the subsequent disease pathway, as well as the associated costs and effectiveness. As the whole history of an individual is tracked and used to determine the transition to the subsequent disease pathway, IBMs do not have the constraints incurred by the memoryless property of Markov models. The method to handle time is flexible for IBMs where time can either be modelled by fixed interval time slices/cycles (as for Markov models) or handled by discrete events where the system clock jumps from event to event only when system state changes.

Due to the flexibility of IBMs, they may be considered when the SDDPs have a large number of health states and/or potential drugs with patient heterogeneity, and when it is essential to model non-Markovian relationships in the model. The “curse of dimensionality” does not affect IBMs as the complexity of IBMs only increase linearly, rather than exponentially, when more drug choices, health states, or time periods are modelled. A time-to-event approach potentially reduces the computational time for modelling SDDPs because the model is only updated when relevant event (e.g., change of health states, change of drugs) happens. Figure ‎2.3 illustrates an example using a DES structure.

Nevertheless, there are certain limitations to DES. Firstly, they require more data than other models, such as input parameters conditional on various individual patients’ history. Secondly, DES models take a relatively long time to calibrate and validate because they may require sampling a large number of patients to increase the accuracy of mean effects. This is also associated with less flexibility of DES models to assess uncertainty due to computational burden. A full sensitivity analysis of DES requires two levels of simulation: one is based on fixed parameters to estimate a single expected value and the other is to sample from a distribution of possible input values[74]. If the DES model runs for 10,000 patients to get the reasonable average costs and effectiveness, for example, conducting the full sensitivity analysis may result in 100 million individual simulations. This may be only feasible for a small proportion of DES models implemented in a fast programming language or by extended computing resources that facilitate parallel runs across multiple processors[75].

|  |
| --- |
| **FOR** individual *i*  1: Sample relevant initial patient attributes (e.g., gender, age, whether or not smoking, etc.).  2: Assign initial drug.  3: Decide the outcome (success/failure) and timing of next health state, and accrue costs and QALYs.  4: Assign the next drug.  5: Decide the outcome (success/failure) and timing of next health state, and accrue costs and QALYs.  6: Repeat step 4-5 until the patient dies or the pre-set simulation time is reached.  **NEXT** individual *i+1* |

Figure .. An example IBM model of SDDPs

## Comparison between sequential drug decision problems and representative combinatorial optimisation problems

Most sequential decision problems, which involved discrete finite state/action spaces and probabilistic transitions, were formulated as an MDP[76-79]. The representative scenarios have the various forms of traveling salesman/shortest path/vehicle routing[80-82], job scheduling[83-85], timetabling[86], inventory control[87-89], facility location[90-93], resource allocation[94-97] and others. If an SDDP of interest tries to control the disease as quickly as possible (i.e., the objective is to minimise the time to control the disease) or to minimise the total treatment costs, SDDP has a connection with the traveling salesman problem (or shortest path problem) in that it also requires finding a permutation of cities that achieves minimum distance or costs[62] (see Table ‎2.2). Considering the interaction between health states and sequential treatment over time, the job-shop scheduling problem, which processes a set of jobs *J=(j1, j2, …, jn)* and a set of machines *M=(m1, m2, …, mm),* is also similar with SDDPs[98, 99]. Many variations of the job-shop scheduling problem exist. In the stochastic job-shop scheduling problems, each operation of job *j* on machine *m* has processing time *tjm* which is assumed to be unknown[85, 100]. In the dynamic job-shop scheduling problems, job release times are random variables described by a known probability distribution[101, 102]. Jobs may have constraints, for example, a job *i* needs to finish before job *j* can be started or single jobs cannot be performed in parallel. There may be the mutual constraints between jobs and machines, for example, certain jobs can be scheduled on some machines only[103-105].

Table .. Comparison between SDDPs and the representative combinatorial optimisation problems: traveling salesman problems and job-shop scheduling problems

|  |  |  |  |
| --- | --- | --- | --- |
|  | Sequential drug decision problems | Traveling salesman problems | Job-shop scheduling problems |
| Problem | To identify a sequence of drugs along the disease pathway of a health condition with the objective of maximising the net benefits of treatment. | To identify the shortest travel route given a list of cities and the distances between each pair of cities. | To allocate the jobs on the capable machines to minimise the total (or average) completion time. |
| Time parameter | Discrete or continuous. | Discrete or continuous. | Discrete or continuous. |
| States | A set of possible health state combinations within the time dimension. | - | A set of jobs that consists of a chain of operations. |
| Actions | A set of possible drug sequences. | The set of permutations of *n* cities. | A set of machines that handles one operation at a time. |
| Random variable | Transition probability between health states depending on action (e.g., treatment success rate). | Travel time and client’s need. | The processing time, release time, demand and deadline of jobs. |
| Constraints | History dependent decision-making and any contraindication of drugs for a specific health state. | The rules for visiting each city (e.g., visiting each city once and returning to the starting city). | Deadline and mutual constraints between jobs and machines. |

The potential differences between SDDPs and the conventional job-shop scheduling problem are that 1) the transition between states are stochastic in the SDDP, whereas the chain of operations is deterministic in most cases of the job-shop scheduling problems; and 2) the drugs in SDDPs are related to each other, whereas the set of machines are assumed to be unrelated parallel in most cases of the job-shop scheduling problems[106-108]. Therefore, the size of the decision space in SDDPs tends to increase more rapidly than the job-shop scheduling problem to consider the potential health state combinations, which could happen stochastically. Unlike most job-shop scheduling problems, furthermore, an SDDP model will need to embed a certain level of memory into the model to consider potential impact of treatment history on the transition between health states. The no-forgetting assumption, which uses all informational predecessors for later decisions[109, 110], causes exponential growth of memory usage, computational complexity and runtime, regardless of the modelling method. As the alternative, the limited-memory assumptions relaxes the no-forgetting assumption to consider only a limited number of previous observations[60, 111, 112]. However, this may be associated with the trade-off between the quality of solution and the computational complexity.

The set of time *T* can be classified in either a discrete set (which is called discrete-time MDP)[113, 114] or a continuous (which is called continuous-time MDP)[115] depending on whether the events are assumed to occur at a discrete time interval or at a point on a continuum. The set of time *T* can be further classified as either finite horizon[116-118] or infinite horizon[119, 120] according to whether the set of time *T* is finite or infinite. The problem formulations in those four cases are almost identical, but computational methods differ considerably. Where the total future expectation is always finite, for example, DP can use the expected total reward over the decision making horizon. For a problem assuming infinite horizon, however, average expected reward per unit time is used because the policy and expected reward can be assumed to be independent of time t over the infinitely long trajectory.

SDDPs can be also specified in different ways depending on the decision-maker’s perspective. Although the decision-makers generally pursue maximising total treatment net benefits in SDDPs, one may be interested in developing an evidence-based stepped-care guideline in a population perspective (i.e., what is the optimal initial drug and then what is the optimal second or third-line drug after the previous drug fails to control the disease), but the other may be interested in dynamic treatment assignment in an individual patient’s perspective to provide a tailored optimal treatment sequence to the patients’ need for treatment.

For the former, the search space can be constructed with a set of complete solutions, which is a set of all possible treatment sequences in the context of SDDPs. In this case, each complete treatment sequence is referred to as deterministic policy because mapping from the current drug to the next drug is already determined by the complete treatment sequence. As the algorithm works with complete solution, it can provide at least a potential answer based on the search experience, wherever it stops. For the underlying evaluation model, cohort models such as decision trees and Markov models would be more relevant.

The latter will need a more flexible approach to generate an individual patient’s disease pathway and to assign a drug to individual health state. Instead of having a fixed patients’ case to optimise, the overall problem can be divided into a set of sub-problems, which have a set of possible health states and treatment options, by decision-making point. A simulation model randomly generates the individual patient’s health state in each period and allows the drug selected the actual instance is revealed. This approach, then, combines the individual or partial solutions to get a complete answer for the overall problem. This enables one to operate the sequential decision-making process, considering inter-patients variability in risk factors and response to treatment over time. The allowable set of incomplete or partial treatment sequences resides in a subset of the original decision space by health state, and then varies as patients’ health state progresses with a given probability. The knowledge about the previous search can be used to advance the search after a change. The decision rule is said to be stochastic (or randomised) because mapping from the current state to the next state is stochastic.

On the premise that SDDPs have a similar property of the stochastic sequential decision problems, the following section mathematically defined SDDPs using the framework of MDP, assuming that the given SDDP is a discrete-time Markov problem having a finite state/action spaces in a finite set of decision times. The decision-maker was assumed to pursue maximising total treatment net benefits in SDDPs from a population perspective. These assumptions were used in the whole thesis, but can be extended to DES using a continuous-time for patient’s perspective in future research.

## Mathematical description of sequential drug decision problems

SDDPs involve patients experiencing a series of health-related and drug-related events over a finite time. A finite set of mutually exclusive health states *h∈H* and drugs *a∈A* are defined. Note that a drug *a* defined here refers to a single treatment regimen, which could be a single drug (potentially with different doses), or a combination of more than one drug in circumstances where multiple drugs may be prescribed at the same time. Given a health state *st∈H* at time *t*, the selected drug *xt∈A* has an impact on both the next health state *st→st+1* and the costs/benefits associated with this transition.

As the health state transitions are not fully known in advance, a transition probability function can be used to represent the probability of the patients being in state *st+1*at time *t+1* if drug *xt* is chosen for health state *st*at time *t*. For simplicity, the transition probability is often assumed to follow the Markov property, which assumes no memory. That is, future states *st+1*depend only upon the present state *st* and *xt,* not on the sequence of events that preceded it. Mathematically, such an SDDP can be defined as *P(T, H, HS, A, SS, DS, Ω, p, r, f),* as follows:

* *T=(t1,t2,…,tn)* represents the time dimension with *n* periods where possible changes in health state and drug use occur.
* *H* represents a set of *l* possible health states *H={h1,h2,…,hl }*.
* *HS* represents the health state space, which is a set of possible health state combinations or disease pathways within the time dimension *HS={θ=(s1,s2,…,sn, sn+1 )},* where *st∈H*. The number of potential health state combinations within *T* is:

, where all patients start with the same health state. Equation 2.1.

* *A* represents a set of *m* possible drug alternatives *A={a1,a2, …,am}*.
* A drug switch is when two different drugs (*ai* and *aj* where *i≠j*) are used sequentially in two adjacent time periods within *T*. Theoretically, the maximum number of drug switches that can possibly occur within *T* is *n* (i.e., if drug switch occurs between all adjacent time periods), but in reality the number of drug switches within *T* may be less than *n* if the same drug *ai* can be used continuously for more than one time period whilst being effective and without any AE. In this definition, it is assumed that a drug can be continuously used for more than one time period, but a drug cannot be re-used if it has been previously used and replaced with another drug.
* *SS* represents the search space, which is a set of possible drug sequences *SS={π=(d1,d2,…,dm)},* where *di∈A. π* represents one potential sequential treatment policy, which is the permutations of *m* possible drug alternatives within *A.* Once *T* is defined the number of possible drug sequences is:

, where *m≤n,*

, where *m>n*

Equation 2.2.

* Decision space *DS={πsx=((s1,x1),(s2,x2),…,(sn,xn))}* represents a set of health state transitions within *T* together with the associated drugs used for each health state, where *st∈H* and *xt∈A*. Unlike the sequential treatment policy *π=(d1,d2,…,dm)*, the drug sequence used for each time period *πx=(x1,x2,…,xn)* allows repetition of the same drug depending on *st* (i.e., a drug can be used continuously for more than one time period if the drug is effective). Depending on the decision when to switch drugs within *T*, there are a set of variations of *πx={=(x1,x2,…,xn)}* for a specific *π=(d1,d2,…,dm).* For example, considering three drugs 1, 2 and 3 for four time periods, one of the six possible sequential treatment policy *π=(1,2,3)* has 11 variations *πx* during *T* as following*:*

*πx = {(1,1,1,1,1),(1,1,1,1,2),(1,1,1,2,2),(1,1,2,2,2),(1,2,2,2,2),(1,1,1,2,3),*

*(1,1,2,3,3), (1,2,3,3,3),(1,1,2,2,3),(1,2,2,3,3)* and *(1,2,2,2,3)}*.

* *Ω* represents the set of probability matrices *ω* for *st+1*, which depends upon either *st* and *xt,* where the Markovian assumption is used, or (*s1,x1,s2,x2,…,st,xt)* where non-Markovian assumption is used. The probability that *θ=(s1,s2,…,sn)* happens for a given drug sequence *πx* is:

,

where

Equation 2.3.

* The reward function is the sum of the partial rewards of selecting drug *x∈A* for health state *s∈H* at time *t*:

Equation 2.4.

* The objective function *f(π)* is the sum of all reward functions *r(θ)* for all possible health state combinations:

Equation 2.5.

In a maximisation problem, the optimal drug sequence *π\*∈SS* satisfying *f(π\*)≥f(π) ∀ π∈SS* is called the globally optimal solution of *P(T, H, HS, A, SS, DS, Ω, p, r, f).* Figure ‎2.4illustrates possible health state transitions and associated drug uses of a simple SDDP diagrammatically where the Markovian assumption is made.



1) ***st*** represents the health state a*t* t; ***xt*** represents the drug choice at *t*; ***ω(st+1|st,xt)*** represents the transition probability from *st*  to *st+1*where *xt* is used; ***r(s t+1|st,xt)*** represents the partial reward where *xt* is used for *st* at *t*; ***r(θ)*** represents the sum of the partial rewards of using drug *πx* for a specific disease pathway *θ=(s1,s2,…,sn)*.

Figure .. Graphical presentation of an SDDP with the Markovian assumption

## Computational complexity of sequential drug decision problems

SDDPs belong to combinatorial optimisation problems, which find a set, or a sequence, of discrete decision variables to achieve the stated objective. Where the search space *SS* consists of a set of possible drug sequences at discrete time points *t=1,2,…,n*, the optimal solution *π\*=(d1,d2,…,dm)* is constructed by the sequence of drugs which maximises the value of the objective function. Such a combinatorial optimisation problem usually has a large decision space which consists of enormous possible solutions. In SDDPs, the size of *DS* depends on the size of *HS, SS* and *δ* which represents the number of variations of drug sequence defined on *T* for a given policy option *π* within *SS*:

Equation 2.6.

As described in the previous sub-section, the size of *HS* increases exponentially with increased number of possible health states *l* and the modelled time periods *n* (see Equation 2.1). The size of *SS* increases linearly with increased number of drug alternatives *m* (see Equation 2.2). When the number of possible drug alternatives *m* is large, the size of *DS* can be reduced if the number of time periods *n* is reduced. One way to reduce the size of *DS* may be to assume a maximum allowed number of drug switches based on clinical grounds. For example, if there are 10 possible drug alternatives for a specific health condition (i.e., *A={1,2,…,10}*, *m=10)*, but clinically most patients would only consider a maximum of three drug switches, the size of the search space *Z(SS)=10\*9\*8\*7=5,040*. Without this clinical constraint, the size of the search space *Z(SS)=10!=3,628,800* which is more than 700 times bigger*.*

Further computational complexity arises because of the dynamic and stochastic nature of SDDPs. The term ‘dynamic’ here describes the varying properties of SDDPs through time and the existence of interaction between the time-dependent components of the model such as patients’ risk factors, health states and treatment effectiveness[121]. Any changes in state can be either pre-specified or occur randomly. In the former, which is called deterministic problem, the state at the next stage is completely determined by the state and policy decision at the current stage. In contrast, an SDDP is a stochastic problem which allows patients’ health state to undergo some modifications, which are not fully known in advance, over time. A transition probability function *p(st+1|st,xt)*, where the Markovian assumption is applied, or *p(st+1|s1,x1,…,st-1,xt-1,st,xt)*, where a non-Markovian assumption is applied, decides the probability that the system is in state *st+1∈H* at time *t+1* if action *xt∈A* is chosen in state *st* at time *t*. The computational issue here is how to compute or store the huge number of transition probabilities for all possible actions where the number of heath states in the decision space becomes very large. This problem gets worse where semi-Markovian assumption is required in SDDPs. The dependency of treatment effectiveness on the timing of the drug to be used (e.g., used as first-line vs. second-line, or used for the first year vs. continuously after 5 years) and on the current and potentially previous health state(s) inevitably needs varying the transition probabilities, which causes the curse of dimensionality.

Furthermore, the computational time tends to increase exponentially as the size of the decision space increases with excessive storage requirement to process all the elements of the transition probability matrices. In many cases, a probabilistic sensitivity analysis (PSA) will be required where the objective function strongly depends on the probabilistic structure of the SDDP model: however, the simulation runs for the evaluation of the objective function will be constrained because of considerable computational time.

In the computational complexity theory, such a dynamic and stochastic sequential decision problem is classified as a non-deterministic polynomial-time hard (NP-hard) decision problem, which is unlikely to have a polynomial algorithm, hence may need exponential computation time to find the optimal solution in a worst-case[122]. Polynomial algorithm is a fast algorithm, which guarantees to solve the problem within a number of steps. For the size of problem *n*, the time or number of steps needed to find the solution is a polynomial function of *n*. On the other hand, NP-hard problems require times that are exponential functions of the problem size *n*; therefore the execution times of the latter grow much more rapidly as the problem size increases.

For such NP-hard problems, classic mathematical programming is known to become inefficient and impractical. The key restrictions can be found in both problem specification using mathematical programming and problem solving procedure. To use mathematical programming, firstly, the objective function and all the constraints of the given problem must be formulated in such a way that it fits the optimisation method being used: however, the sequential decision problems are likely to be too complicated to manipulate or to express as explicit functions of the decision variables because of the non-linear, non-additive and probabilistic elements. Furthermore, the classical mathematical programming is useful in finding the optimum of continuous and differentiable functions: however, most sequential decision problems involve objective functions that are not continuous and/or differentiable. Lastly, mathematical programming often involves large numbers of variables and constraints because of the characteristics of combinatorial optimisation problems, which has an enormous number of feasible solutions. This makes the direct enumeration approach infeasible.

As the alternative, approximate optimisation methods have been widely used in computer science, engineering, artificial intelligence, operational research, business management, bioinformatics, manufacturing, public transportation, military, financing/investment and so on. Approximate optimisation methods, which are generally called heuristic methods in operational research, do not guarantee an optimal solution, but can be attractive because the intelligent function approximation and search strategies provide ‘near-optimal’ solutions in a reasonable amount of time[62]. The reasons of exploring heuristic techniques could be 1) the development of the concept of computational complexity has provided a rational basis for using heuristics rather than pursuing the optimality, and 2) a significant increase in the power and efficiency of the more modern heuristic approaches[53]. Hence this thesis focuses on approximate optimisation methods in the following chapters.

# Potential optimisation methods for sequential drug decision problems

## Chapter overview

In Chapter 3, a systematic review, which was conducted to identify the potential approximate optimisation methods to solve SDDPs, provides a comprehensive insight into the approximate optimisation methods that have been applied to solve sequential decision problems. The theoretical background and methodological application of the potential optimisation methods, which were identified in the systematic review are explained. A decision algorithm to guide an appropriate model structure to solve an SDDP is proposed. A hypothetical SDDP case study is also investigated to help understand SDDPs and to test the feasibility of some of the proposed methods.

## Systematic review on approximate optimisation methods

A systematic review was conducted to provide a comprehensive insight into the approximate optimisation methods that have been applied to solve sequential decision problems. The search was not restricted to literature related to healthcare because 1) an initial pilot search found that there are very few studies, which specifically applied these methods on healthcare related problems, and 2) there may be other efficient and useful methods that have been applied to sequential decision problems in other areas but have not been applied to healthcare problems. This systematic review was carried out in the following series of steps: 1) selection of the search databases, 2) definition of the search topic, 3) preliminary search and selection of target papers, 4) construction of search strategy, 5) definition of inclusion and exclusion criteria, 6) processing of the search result and 7) discussion of the methods. Based on the search results, the key characteristics of the identified methods and the applicability to the SDDPs were discussed.

### Selection of the search database

Because this systematic review had a broad and generic objective and was not restricted to healthcare related literature, two generic databases, *Web of Science (SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH)* and *Scopus (1966 to present)* were selected. Both databases provide access to multiple databases, which cover specialized subfields within an academic or scientific discipline including literature from computer science, engineering, mathematics, health sciences, and operational research. The most widely used health-specific databases, which are *MEDLINE (Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)1946 to Present)* and *EMBASE(1974 to 2012 March 15)*, were also selected in order to retrieve the literature, which addressed a sequential decision problem using an approximate optimisation method in healthcare, especially in cost-effectiveness analysis (CEA) modelling.

### Definition of the search topic

The search strategies were constructed with the combination of three main topics, which were sequential decision problem, approximate methods (or heuristics) and optimisation. These topics were defined as following:

1. *Sequential decision problem*: SDDPs are characterized as making multi-stage decisions sequentially over time. Successive Markov decision tree, which is called MDP, has been widely used to describe stochastic multi-stage decision problems whose transition mechanism can be controlled over time. Due to the dynamic, stochastic and combinatorial nature of the given problem, the problem can be classified as an NP-hard decision problem. Therefore, the search strategy was constructed to cover broadly not just for sequential decision problems but also any problem which can be depicted by an MDP or classified as any NP-hard decision problem.
2. *Approximate methods/Heuristics*: Heuristics aim to identify near-optimal solutions at a reasonable computational time by introducing certain pre-set subjective factors. As heuristics do not guarantee to find a global optimum, the term “heuristics” often means approximate methods in the context of optimisation. In this study, thus, “heuristics” are equivalent to approximate optimisation method. Heuristics also include meta-heuristics, which are a set of heuristic methods aimed at efficiently and effectively exploring a search space.
3. *Optimisation*: Optimisation is the process to find the solutions that give the maximum or minimum value of the objective function under given circumstances[46]. The process of solving SDDPs can be broadly viewed as optimisation, which is the act of obtaining the best result under the given circumstances.

### Pilot search

A pilot search was carried out to identify studies, which addressed a sequential decision problem in healthcare using a heuristic method. The results of the pilot search were used to develop the search strategies for the full literature search. The generally known terms related to NP-hard sequential decision problem, heuristic methods, optimisation and CEA were used for this pilot search. Target papers were selected if the study addressed ‘A stochastic optimisation problem, which assigns an optimal strategy, such as healthcare policy, diagnosis, treatment or drug dose strategy sequentially, to achieve a treatment goal, using a heuristic or approximate method’. In total nine out of 1,036 studies were selected as target papers. The summary table of the target papers is given in Appendix 2.

### Construction of search strategy

A series of search keywords were chosen for each of the three topics. Starting with these initial keywords, the search strategies were further refined so that the nine target papers identified by the pilot search could also be identified by the full literature search. Figure ‎3.1 presents the full process of refining the search strategies. Some health-related keywords such as multi-drug, treatment, regimen and therapy were also included in the final search strategies in order to improve the specificity of the search and to make sure the full search would pick up all the target papers identified in the pilot search.



Figure .. The process of refining the search strategy

The final search strategies and the search keywords were A’’, B’ and C in Figure ‎3.1. The three topics were combined using the “AND” Boolean operator. Search fields were limited to title, abstract and keyword. Literature not written in English, published before 1990 and conference, symposium or workshop papers, books, letters, editorials or corrections were excluded using the limit function in the database. The electronic database search was conducted on 22nd March 2012.

### Inclusion and exclusion criteria

A study was regarded as a potentially relevant study if it deals with ‘A stochastic sequential optimisation problem using a heuristic or optimisation method regardless of the type of problem’. Although this literature search mainly focused on heuristic methods, the studies, which used an optimisation method (i.e., mathematical programming methods), were not excluded at this stage in order to retain the possibility of considering a mathematical programming method for an SDDP if necessary.

### Processing of the search result

The total number of retrieved hits from the four electronic databases was 10,517 including all the nine target papers identified by the pilot search. Table ‎3.1 shows the number of papers retrieved from four electronic databases. Full search strategies by database and the results of the varied combinations of search strategies are presented in Appendix 3.

The search results were transferred to EndNote together with abstract. After excluding 3,603 duplications, 6,914 potentially relevant studies were left. The title and abstract of these papers were manually reviewed to decide whether they meet the inclusion criteria. During this step, 6,211 studies were excluded because they did not address a stochastic sequential or multistage optimisation problem. 191 studies were excluded because they did not use a heuristic or optimisation method. Finally 512 studies that met the inclusion criteria were left. Figure ‎3.2 shows the flow chart of study selection.

Table .. The number of papers retrieved from four electronic databases by search strategy

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Database | | | | Total1) | Retrieval rate of the target paper2) |
|  | Search  strategy | WOS | Scopus | Ovid | Embase |
| 1 | A | 2,040,041 | 1,948,450 | 858,663 | 968,771 | 5,815,925 | n/a |
| 2 | A' | 53,400 | 50,124 | 9,409 | 10,861 | 123,794 |
| 3 | A'' | 77,965 | 80,102 | 30,134 | 38,284 | 226,485 |
| 4 | B | 585,439 | 684,764 | 109,279 | 118,667 | 1,498,149 |
| 5 | B' | 172,268 | 233,930 | 25,113 | 25,061 | 456,372 |
| 6 | C | 2,064,178 | 2,222,123 | 961,438 | 1,157,020 | 6,404,759 |
| 7 | A∩B | 125,449 | 119,961 | 20,703 | 22,356 | 288,469 |
| 8 | A'∩B' | 6,011 | 7,653 | 248 | 254 | 14,166 |
| 9 | A''∩B' | 6,170 | 7,817 | 307 | 341 | 14,635 |
| 10 | A∩B∩C | 51,068 | 47,774 | 6,414 | 6,877 | 112,133 | 9/9 |
| 11 | A'∩B'∩C | 4,339 | 5,394 | 158 | 152 | 10,043 | 6/9 |
| 12 | A''∩B'∩C | 4,342 | 5,834 | 182 | 159 | 10,517 | 9/9 |

1) Duplication is not excluded.

2) The number of target papers retrieved in the search stage / the number of target papers.

3) The search strategy in grey is the final search strategy.



Figure .. Flow-chart of study selection

Based on the information in the title and abstract, these 512 studies were classified according to the heuristic and optimisation method(s) used. The methods were divided into two broad categories, which were mathematical programming and heuristics. For the classification, mathematical programming was defined as the exact algorithm as it guarantees to find the global optimal solution where the benefit or the constraints can be described as the functions of certain decision variables. In contrast, heuristics were defined as the approximate method, which identifies an optimal or near optimal solutions using a subjective heuristic rule.

In the review stage, heuristics were further divided into constructive methods, local search methods and other heuristic methods. The difference between constructive heuristic methods and local search methods defined in this study is the way to construct the search space. Constructive methods construct the decision space with partial solutions (i.e. potential individual drugs in the case of SDDPs) and combine the partial solutions of each sub-problem to construct a solution to the whole problem, whereas local search methods construct the decision space with complete solutions (i.e., potential drug sequences in the case of SDDPs). Local search methods were further distinguished between 1) single solution methods and 2) population-based methods depending on the number of candidate solutions used at the same time (see Table ‎3.2).

Table .. The characteristics of each category

|  |  |
| --- | --- |
| Classification | Characteristics |
| Approximate mathematical programming | * Mathematically describe the problem with the objective function and/or the constraints. * Find the optimum of continuous and differentiable functions using linear, integer, nonlinear or mixed programming method. * Use the backward approach where DP is applied. |
| Heuristics  (Constructive methods) | * Organize the search space into a tree. * Begin with an empty or partial solution. * Construct the complete solution adding one by one. |
| Heuristics  (Local search methods) | * Start with one complete solution (Single solution method) or some complete solutions (Population-based method). * Replace the current solution by a better solution iteratively in a defined neighbourhood. |

Table ‎3.3 summarises the identified list of heuristic methods and optimisation methods that have been applied in the 518 identified papers. 228 studies used more than one heuristic method to compare with each other. 62 studies hybridised more than one heuristics method to improve the search procedure and the quality of solution. Therefore, one study may satisfy more than one category in Table ‎3.3.

Table .. Potential heuristic and optimisation methods for sequential decision problems

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | | | | SDP | SDP in Healthcare |
| (Approximate) Mathematical programming | | | | 283 | 7 |
|  | Dynamic programming  Linear programming  Mixed integer programming  Integer programming  Others | | | 206  29  5  3  48 | 7  0  0  0  0 |
| Heuristic method | | | | 402 | 5 |
|  | Constructive methods | | | 23 | 0 |
|  | Greedy-based method  Branch and bound  Others constructive method | | | 10  7  4 | 0  0  0 |
|  | Local search methods | | | 129 | 5 |
|  | Single solution heuristics | | |  |  |
|  | | Simulated annealing  Tabu search  Variable neighbourhood search  Guided local search  Greedy randomised adaptive search procedure (GRASP) | | 12  6  5  1  1 | 1  0  0  0  0 |
|  | Population-based heuristics | | |  |  |
|  | | Evolutionary algorithm | | 22 | 0 |
|  | | | * Genetic algorithm * Differential evolution algorithm * Evolutionary programming * Estimation of distribution algorithms * Memetic algorithm * Scatter search (path-relinking) | 12  2  1  1  1  1 | 0  0  0  0  1  0 |
|  | | Particle swarm optimisation | | 2 | 0 |
|  | | Artificial bee colony algorithm | | 1 | 0 |
|  | Other local search methods | | | 86 | 4 |
|  | Problem-specific heuristics | | | 290 | 0 |
| Hybrid heuristics | | | | 62 | 0 |

1) SDP stands for sequential decision problem under uncertainty.

2) The numbers in dark rows represent the number of papers, which used the specified method, not the sum of the subgroups.

### Summary of the systematic review

#### 1) Mathematical programming

206 studies, which were classified as DP, mostly used approximate dynamic programming (ADP), which includes simulation and/or a function approximation under the theoretical foundations in the traditional DP. Whereas DP is the standard methods to solve sequential decision problems in theory, it has been recognized that classic DP is limited in its suitability to directly treat large and complex sequential decision problems encountered in the real-world because of the curse of dimensionality and computational requirements[51]. The systematic review also confirmed that classic DP on its own is considerably limited in its usefulness for large and complex real decision problems. This has motivated the development of ADP for solving large and complex sequential decision problems.

The most widely used ADP was RL, which is a simulation-based DP approach. Instead of computing or storing transition probabilities like DP, RL uses a stochastic approximation of Q-value, which is the expected value of each state-action pair for a certain period, within the simulation (this is further explained in section 3.5). Variations of this algorithm have been proposed for the transformation of Q-value[123-126]. It also has been applied for discovering effective therapeutic regimens in clinical setting[127-133]. Neuro-dynamic programming (NDP) is another name of RL where a Bellman’s value function is approximated using neural network architectures of simulated data[134, 135].

29 studies, which were classified as linear programming, attempted to alleviate the curse of dimensionality by fitting a linear combination of pre-selected basis functions to the Bellman’s value function[136]. As this involved the DP procedure for optimisation, it was also called LP-based ADP or approximate linear programming[137]. Various problem-specific methods for fitting the linear value function approximation have been proposed in the context of interactive multi-objective decision-making[138], stochastic inventory/routing[139], queuing control[136], capacity of production line[140], noisy prediction problem[141] and fleet size and vehicle transfer problem[142] and other large and complex MDP problems[143-145].

Where sequential decision problems were formulated as integer or mixed integer programming, problem-specific heuristics were incorporated into the algorithms to search the decision space efficiently. Most heuristics used were based on “branch-and-bound” (see more information in the following sub-section)[146-152].

#### 2) Heuristics: Constructive methods

Given the search space is structured as a tree, constructive methods try to overcome the computational complexity by eliminating parts of the branches where it is unlikely to find an optimum solution. Various strategies for partitioning allow selective exploration of the active nodes of the trees to obtain an optimal or near optimal solutions for the problem.

The greedy algorithm, which is the simplest constructive heuristic method, moves one by one to make the best available decision at each stage[153]. As this is a simple but short-sighted method to solve a large and complex decision problem, the algorithm has been often used as an extended version[154-156] or as a part of meta-heuristics to improve the problem solving procedure[157-159].

The branch-and-bound algorithm uses a lower bound (or upper bound for a maximisation problem) to avoid searching worse branches than the currently best branch identified from the previous search. Several derivatives of the branch-and-bound algorithm have been proposed. Best-first search explores the most promising node first based on a heuristic rule[160, 161]. Breadth-first search explores all the nodes on one level first before moving to the next level[162, 163]. Depth-first search proceeds down in the tree as deep as possible in an arbitrary pattern before making any decision and then backtracks out through the tree[164, 165]. Branch-and-price[166, 167], branch-and-cut[168] and A-algorithm[169, 170] were also introduced.

Constructive methods are typically the fastest approximate methods, but limited when the decision space becomes very large. Therefore, various heuristics have been incorporated into the branch-and-bound algorithms. Garaix et al applied the greedy insertion procedure to construct a possible sequence, a descent method to identify the best solution on the first hierarchical level of the objective function, and a scheduling method to re-optimise the initial solution based on the second hierarchical level of the objective function[167]. Dell'Amico et al introduced greedy heuristics incorporated with a local search and a scatter search[165]. Local search methods, GA[171] and SA[172], also has been combined with the branch-and-bound algorithm. These studies showed that heuristics applied to the branch-and-bound algorithm improved the quality of solution with reasonable computational requirements.

#### 3) Heuristics: Local search methods

Within the local search method category, five single solution meta-heuristic methods and eight population-based meta-heuristic methods were identified. The rank of these meta-heuristic methods (in terms of the number of times that a method was identified in the 512 studies) was more related to the age of the algorithm rather than the accuracy or efficiency.

Most meta-heuristic methods such as tabu search, SA and evolutionary methods are primarily to be viewed as repetitive improvement methods based on local search. These methods have their own subjective strategy, which differentiates themselves from each other. For example, SA has a mechanism to move to the worse solution to overcome the problem of descent strategies, which always move towards the bottom of the valley containing the starting point[173]. A distinctive feature of the tabu search is the tabu list, which stores the short and long-term search history to restrict the moves to the areas placed in the tabu list[174, 175]. In the guided local search, the objective function is modified depending on the solution features, which is associated with a penalty, while the set of solutions and the neighbourhood structure are kept fixed[176]. Variable neighbourhood search changes neighbourhoods where no improvement is observed[177]. Greedy randomised adaptive search uses a constructive heuristics for solution construction and a local search for solution improvement[178]. Evolutionary algorithms are different with the algorithms mentioned above in the sense that evolutionary methods maintain a population of solutions[179]. At each iteration a number of operators, which are called recombination, mutation and selection, are applied to the individuals of the current population to generate the fitted individuals of the population of the next iteration. All these characteristics of meta-heuristics are associated with intensification, which searches carefully and intensively around good solutions found in the past search, and diversification, which guides the search to unvisited regions. Although meta-heuristics cannot guarantee the globally optimal solution, they can escape from local minima and proceed to the ‘global’ optima successfully where the intensification and diversification are well balanced.

Recently, interest in hybrid meta-heuristics, which cooperatively use the strengths of different methods, has increased considerably[180]. SA was supplemented with a tabu list[181], and variable neighbourhood search was used as an improvement procedure in the last step of the GA[182]. In Roach and Nagi’ study, the GA randomly generated candidate solutions, while the SA focused these to "local" optima[183]. Ho and Ewe used a GA within the search procedure of ant colony optimisation to quickly achieve adaptation by refocusing the search process around promising areas of the search space[184]. Behnamian et al hybridised ant colony optimisation for initial population generation, SA for solution evolution and a variable neighbourhood search to improve the population[185]. Tseng and Liang proposed a hybrid meta-heuristic called ANGEL, which combines the ant colony optimisation, the GA and a local search method[186]. Experimental results showed that these hybrid heuristics enhance the performance of individual heuristics in terms of the quality of solution and computational time.

#### 4) Other local search and problem-specific heuristic methods

86 studies, which were classified as other local search, employed a form of neighbourhood search within their own heuristic framework or together with other optimisation methods. Rather than examining all possibilities to the problem, local searches focused on searching a neighbourhood of particular solutions by introducing a mechanism to define a neighbourhood structure and to evaluate the costs or benefits of moving from the current solution to others within the same neighbourhood.

290 studies were classified as the problem-specific heuristic category because the heuristic methods cannot be classified as any of the categories discussed earlier or the author(s) did not clearly state the specific information about the type of heuristic methods. Most problem-specific heuristics implied a specific heuristic approach to a particular problem based on the given prior information in that area, whereas meta-heuristics is a set of heuristic concepts that can be used to a wide set of different problems.

*5) Sequential decision problems in healthcare*

Among the 512 identified studies, 19 studies addressed healthcare-related sequential decision problems. There were six studies associated with identifying an optimal treatment strategy in clinical practice[59, 60, 130, 132, 187, 188], two studies associated with dynamic treatment regimen in clinical trials[189, 190], two studies associated with screening strategies[191, 192], two studies associated with public health policies to control outbreaks of infectious disease[58, 193], four studies associated with the optimal diagnosis by medical imaging or diagnostic device[194-197] and two studies were associated with hospital management[198, 199]. The dynamic decision process with patient’s stochastic response to the treatment decision was depicted in partially observable MDP[59], dynamic limited-memory influence diagrams[60] and probabilistic Boolean Networks[187]. For the optimisation procedure, most of them used DP where patient level data was available.

### Identification of the candidate methods

In previous chapters, it was stated that a classic DP has a limited capacity in most large, complex and uncertain SDDPs that have a non-linear objective function with a large number of probabilistic elements. Sutton and Barto said the key assumptions to solve the Bellman optimality equation: 1) the dynamics of the environment is known exactly (2) computational resources are enough to complete the computation of the solution; and (3) Markov property[200]. For general SDDPs, various combinations of these assumptions are likely to be violated. Firstly the dynamics of the health state in SDDPs involve random events, which results from the probabilistic nature of stochastic models. The Markov assumption would be also restrictive for most real SDDPs because previous drug uses or health states may have a substantial impact on the subsequent drug decision and health state transitions. In addition, the number of possible health states and treatment options for a long-term follow-up period significantly increase the number of the transition probabilities and the transition rewards to be computed and cause the curses of modelling and dimensionality.

As the alternative, this thesis focused on approximate optimisation methods, which usually use a simulation model to approximate the value function (see Figure ‎3.3). The underlying evaluation model could be a cohort model or an IBM depending on the size of the health state space and the assumptions in the transitions between the health states. If the number of potential disease pathways is manageable, the SDDP can be depicted in a successive decision tree; otherwise, more efficient modelling methods to handle the large number of disease pathways, such as Markov model or IBM, needs to be considered. If a cohort model is capable of handling the complexity of the SDDP or an efficient and flexible programming language is available, a Markov model can be used. With the memoryless assumption, however, it may be restricted to consider the dependency of drug effectiveness on the timing of the drug used and on the current and potentially previous health states. In this case, a semi-Markov model would be appropriate for the SDDP. DES can be a better option where a cohort model is inefficient or insufficient to describe the dynamic relationship between the disease pathway and time-dependent variables of patients.

|  |  |
| --- | --- |
|  | 1) The methods tested in this thesis are in grey.  Figure .. A decision algorithm to select the optimisation method for SDDPs |

Once the underlying evaluation model is decided, a search method should be decided based on the given time to make a decision. If the time available for making the decision is sufficient, enumeration will guarantee the optimal solution; otherwise, various heuristics (or meta-heuristics) can be applied to search for near-optimal solutions in a feasible time. All the heuristic methods in Table ‎3.3 are potentially applicable to SDDPs: however, SA and GA were selected as the representatives of meta-heuristics as they work differently each other but both are theoretically well established with a plenty of evidence in their performance. Because of the generality, SA and GA have been widely applied to various optimisation problems and shown that they can provide a good solution for large and complex problems where the enumeration is practically inefficient and impractical.

The basic idea is that a random choice is made between available moves from the current neighbourhood to a neighbouring solution. The neighbourhood is a set of candidate solutions, which can be generated by a small perturbation to the current solution. Searching within a neighbourhood of the current solution is a useful compromise because the current solution imposes a bias on the next search area, retaining the information obtained in the earlier search process[153]. SA and GA are also flexible to combine with a simulation model and other heuristic concepts such as the decomposition method if necessary.

The difference between SA and GA is the number of candidate solutions used at the same time. SA, which is a single solution heuristic method, explores a trajectory of the objective value during the search process. In contrast, GA, which is a population-based heuristic method, deals with a set of solutions in every iteration and describes the evolution of a set of points in the search space. The performance of SA depends on the problem representation and the neighbourhood structure, whereas the performance of GA depends on the way the population is manipulated.

RL, which is a kind of ADP, is another promising method to solve SDDP. In a broad sense, RL is also included in the category of simulation-based optimisation as it incorporates simulation into the DP procedure. The way that RL works is considerably different with local search methods such as SA and GA. Where the decision space is decomposed into a set of sub-problems *DS1, DS2,…, DSn* defined by time periods, RL solves the sub-problems sequentially[201, 202]. Each decomposed problem involves a decomposed health state space *HSt,* which is the same with a set of *l* possible health states *H={h1,h2,…,hl }* where the Markovian assumption is used, and a decomposed search space *SSt*, which is the same with a set of *m* possible drug alternatives *A={a1,a2, …,am}* if there are no constraints in the use of drugs depending on the medical history. Where a semi-Markov assumption is used, the size of *HSt* can be increased, as seen in Equation 3.1, to consider the different transition probabilities according to the disease history. The number of potential drugs, *m,* can be further reduced by reference to the decision-making rules for each health state;e.g., where the contraindications for a specific health condition are considered, or where a drug cannot be re-used if it has been previously used for treatment.

, where the Markovian assumption is used,

, where a semi-Markovian assumption is used.

where *l* is the number of potential health states; *m* is the number of potential drugs; and *n* is the time periods.

Equation 3.1.

The use of the decomposition method is useful to speed-up the searching process because the size of the decision space can be significantly reduced compared to the decision space defined in Equation 2.6. However, additional computational complexity occurs to combine those decomposed states and solutions.

Where the decision space is decomposed, the problem solving procedure can work either forward or backward. Where the algorithm works forward, the optimal solution for *s* at *t* maximises the expected rewards *r* from one-step transition or multiple transitions depending on the value function works (see Equation 3.2). This approach is expected to facilitate considering the impact of medical history on the total net benefit and the contraindications for a specific health condition. However, in many situations of decision-making, short-sighted approaches, which take the optimal actions at each separate step based on the largest immediate reward, may not be good enough in the long-term because the action selected at present affects the subsequent events of the problem.

Equation 3.2.

In contrast, a backward approach tries to find the global optimum by balancing the immediate reward and the future reward. As they work backward, the estimates of the value function at *i* are conditional on using the optimal drug at *i-1* (see more discussion in section 3.5.2). However, there is a concern about how to implement the backward approach in economic evaluation modelling framework, whose cost and effectiveness are dependent on the patient’s medical history.

In the following sections, the theoretical background and practical application of the three key methods is discussed in detail. The application of the three key methods to the simple hypothetical SDDP provides the further discussion about the feasibility and applicability of each method to a real SDDP.

## Simulated annealing

SA was motivated by the traditional annealing process of metals[203]. During the annealing process, the system state heats up to a high temperature and then cools down slowly until it converges to a steady ‘frozen’ state. Kirkpatrick et al mapped the behaviour of the physical cooling process onto the elements of a discrete optimisation problem, with the objective of solving an optimisation problem[173].

The algorithm starts from an initial solution that is either randomly or heuristically selected (see Figure ‎3.4). Incorporating knowledge into the initial solution can save a substantial amount of computational time; however, if the initial solution is too good, the algorithm may never fully escape from the neighbourhood of the starting state[53].

The neighbourhood is a set of candidate solutions which can be generated by a small perturbation to the current solution. They can be defined in various ways depending on the characteristics of a given problem. However, it should be noted that there is an implicit trade-off between the size of the neighbourhood and the efficiency of the search[53, 121, 153]. That is, if the size of the neighbourhood is large, it is more likely to converge nearer to the global optimum, but to take a long time to complete the required calculations. If the size of the neighbourhood is small, the algorithm is able to search the neighbourhood quickly, but more likely to become trapped at a local optimum. In general, small simple neighbourhoods are preferable to large complex ones[53].

The method used to decrease the temperature is generally called cooling schedule, which consists of four components: initial temperature, final temperature, temperature decrement and iterations at each temperature. The choice of an appropriate cooling schedule is crucial for the performance of SA. The initial temperature *T* should be hot enough to allow most neighbours to be accepted and to have the final solution, which is independent of the starting solutions[173]. There are a few studies that suggest a method for finding a suitable initial temperature[204-207]. In this thesis the initial temperature is 1, which is the highest temperature. The temperature *T* is gradually decreased to a value close to zero during the search process. Temperature decrement may be consistent or vary during the search, with the aim of tuning the balance between diversification and intensification. For example, at the beginning of the search *T* might be constant or linearly decreasing in order to explore the search space, and then follow a geometric rule to converge to a local minimum at the end of the search[208].

SA is a variant of the traditional descent methods in which the search always moves in a direction of improvement. The weakness of the traditional descent methods is that the final solution is dependent on the starting solution(s) employed and often results in convergence to a local optimum as it always move to a better solution in the neighbourhood[53]. However, SA offers a way to escape from a local optimum by allowing some uphill moves (i.e., moves to a solution inferior to the current solution) in a controlled manner. The probability of accepting a move to a worse solution is governed by a probability function, which follows the Boltzmann distribution:

Equation 3.3.

where *δE* is *f(π’)-f(π)*, *t* is temperature and *k* is a physical constant known as Boltzmann’s constant.

A solution *π’N(π)* is randomly sampled at each iteration and accepted as the new current solution depending on *f(π)*, *f(π’)* and *T*. That is, *π’* replaces *π* if *f(π’)>f(π)* or, in the case of *f(π’)≤ f(π)*, with a probability, which is a function of *T* and *f(π’)-f(π)*. At the beginning of the search, the probability of accepting a worse solution is high but gradually decreases to zero.

The stopping criteria can include a minimum value of the temperature parameter, a maximum number of total iterations[60, 209], a maximum number of non-improving iterations[102] or a maximum number of accepted worse solutions[210]. These rules need to be carefully tuned with the other parameters to ensure convergence at a sufficiently low temperature.

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| Select the initial solution *π*.  Initialize the temperature *T*.  **WHILE** The stopping rule is satisfied.  Pick a new solution π’ randomly in the neighbourhood of the current solution *(N(π))*.  **IF** *f(π’)* > *f(π)* for a maximisation problem (f(π’) < f(π) for a minimisation problem).  **THEN** Replace the current solution π with the new solution *π’*.  **ELSE** Accept the new solution π’ with (Equation 3.3).  **END**  Update the temperature *T*.  **LOOP** |

Figure .. Pseudo-code of SA[208]

## Genetic algorithm

GA is a computational model of evolutionary processes, which mimics natural biological evolution. GA applies the principle of survival of the fittest on a population of potential solutions encoded as a form of chromosomes to produce a solution[179]. The first step in the GA is to generate an initial population including *n* individuals (i.e., *n* sequential treatment policies in SDDPs) (see Figure ‎3.5). Small populations may run the risk of seriously under-covering the solution space, while large populations incur severe computational cost. The ideal size of population is problem-specific. It has been varied from 8[211] to 3000[100]. Reeves said that population sizes as small as 30 are adequate in many cases[53].

Individuals are usually encoded in a string of standard binary (0,1) digits[211-213], real numbers[85, 214] or multiple characters[215]. The assumption is that the components of individuals (which are called chromosomes) represent the genetic structure of the parent, and the superior elements are encouraged to find their way into the chromosomes of the offspring. At each generation, a new set of chromosomes is created by selecting individuals according to their level of fitness in the problem domain (i.e., the value of an objective function or the result of a simulation experiment) and then breeding them together using a number of genetic operators.

The selection operator selects certain number of chromosomes for the succeeding generation from the current population. A simple approach, which is called the elitist method, uses the value of the objective function associated with each chromosome[211, 216]. The fittest individuals are deterministically allowed to propagate through successive generations. Although the elitist method guarantees the preservation of the current best chromosomes, it is not usually recommended because of the risk of premature convergence to a poor local optimum[53]. As an alternative, the tournament selection method compares two individuals selected at random and then selects the best as a parent until a certain number of parents are selected in this way[85, 214]. The roulette wheel selection method selects the individuals according to their probabilities of selection based on their fitness[100, 217, 218]. That is, individuals with a higher fitness have a higher probability to be chosen as members of the population of the next iteration.

After the selection step, the selected population are paired into parents. A crossover operator splits the parent chromosomes at a chosen splice point and then swaps all data beyond that point with the other chromosomes to create offspring. The split point can be one, which is called single-point crossover, or multiple, which is called multi-point crossover. The crossover point is often selected by sampling from a uniform probability distribution[211, 213, 217]. Crossover rate, which is the probability of crossover occurring between pairs of individuals, ranged from 0.4%[211] to 1.0%[213] in the studies included in the systematic review[211, 213, 215].

Mutation causes a random change of one or more bits on the offspring’s chromosomes with low probability in order to prevent the search from diversifying too rapidly, typically in the range 0.1% and 0.5%[213, 214]. In this way GA reduces the dependence of the solution on its starting chromosomes, but preserves the good chromosomes created through crossover. When the offspring is infeasible, the infeasible offspring is handled by rejecting or repairing the infeasible solutions or applying a penalty function. GA generally terminates after a pre-specified number of generations. If no acceptable solutions are found, the GA may be restarted or a fresh search initiated.

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| Generate the initial population *P*.  Evaluate the individuals in the initial population.  **WHILE** The stopping rule is satisfied.   * Select the superior individuals from the current population. * Recombine the elements of the parents’ chromosomes to produce new individuals. * Replace each element of the new individuals with a low probability. * Evaluate the individuals in the current population.   **LOOP** |

Figure ‎3.5. Pseudo-code of GA[208]

## Reinforcement learning

### Bridge between DP, ADP, RL and Q-learning

DP is a well-known and efficient mathematical programming method to solve sequential or multi-stage decision problems using the Bellman’s value function. However, it has been recognized that classic DP is limited in its suitability to directly solve large and complex sequential decision problems encountered in the real-world because of the curse of dimensionality and computational requirements[51]. This causes an increasing interest in ADP, which uses simulation and/or a function approximation for solving large and complex sequential decision problems under the theoretical foundations in the traditional DP.

The most widely used ADP is RL, which is a computational model using animals’ complex behaviours to learn by experience[200]. In the conventional framework of RL, the agent does not initially know what immediate rewards or penalties its actions will produce. Instead it gradually learns which action is best at each state to maximize its long-term reward by trying various actions at various states.

Q-learning is a specific type of RL, which stores the value function in a state-action pair (called Q-values) during simulation. The learned action-value function is directly used to approximate the optimal action-value function, independent of the action being followed. This simply repeated procedure showed early convergence proofs where all pairs of state-action were continuously updated. The theoretical background and methodological application of DP, RL and Q-learning are detailed in the following sections.

### Dynamic programming

DP divides the overall problem into several sub-problems by consecutive time cycles. Each sub-problem has a number of possible states *st+1* associated with the beginning of that state *s*, possible actions *a* and the immediate (i.e., one-step) reward *r* from using *a* for *s* at each time period *t*. Where *i=T-t,* and *T* and *t* refer to total and current time periods, respectively and γ represents the discount rate, the Bellman’s value function of policy for *i* steps to go is as following[54]:

*, i=1*

*i>1*

Equation 3.4.

The optimal policy *π\*: S→X* is:

Equation 3.5.

The solution procedure starts with a small portion of the original problem and gradually enlarges to the overall problem. The selected actions transform the current state to a next state according to a probability distribution . The expected reward assigned to the transition from the current state to the next state usually can be interpreted as the immediate from making the decision for . The best policy for the remaining states is the action, which maximises the value function as Equation 3.5. The difference between the reward function and the value function is that the value function is defined over states that gives an estimate of the total (possibly discounted) reward expected in the long run, following a particular policy for each state, whereas reward is an immediate, possibly stochastic, payoff that results from performing an action in a state.

The basis of DP is the Bellman’s Optimality Principle, which states that “An optimal policy has the property that whatever the initial state and initial decision are, the remaining decisions must constitute an optimal policy with regard to the state resulting from the first decision”[54]. This means that the optimal decision depends on only the current state and not on how to get there. The decision maker is usually assumed to have a linear, additive and risk neutral utility function over time. Any decision problem, which does not satisfy those assumptions, may be restricted to formulate and solve the problem using classic DP.

Classic algorithms to solve DP are value iteration or policy iteration[54]. Value iteration starts with some arbitrary values for the value function vector and keeps updating its elements. The idea behind this is that value iteration guarantees convergence to the optimal solution by updating the value function, where the true value of the state *s∊Hi* is not known initially (see Figure ‎3.6).

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| **INPUT** transition-probability matrices and reward matrices.  **FOR** *i=1:T*  **FOR** all states *s∊Hi*  Initialize *Vi(s)=0* (or select an arbitrary number), for all states *s∊H.*  **WHILE** is not changed.  **LOOP**  **LOOP**  **LOOP** |

Figure .. Value iteration algorithm[200]

Policy iteration starts with an arbitrary policy and repeats replacing the current policy by a better one until an optimal policy is achieved. Since there are a finite number of states and actions, the algorithm will eventually terminate with a policy that cannot be further improved (see Figure ‎3.7).

|  |
| --- |
| **INPUT** transition-probability matrices and reward matrices**.**  **FOR** *i=1:T*  **FOR** all states *s∊Hi.*  **WHILE** is not changed.  Select a random policy *a∊Ai(s).*  Compute the value of the current policy for the given state.  **IF** *i*=1, *,*  **ELSE,**  **END**  Update the optimal policy for the given state.  **LOOP**  **LOOP**  **LOOP** |

Figure .. Policy iteration algorithm[200]

The backward approach involved in DP reduces the computational burden by chopping down the branches, which are unlikely to have a better future value of the objective function. The idea of separating past and future costs enables DP to provide the global optimal solution by balancing the immediate reward and the future reward. The proof of convergence to an optimal policy in DP can be found in most optimisation text books[56, 57, 219].

In contrast, DP is known to be limited for many large and complex real problems, because of the amount of computational requirements (e.g., computation of the matrices of transition probability and the rewards for the transition times for every decision). Particularly, where the sub-problems are dependent upon each other (i.e., if past states or decisions affect the current decision), obtaining or storing those data can be very challenging and computationally expensive: this motivated the development of various ADP techniques.

### Reinforcement learning

One of the most widely used ADP techniques is RL, which uses simulation to overcome the curse of modelling and dimensionality of classic DP: therefore this is often called simulation-based DP[200]. RL needs the elements of the value function of DP but not the transition matrices. Rather RL calculates the transition probabilities and rewards within a simulator, which governs the environment including the random variables. The fundamental idea is that a goal-directed agent does not initially know what effect its actions will produce and keeps interacting within an uncertain environment to gradually learn what the best action to do is at each state.

The conventional approach to learn the value function is temporal differences (TD), which looks ahead for a sampled successor state like the Monte Carlo method, and then updates the value for the current state using an estimate of the successor state like DP (which is called bootstrapping). It does not need to wait until the actual return is known at the terminal state like the Monte Carlo method nor does it need to know the actual value function of the optimal solutions following *st* like DP. Rather TD samples *n* transitions from the current state and uses the sum or a weighted average of *n*-step returns to come as the expected return from the current state. The general form of TD learning is:

,

where *ɑ* is the learning rate and *γ* is the discount rate. Equation 3.6.

is the actual one-step return after time *t*. The target to maximise for the TD update is , which is gradually updated with the difference between the old estimate and the new estimate . The discount rate *γ*=[0,1] determines the importance of considering the future rewards in decision-making. As *γ* tends to 1, higher weight is placed on the future rewards. ɑ is the learning rate or step-size parameter *ɑ* (e.g., *ɑ=1/t*) controls to what extent the new information (i.e., the difference between the old information and the new information) will be considered. The learning rate starts at *ɑ* and gradually decays to 0 so that a learning algorithm converges to a single answer independent of the learning rate *ɑ*. If *ɑ* is small, the agent tends to rely on the old information, whereas the agent tends to replace the old information with the newly obtained information if *ɑ* is large. TD learning can be easily extended to the control problem, which is learning the optimal policy . One widely used learning algorithm is Q-learning, which a specific kind of RL that assigns values to action-state pairs.

### Q-learning

Q-learning is a simple incremental learning method that repeatedly updates Q-values based on the new cases until it converges upon the optimal solution[200]. While a simulator explores the subsequent states and actions following the current state *s*, the rewards are stored in the form of the so-called Q-factors, which is a state-action pair at *t.* Thesimplest Q-learning uses the observations of what happened in two cycles - the immediate reward, and the Q-values of other states in the future (see Equation 3.7).

where *ɑ* is the learning rate and *γ* is the discount rate. Equation 3.7.

The value of the state one step later represents the remaining rewards in the future. They are initially set to 0 and gradually updated as the simulator goes through the corresponding health state and drug. Where the feedback is from multiple transitions, the feedback is either the sum (or weighted sum) of *n*-step rewards (see Equation 3.8) or the average of *n*-step rewards (See Equation 3.9). Positive feedback strengthens the action tested by increasing, while negative feedback weakens the action tested. All that is required for correct convergence is that all pairs continue to be updated.

Equation 3.8.

Equation 3.9.

The commonly used action selection rule is *∊*-greedy (or near-greedy), which randomly selects an action at each time step with a fixed probability (e.g., *∊=1-(1/log(n+2)).* Where *n* is the number of experiences and *0≤ρ≤1* is a uniform random number drawn at each time step, the agent selects action *x* randomly, if *ρ>∊*. Otherwise, action *x* is one of the learned optimal policy with the highest estimated Q-value (see Equation 3.10). *∊* increases as the number of cases *n* increases, therefore the algorithm is more likely to explore the search space in the early stage of learning and to exploit the previous experience to maximise the Q-value at the end of the learning. This implies that the selection of action converges to the optimal solution where a sufficiently large number of trials are obtained.

Equation 3.10.

The Q-learning algorithm starts with initialising a Q-table, which has a two dimensions containing the pairs of all possible states and all possible actions at *t* (see Figure ‎3.8). Starting from an initial state at *t1*, a simulator spontaneously generates the current state and the subsequent states with the action selected by the ε-greedy method until a terminal state is reached at the end of the follow-up period. All the immediate rewards received from the transition between *st* and *st+1*are saved in the Q-table at *t* and used to update the Q-value for the current state *st*. All that is required for correct convergence is that all pairs are continuously updated in an infinite number of times so that they are independent of the action being followed. At the end of the learning procedure, the action *a*, which maximises the Q-value for *st*, is selected as the optimal solution for *st.*

|  |
| --- |
| Initialise all Q-values arbitrarily.  **FOR** An infinite number of times.  Randomly simulate the initial state *st*.  **FOR** each step of episode   * Choose *a* from *s* using policy derived from Q-values, using the ε-greedy method. * Take action *a*, observe *st+1* and *r.* * *st*←*st+1* until *st* is terminal.   **END**  **END** |

Figure .. Q-learning algorithm[200]

## Application of the key optimisation methods on a hypothetical case

### Description of the simple hypothetical sequential drug decision problem

A simple hypothetical SDDP was used to allow full enumeration and to illustrate how some of the proposed optimisation methods can be applied. As this simple example was of low complexity, a successive semi-Markov decision-tree model was used to calculate the value of the objective function (seeFigure ‎3.9). Four optimisation methods – enumeration, DP, SA and RL (i.e., Q-learning) - were tested and compared in the context of computational efficiency, intensity and the quality of solution for SDDPs. DP was applicable due to the low complexity of the hypothetical case, whereas GA was not included because SA was enough to represent the nature of meta-heuristics in such a small problem. The Matlab version 7.6.0, R2008a (The MathWorks, Natick, Massachusetts, U.S.A) was used to develop both the evaluation and optimisation models.



Figure .. Decision-tree of the hypothetical simple SDDP

The problem was mathematically defined as follows:

* The total follow-up period is divided into three 3-monthly decision-making periods *T=(t1,t2,t3).* A maximum number of two drug switches are allowed.
* There are three possible health states *H={Hu,He,Hn},* where *Hu* represents the undesirable health condition, *He* represents occurring AEs and *Hn* represents the health condition under control. There are 27 possible disease pathways, where the initial health state *s1* is *Hu* and the subsequent health states *s2, s3* and *s4∈H*.

*HS={ θ1=(Hu,Hu,Hu,Hu), θ2=(Hu,Hu,Hu,He), θ3=(Hu,Hu,Hu,Hn),*

*θ4=(Hu,Hu,He,Hu), θ5=(Hu,Hu,He,He),θ6={(Hu,Hu,He,Hn),*

*θ7=(Hu,Hu,Hn,Hu), θ8=(Hu,Hu,Hn,He), θ9=(Hu,Hu,Hn,Hn),*

*θ10=(Hu,He,Hu,Hu), θ11=(Hu,He,Hu,He), θ12=(Hu,He,Hu,Hn),*

*θ13=(Hu,He,He,Hu), θ14=(Hu,He,He,He), θ15=(Hu,He,He,Hn),*

*θ16=(Hu,He,Hn,Hu), θ17=(Hu,He,Hn,He), θ18=(Hu,He,Hn,Hn),*

*θ19=(Hu,Hn,Hu,Hu), θ20=(Hu,Hn,Hu,He), θ21=(Hu,Hn,Hu,Hn),*

*θ22=(Hu,Hn,He,Hu), θ23=(Hu,Hn,He,He), θ24=(Hu,Hn,He,Hn),*

*θ25=(Hu,Hn,Hn,Hu), θ26=(Hu,Hn,Hn,He), θ27=(Hu,Hn,Hn,Hn) }.*

* Where a decomposition method is used (i.e., where DP and Q-learning are used), the health state space *HSt* in each period is constructed as following so that the model considers the different transition probabilities depending on the disease history:

*HS1={Hu}*

*HS2={ θ1=(Hu,Hu), θ2=(Hu,He), θ3=(Hu,Hn) }*

*HS3={ θ1=(Hu,Hu,Hu), θ1=(Hu,Hu,He), θ1=(Hu,Hu,Hn),*

*θ2=(Hu,He,Hu), θ2=(Hu,He,He), θ2=(Hu,He,Hn),*

*θ3=(Hu,Hn,Hu), θ3=(Hu,Hn,He), θ3=(Hu,Hn,Hn) }*

*HS4={ θ1=(Hu,Hu,Hu,Hu), θ2=(Hu,Hu,Hu,He), θ3=(Hu,Hu,Hu,Hn),*

*θ4=(Hu,Hu,He,Hu), θ5=(Hu,Hu,He,He),θ6={(Hu,Hu,He,Hn),*

*θ7=(Hu,Hu,Hn,Hu), θ8=(Hu,Hu,Hn,He), θ9=(Hu,Hu,Hn,Hn),*

*θ10=(Hu,He,Hu,Hu), θ11=(Hu,He,Hu,He), θ12=(Hu,He,Hu,Hn),*

*θ13=(Hu,He,He,Hu), θ14=(Hu,He,He,He), θ15=(Hu,He,He,Hn),*

*θ16=(Hu,He,Hn,Hu), θ17=(Hu,He,Hn,He), θ18=(Hu,He,Hn,Hn),*

*θ19=(Hu,Hn,Hu,Hu), θ20=(Hu,Hn,Hu,He), θ21=(Hu,Hn,Hu,Hn),*

*θ22=(Hu,Hn,He,Hu), θ23=(Hu,Hn,He,He), θ24=(Hu,Hn,He,Hn),*

*θ25=(Hu,Hn,Hn,Hu), θ26=(Hu,Hn,Hn,He), θ27=(Hu,Hn,Hn,Hn) }.*

The health states at *t4* are the terminal states from sequential drug use. No decisions are made at this stage.

* There are three possible drug treatment options *A={drug1,drug2,drug3},* where *drug1* has smaller treatment effect but lower risk of AEs; *drug2* has moderate treatment effect and moderate risk of AEs; and *drug3* has larger treatment effect but higher risk of AEs. There are six possible sequential treatment policies, where the problem is not decomposed, as following:

*SS={ π1=(drug1,drug2,drug3), π2=(drug1,drug3,drug2), π3=(drug2,drug1,drug3), π4=(drug2,drug3,drug1), π5=(drug3,drug1,drug2), π6 =(drug3,drug2,drug1) }.*

* Where the decomposition method is applied (i.e., where DP and Q-learning are used), the search space *SS* is equivalent to *A.* The feasibility of each drug for each state is considered by a penalty function, which forces the net benefit to 0.

*SS1 = SS2 = SS3* = *A = {drug1,drug2,drug3}.*

* It is assumed that a drug is switched to another drug in the case of *Hu* or *He* (i.e., treatment failure) and the same drug is continued in case of *Hn* (i.e., treatment success).
* To consider the impact of disease history, it was assumed that the baseline risk of *Hu* increases by 5% after two successive treatment failures (i.e. for the patients who went through *Hu*-*Hu*-*Hu* in previous periods) and by 10% after relapse (i.e. for the patients who went through *Hu*-*Hn*-*Hu* in previous periods). For the patients who had a relapse, treatment effectiveness was also assumed to decrease by 20% for *drug1*, 10% for *drug2* and 5% for *drug3*. The data used to populate the model are presented in an Appendix 4.
* The objective function to maximise the treatment net benefit was:

Equation 3.11.

### Enumeration

The algorithm was repeated to examine the six policies included in the search space SS (see Figure ‎3.10). The total net benefit TotalReward was calculated through the successive decision-tree model function\_SemiMarkov. The variations of each sequential treatment policy *πx* were applied depending on the subsequent health states. Taking an example of *π1=(drug1,drug2,drug3),* the variations are:

*πx={ (drug1,drug1,drug1),(drug1,drug1,drug2),(drug1,drug2,drug2),(drug1,drug2,drug3) }*

The optimal solution OptSol was determined by directly comparing the total net benefits of six sequential treatment policies.

|  |
| --- |
| T = 3; % The number of time periods.  A = 6; % The number of possible treatment sequences.  S = 27; % The number of possible disease pathways.  % Possible treatment pathways where 1=*drug1*, 2=*drug2* and 3=*drug3*.  SS = [1,2,3;1,3,2;2,1,3;2,3,1;3,1,2;3,2,1];  % Estimate the total net benefit of each sequential treatment policy using ‘function\_SemiMarkov’.  **FOR** a = 1:A  Policy = SS(a,:);  TotalReward(a,1) = function\_SemiMarkov(Policy);  **END**  % Decide the optimal solution based on the total net benefits of six sequential treatment policies.  [MaxReward,OptSol] = max(TotalReward(:,1)); |

Figure .. Pseudo-code of the enumeration used for the simple hypothetical case

### Dynamic programming

DP used the Bellman’s value function in Equation 3.4-3.5, where the search space was constructed with a set of individual drugs SS(see Figure ‎3.11). To consider the different transition probabilities depending on the disease history, the health state transition space HS was constructed with the possible health state combinations until the time period considered: thus the number of possible health states increased from 1 at *t1* to 27 at *t4*. All matrices of potential transitions mTransition and one-step rewards mReward were calculated before the optimisation procedure started. The problem solving procedure was started from the last decision period i. Policy iteration compared the estimates of the value function V{i}(s,a)where a∈SS was used for s∈HSiand identified the best solution for each health state s in each period i. Once the optimal solution in the last period was identified, the optimal solution was selected under the policy of using in i=1. This process was followed until the optimal drug sequence was identified for the first time period. DP had a limitation to restrict the infeasible solutions under the decision-rule assumed in the hypothetical SDDP (i.e., non-repetition of drugs after treatment failure and the continuous use of the current drug after treatment success). As its optimal solution was calculated backward in time, medical and drug use history was not known when the decision was made so health states or drug uses in previous time periods cannot be considered when working out the optimal drug at current time.

|  |
| --- |
| T = 3; % The number of time periods.  SS = 3; % The number of possible treatment options. They are same in *SS1*, *SS2*, *SS3* and *SS4*.  HS = [3^0,3^1,3^2,3^3] % The number of possible health states (with disease history) at *t*, where *HS1*=3^0, *HS2*=3^1, *HS3*=3^2 and *HS4*=3^3.  % Calculate all possible transition probabilities from *st* to *st+1* by drug *a∊SS* using ‘function\_Transition’.  [mTransition{t}(s,s’,a)] = function\_Transition;  % Calculate all immediate rewards using ‘function\_Reward’.  [mReward{t}(s,a)] = function\_Reward(mUtility,mCost);  DR = 0.8; % Discount rate.  % Start the problem solving procedure from the last stage *i*.  **FOR** i = 1:T  **IF** i == 1  **FOR** s = 1:HSi  **FOR** a = 1:SS  V{i}(s,a)= sum(mTransition{i}(s,:,a).\*mReward{i}(:,a));  **END**  **END**  **ELSE**  **FOR** s=1:HSi  **FOR** a = 1:SS  V{i}(s,a) = sum(mTransition{i}(s,:,a).\*mReward{i}(:,a))+  DR^(t-1)\*(mTransition{i}(s,:,a).\* (:));  **END**  **END**  % Return the optimal value and the location of the optimal value (i.e., optimal solution) in each column (i.e., for each state).  [(:),(:)] = max(V{i}(:,:),[],1);    **END** |

Figure .. Pseudo-code of the DP used for the simple hypothetical case

### Simulated Annealing

As an example of meta-heuristics, SA was applied to the hypothetical simple SDDP. The same search space was used as for the enumeration algorithm. The process started with *π1=(drug1,drug2,drug3)*, and then iterated by randomly searching a search space to seek better policies (see Figure ‎3.12). The neighbourhood was not defined in this simple hypothetical SDDP as the size of the search space was very small. If a new sequential treatment policy nPolicy was better than the initial policy cPolicy based on the total treatment benefit, the search process re-started with this newly found improved policy and continued to iterate in this way until no further improvement was found. The initial temperature InitTemp was set to 1. The cooling rate CoolSched was assumed to be 0.8. The SA algorithm stopped if the temperature T reached 0.001, new policies were consecutively rejected five times (i.e., MaxConsRej), old policy was consecutively successful five times (i.e., MaxSuccess) or the total iteration number reached 100 (i.e., MaxTries).

|  |
| --- |
| % Main parameter settings.  def = struct('CoolSched',@(T) (.8\*T),... % Cooling schedule.  'InitTemp',1,... % Initial temperature.  'MaxConsRej',5,... % Max no. of consecutive rejections.  'MaxSuccess',5,... % Max no. of consecutive success.  'MaxTries',100,... % Max no. of total tries.  'StopTemp',0.001, ... % Stopping temperature.  'k',1); % Boltzmann constant.  % Initial solution and the reward from the initial policy.  cPolicy = 1; [OldReward] = function\_SemiMarkov(cPolicy);  **WHILE** ~Finished;  itry = itry+1; % An iteration counter.    % Stop / decrement *T* criteria.  **IF** itry >= MaxTries || Success >= MaxSuccess;  **IF** T < StopTemp || Consec >= MaxConsRej;  Finished = 1;  total\_iter = total\_iter + itry;  **Break**;  **ELSE**  T = CoolSched(T); % Decrease *T* according to ‘*CoolSched’*.  total\_iter = total\_iter + itry;  itry = 1; Success = 1;  **END**  **END**  % Random generation of new policy and the reward from the new policy.  nPolicy = round(1+(rand(1)\*5));  [NewReward] = function\_SemiMarkov(nPolicy);  incNewReward = NewReward-OldReward;  % If the new solution is better than the old solution, replace the old solution with the new solution.  **IF** (incNewReward > 1e-6)  cPolicy = nPolicy; OldReward = NewReward;  Success = Success+1; Consec = 0;  % Otherwise, accept the new solution with a probability, which follows the Boltzmann distribution.  **ELSE**  **IF** (rand > exp((-incNewReward)/(k\*T)));  cPolicy = nPolicy;  OldReward = NewReward;  Success = Success+1;  **ELSE**  Consec = Consec+1;  **END**  **END**  **END**  % Identification of the optimal solution and the maximum value.  OptSol = cPolicy; OptValue = OldReward; |

Figure .. Pseudo-code of the SA used for the simple hypothetical case

### Reinforcement learning: Q-learning

Q-learning was used to solve the simple SDDP, where the health state space and the search space were constructed as with DP (see Figure ‎3.13). Four Q-tables Q1-Q4 were defined by the number of possible health states and the number of possible drugs (i.e., 1x3 for Q1, 3x3 for Q2, 9x3 for Q3 and 27x3 for Q4). The values in the Q-values were set to 0 initially and gradually updated as the simulator went through the corresponding state and action at t. 10,000 cases were randomly simulated, which were large enough to observe the Q-values from all possible cases and to achieve the convergence. The target to maximise is the sum of the one-step reward IR from the transition between the current state cState and the next state nState and the Q-value, which maximised the one-step future reward from nState (i.e., max(Q{t+1}(nStateIdx,:)), where the discount rate DRwas set to0.8. The future reward Q{t+1}(nStateIdx,:) was 0 until the corresponding health state was observed during the simulation procedure.

The problem solving procedure worked forward from t1 to t4. Starting from the initial health state cState, subsequent health states nState and drugs drug were also simulated until a terminal state at t4. For each state, a drug was chosen by *∊*-greedy action selection method, which assumed an increasing probability by ∊=1-(1/log(n+2)).

The Q-values were updated by the difference between the old Q-value and the newly observed Q-value dQ. As the learning rate 1/sqrt(n+2) was gradually decreased*,* the Q-values were also gradually converged to the certain numbers. An additional memory variable discrepancy was included to track the variations in the Q-values. mdiscrepancy saved the mean of the discrepancies every 100 cases. The optimal solution for each state OptSol(:,:) was selected based on the values in the Q-table Q{t} at the end of the learning procedure. A feasibility test was included to prevent the repetition of the same drug in the case of *Hu* and *He* and to continue using the same drug in the case of *Hn*.

|  |
| --- |
| T = 3; % The number of time periods.  SS = 3; % The number of possible treatment options.  HS = 3; % The number of possible health states.  N = 10000; % The number of cases.  DR = 0.8; % Discount rate.  mdiscrepancy = []; % Q-variations.  % Define the possible health states (including the disease history) in each time period.  SqDiz1 = 1;  SqDiz2 = [1,1;1,2;1,3];  SqDiz3 = [1,1,1;1,1,2;1,1,3;1,2,1;1,2,2;1,2,3;1,3,1;1,3,2;1,3,3];  SqDiz4 = [1,1,1,1;1,1,1,2;1,1,1,3;1,1,2,1;1,1,2,2;1,1,2,3;...  1,1,3,1;1,1,3,2;1,1,3,3;1,2,1,1;1,2,1,2;1,2,1,3;...  1,2,2,1;1,2,2,2;1,2,2,3;1,2,3,1;1,2,3,2;1,2,3,3;...  1,3,1,1;1,3,1,2;1,3,1,3;1,3,2,1;1,3,2,2;1,3,2,3;...  1,3,3,1;1,3,3,2;1,3,3,3];  SqDiz = {SqDiz1,SqDiz2,SqDiz3,SqDiz4};    % Initialize the Q-tables for each time period to 0.  Q1 = zeros(HS^0,A); % Q-table at t1.  Q2 = zeros(HS^1,A); % Q-table at t2.  Q3 = zeros(HS^2,A); % Q-table at t3.  Q4 = zeros(HS^3,A); % Q-table at t4.  Q = {Q1,Q2,Q3,Q4};  **FOR** n = 1:N % For each time period,  **FOR** t = 1:T % Observe *N* cases.  cState = 1; % Current health state.  cStateIdx = 1; % Location in the Q-table.  fdHist = 1; % Memory variable to save the disease history.  tHist = []; % Memory variable to save the treatment history.  cProb = 1; % The probability of the current state.    % ∊-greedy action choice: by 1-(1/log(*n*+2)).  pn = rand(1);  **IF** pn < (1-(1/log(n+2))),  [nil,drug] = max(Q{t}(cState,:));  **ELSE** drug = randi([1,SS]); **END**  % Randomly generate a new event and update the disease history.  nState = randi([1,3]); fdHist = [fdHist,nState];  % Find the location in the Q-table.  [~,nStateIdx] = ismember(fdHist,SqDiz{t+1}(:,:),'rows');  % Calculate the immediate reward associated to <*s,a,s’*>.  [nprob,IR] = function\_IPR(t,cState,drug,cProb);    % Update the value of *Q*. Step-size parameter alpha=(1/sqrt(*n*+1)).  delta = IR+DR\*max(Q{t+1}(nStateIdx,:))-  Q{t}(cStateIdx,drug);  dQ = (1/sqrt(n+2))\*delta;  Q{t}(cStateIdx,drug) = Q{t}(cStateIdx,drug)+dQ;    % Save the Q-variation and compute means over 100 Q-variation values.  discrepancy(mod(n,100)+1) = abs(dQ);  **IF** (length(discrepancy) == 100)  mdiscrepancy = [mdiscrepancy,mean(discrepancy)];  discrepancy = [];  **END**;  % Update the current state and the probability with the next state.  cState = fdHist(1,end);  cStateIdx = nStateIdx;  cProb = nextprob(1,nEvent);  **END**  **END**  **END**  % Decide the optimal solution based on the values in the Q-tables and the feasibility test.  **FOR** t = 1:T  **FOR** h = 1:size(Q{t},1)  [v,idx] = sort(Q{t}(h,:),'descend');  **FOR** a = 1:size(v,2)  **IF** The feasibility assumptions is satisfied,  **Break**  **END**  [OptV(:,:),OptSol(:,:)] = max(Q{t},[],2);  **END**  **END**  **END** |

Figure .. Pseudo-code for the Q-learning used for the simple hypothetical case

### Comparison of the optimal solution from the different optimisation approaches

Table ‎3.4 compares the different optimisation approaches in terms of the size of the decision space*,* the objective function, the number of search and the optimal solution. According to the results from enumeration, the global optimal solution in the simple hypothetical SDDP was *π6=(drug3,drug2,drug1)* whose total net benefit was £85,716. SA tested in the simple SDDP also found exactly the same optimal solution as the enumeration method. However, the number of iterations in SA was slightly higher than enumeration: this demonstrates that the possible advantage of SA in computational efficiency may not appear in a small size of decision problem.

Classic DP gave the optimal solution, which had the higher net benefits of £86,004. There are two possible reasons for this. Firstly, the higher net benefit from DP may be attributed to infeasible solutions because classic DP was limited to consider the medical history under the backward induction. Table ‎3.5 showed that the optimal treatment pathway, which was identified by DP, included infeasible solutions against our assumption, which did not allow using the same drug when the drug was not effective. For example, *drug3* was the optimal drug in the second period if the initial optimal drug, which was also *drug3,* failed to control *Hu*. This is an important finding in this simple example of SDDP as this results show that it would be better to continue the current drug for one or two more cycles rather than switching to another drug straight away, considering the cost-effectiveness from the subsequent treatments in future. This also brings up an issue about whether the assumptions made in the model are wrong or the model is missing some negative impact on the total net benefit from infeasible solution. Although this thesis did not further discuss this issue in the simple hypothetical SDDP, the feasibility assumptions need to be fully justified and discussed if this happens in the real SDDP.

This improvement over enumeration from DP is also partially because of the stochastic scheme for choosing a next action where a problem is decomposed. Whereas enumeration or SA worked with complete solutions whose next drug is already determined in both cases of *Hu* and *He* by the pre-set sequential treatment policy, DP or Q-learning is free of the pre-set sequential treatment policy so that any drug with the highest net benefit in *Hu* and *He* can be adapted separately. In Table ‎3.5, for example, the optimal solution for *Hu* and *He* were *drug3* and *drug1*, respectively, where DP was used, whereas enumeration was forced to allocate the same drug for *Hu* and *He* at *t=2.* Even after the feasibility of solutions was considered (i.e., a drug is switched to another drug in case of treatment failure and the same drug is continued in case of treatment success), the Q-learning provided the solution with a total net benefit of £85,804, which was higher than enumeration, but lower than DP. This implies that the total net benefit could be improved by assigning a tailored treatment depending on the patient’s health state rather than recommending the fixed treatment sequence.

The number of iterations should be carefully compared as the time periods considered in each iteration are different. For enumeration and SA, each iteration passes the whole successive decision tree to calculate the total net benefit for nine months, whereas each iteration in DP and Q-learning involves calculating one or two-step rewards from the decomposed decision tree. Computational intensity was higher in DP and Q-learning compared with enumeration and SA. In particular, the applied Q-learning required a large number of cases, which was more than 10 times the number of all possible combinations of health states and drugs (i.e., *3H3*\**3H3*=729), to achieve the convergence to the optimum. Thus, Q-learning is only recommended where the size and complexity of the given problem is large enough to justify the computational time and effort required to implement Q-learning.

Table .. Comparison of different optimisation approaches proposed in the classification

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Enumeration | Simulated annealing | Dynamic programming | Q-learning |
| Construction of decision space | A set of possible treatment sequences | | A set of possible drugs | |
| The size of health state transition space *Z(HS)* | *Z(HS)*=27 | | *Z(HS1)*=3^0  *Z(HS2)*=3^1  *Z(HS3)*=3^2  *Z(HS4)*=3^3 | |
| The size of the search space *Z(SS)* | *Z(SS)*=6 | | *Z(SS1)*=3  *Z(SS2)*=3  *Z(SS3)*=3 | |
| The size of the decision space *Z(DS)* | *Z(DS)*=6\*4\*27=648 | | *Z(DS1)*=3^0x3=3  *Z(DS2)*=3^1x3=9  *Z(DS3)*=3^2x3=27 | |
| The calculation of reward | Equation 2.4-2.5 | | Equation 3.4-3.5 | Equation 3.7 |
| The number of search | 6 | 15 | 39 | 30,000 |
| Computational intensity | Low | Medium | High | High |
| Optimal drug sequence | π6 =(drug3,drug2,drug1) | | See Table 3.5. | See Table 3.5. |
| Total net benefit from the optimal solution | £85,716 | | £86,004 | £85,804 |

1) Computational time was not provided as it was very short for all methods in this small size problem.

Table .. Optimal treatment pathway obtained from the different optimisation approaches

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Possible disease pathways at *t* | Enumeration | Simulated annealing | Dynamic programming | Q-learning |
| t=1 | Hu | drug3 | drug3 | drug3 | drug3 |
| t=2 | Hu-Hu | drug2 | drug2 | drug3 | drug2 |
| Hu-He | drug2 | drug2 | drug1 | drug1 |
| Hu-Hn | drug3 | drug3 | drug1 | drug3 |
| t=3 | Hu-Hu-Hu | drug1 | drug1 | drug3 | drug1 |
| Hu-Hu-He | drug1 | drug1 | drug1 | drug1 |
| Hu-Hu-Hn | drug2 | drug2 | drug1 | drug2 |
| Hu-He-Hu | drug1 | drug1 | drug3 | drug2 |
| Hu-He-He | drug1 | drug1 | drug1 | drug2 |
| Hu-He-Hn | drug2 | drug2 | drug1 | drug1 |
| Hu-Hn-Hu | drug2 | drug2 | drug3 | drug2 |
| Hu-Hn-He | drug2 | drug2 | drug1 | drug1 |
| Hu-Hn-Hn | drug3 | drug3 | drug1 | drug3 |
| Total net benefits | | £85,716 | £85,716 | £86,004 | £85,804 |

1) The solutions in grey are infeasible, which are against the assumptions made in the hypothetical case study.

# Modelling sequential drug decision problem for hypertension: Overview

## Chapter overview

This chapter includes a general description about hypertension and the pharmacological treatment of primary hypertension. A literature review of previous economic evaluations of antihypertensive drugs in primary hypertension summarises the cost-effectiveness results of major antihypertensive drugs and discusses the structures of previous CEA models and their limitations regarding the consideration of drug switching. A conceptual framework of the hypertension SDDP model is presented graphically based on the major clinical guidelines and the previous CEA model structures in primary hypertension. The decision problem is defined with the elements used for the mathematical description of SDDPs in section 2.4.

## Hypertension and pharmacologic management

### Epidemiological aspects of hypertension

Hypertension is a common chronic condition in which the arterial blood pressure is consistently elevated above systolic blood pressure (SBP) 140 mmHg or diastolic blood pressure (DBP) 90 mmHg (see Table ‎4.1). Globally, 40% of the adult population aged 20 years or older had hypertension in 2008[220]. In England, the hypertension prevalence was 31% of men and 28% of women in 2011 in those aged 16 and over[221]. The prevalence increases with advancing age (see Figure ‎4.1).

Table .. Blood pressure classification from the NICE guideline[63]

|  |  |  |
| --- | --- | --- |
|  | Clinic BP1) | ABPM2) or HBPM3) BP |
| Normotensive | < 140/90 mmHg | < 135/85 mmHg |
| Stage 1 hypertension | ≥140/90 mmHg | ≥135/85 mmHg |
| Stage 2 hypertension | ≥160/100 mmHg | ≥150/95 mmHg |
| Stage 3 hypertension | ≥180/110 mmHg | ≥180/110 mmHg |

1) **BP** represents blood pressure; 2) **Ambulatory blood pressure monitoring (ABPM)** represents daytime average blood pressure; 3) **Home blood pressure monitoring (HBPM)** represents average blood pressure

|  |
| --- |
|  |
|  |

1) **Hypertensive controlled**: SBP below 140 mmHg and DBP below 90 mmHg, currently taking medication specifically prescribed to treat their high blood pressure; **Hypertensive uncontrolled**: SBP at least 140 mmHg or DBP at least 90 mmHg, currently taking medication specifically prescribed to treat their high blood pressure; **Hypertension untreated**: SBP at least 140 mmHg or DBP at least 90 mmHg, not currently taking medication specifically prescribed to treat their high blood pressure.

Figure .. The prevalence of hypertension in 2011, by age and gender[221]

Figure .. Mean SBP in 2011, by age and gender in England[221]

Figure .. Mean DBP in 2011, by age and gender in England[221]

The majority of patients with hypertension have primary (or essential) hypertension. Key causal factors identified are excess body weight, excess dietary sodium or alcohol intake, reduced physical activity, inadequate intake of fruits, vegetables and potassium[9]. Other factors are sympathetic nervous system hyperactivity, abnormal cardiovascular development, rennin-angiotensin system activity and defect in natriuresis, intracellular sodium and calcium[222].

5-10% of the hypertension is secondary hypertension, which has a specific identified cause for the elevated blood pressure, such as chronic kidney disease (CKD), chronic steroid therapy and Cushing’s syndrome, renovascular disease, pheochromocytoma, aldosteronism and so on. Secondary hypertension is more likely to worsen suddenly and to respond poorly to treatment, but the causes of secondary hypertension are potentially correctable.

Hypertension is not a disease itself, but is one of the most significant risk factors that may increase the chance of cardiovascular morbidity and mortality[223]. The strong relationship between blood pressure and cardiovascular risk is firmly established for those with and without existing heart disease. MacMahon et al performed an analysis of nine observational studies, involving 420,000 individuals, and found that long-term reductions in usual DBP of 5-10 mmHg were associated with 34-56% reduction in the relative risk (RR) of stroke and 21-37% reduction in the RR of CHD[224]. The similar relationship between DBP and CHD and stroke was also found in Collins et al’s systematic review of 14 randomised trials of antihypertensive drugs[225]. With 5-6 mmHg reduction in DBP over 5 years, the reduction in the odds of stroke and CHD were 42% and 14%, respectively. Even in persons whose blood pressure was in the normal range, CV event rates increased with an increase in DBP[226]. Compared with optimal blood pressure (i.e., BP<120/80 mmHg), the hazard ratio (HR) for cardiovascular disease (CVD) was 2.5 among women and 1.6 among men in the high normal group (i.e., 130/85≤BP≤139/89 mmHg). A stronger relationship between blood pressure and vascular mortality was observed in middle age than in old age[227]. Given a 20 mmHg SBP or 10 mmHg DBP reduction, the HR in stroke mortality was 0.36 at ages 40-69 years, whereas 0.67 at ages 80-89 years.

### Antihypertensive drugs[[1]](#footnote-1)

#### (1) Thiazide-type diuretics

Thiazide-type diuretics (Ds) lower blood pressure initially by decreasing plasma volume (by suppressing tubular reabsorption of sodium, thus increasing the excretion of sodium and water) and cardiac output, but during long-term therapy their major hemodynamic effect is reduction of peripheral vascular resistance. Generally they are well tolerated and achieve the treatment goal at low dosages. They are especially effective in the elderly.

The thiazides, which are a type of diuretics, are the most widely used antihypertensive drugs for primary hypertension. A further type, loop-diuretics, may lead to electrolyte and volume depletion more readily than the thiazides and have short durations of action. Therefore, loop Ds should not be used in hypertension except in the presence of renal dysfunction.

Metabolic changes in blood glucose, triglycerides, low-density lipoprotein cholesterol (LDL) and plasma insulin are dose related. These effects are relatively minor during long-term low-dose therapy, but were problematic when high doses of older drugs were used (e.g., hydrochlorothiazide 100 to 200mg per day). If higher doses of Ds are required, the drug should be used in combinations with a potassium-sparing agent or with an angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB).

#### (2) Beta-blockers (or beta-adrenergic blocking agents)

Beta-blockers (BBs) directly work on the cardiovascular system. They reduce the heart rate, cardiac contractility and output; renin release from the kidney and central release of adrenergic substances; and inhibit norepinephrine release peripherally. All these contribute to their antihypertensive effects. They are especially useful in patients with angina pectoris, previous MI, stable angina pectoris, migraine headaches and somatic manifestations of anxiety.

BBs are used cautiously in patients with type 1 DM, since they can mask the symptoms of hypoglycemia and prolong these episodes by inhibiting gluconeofenesis. They are also associated with rest pain or non-healing ulcers in patients with advanced peripheral vascular disease. The AEs include exacerbating bronchospasm in those with asthma and some patients with chronic obstructive pulmonary disease (COPD); sinus node dysfunction and atrioventricular conduction depression; precipitating or worsening clinically important left ventricular failure; nasal congestion; Raynaud’s phenomenon; and central depression and confusion. Adverse biochemical effects include altered lipids and increased glucose concentrations.

Because of the lack of efficacy in prevention of MI and inferiority compared with other drugs in prevention of stroke and left ventricular hypertrophy, there is now increasing doubt whether BBs should still be regarded as ideal first-line drugs in the treatment of hypertension without specific compelling indications[230, 231].

#### (3) Calcium channel blockers (or calcium channel blocking agents)

Calcium channel blockers (CCBs) act by causing peripheral vasodilation but with less reflex tachycardia and fluid retention than other vasodilators. There are 2 types of CCBs - non-dihydropyridine agents and dyhydropyridine agents. Non-dihydropyridine CCBs (including verapamil and diltiazem) directly block the AV node and decrease heart rate and cardiac concentration, whereas the dyhydropyridine agents are primarily vasodilators that can cause a reflex tachycardia. The protective effect against stroke is well established. Nevertheless, they are rarely recommended for patients with heart failure (HF) because negative inotropic effects of CCBs may worsen HF and increase the risk of death[232-235]. Diabetic patients receiving CCBs may have higher rates of HF and MI. The most common AEs are headache, peripheral edema, bradycardia and constipation.

#### (4) Angiotensin-Converting Enzyme Inhibitors

Angiotensin-Converting Enzyme Inhibitors (ACEIs) directly inhibit angiotensin-converting enzyme and block the conversion of angiotensin I to angiotension II. This action reduces angiotensin II mediated vasoconstriction and aldosterone secretion, and hence lowers blood pressure.

ACEIs are a drug of choice in persons with DM renal dysfunction by delaying the progression to end-stage RD; and in patients with congestive HF and asymptomatic patients by reducing ejection fractions whether due to MI or to other causes. An advantage of the ACEIs is less AEs, but a chronic dry cough is common, seen in 10% of patients or more, and may require stopping the drug.

#### (5) Angiotensin II Receptor Blockers

Angiotensin II Receptor Blockers (ARBs) are the newest antihypertensive drugs. They modulate the rennin-angiotensin-aldosterone system by directly blocking the angiotensin II type 1 receptor site, thus blocking angiotensin II mediated vasoconstriction and aldosterone release.

Although losartan, the first drug of ARBs, was less potent than high doses of ACEIs in reducing blood pressure, the newer ARBs (such as valsartan, irbesartan, candesartan, telmisartan and eprosartan) appear to be equipotent to ACEIs. ARBs can improve cardiovascular outcomes in patients with HF and type 2 DM with nephropathy. Due to the absence of long-term data, ARBs are commonly recommended in the case of ACEIs intolerance[236].

#### (6) Other antihypertensive drugs

α-Adrenoceptor Antagonists (or α-blockers) block postsynaptic α1-receptors, relax smooth muscle and reduce blood pressure by lowering peripheral vascular resistance. These drugs are effective as monotherapy in some individuals, but tachyphylaxis may appear during long-term therapy and AEs are relatively common. The most prominent side effect is hypotension. Thus, they should generally not be used as initial drugs to treat hypertension except in men with symptomatic prostatism.

Drugs with central sympatholytic action lower blood pressure by stimulating α-adrenergic receptors in the central nervous system, thus reducing efferent peripheral sympathetic outflow. These drugs are effective as monotherapy in some patients, but they are usually used as second or third-line drugs because of the high frequency of drug intolerance, including sedation, fatigue, dry mouth, postural hypotension and impotence.

Arteriolar dilators relax vascular smooth muscle and produce peripheral vasodilation. When given alone, they stimulate reflex tachycardia, increase myocardial contractility and cause headache, palpitations and fluid retention. They are usually given in combination with Ds and BBs in resistant patients.

### Pharmacologic treatment recommendations

Antihypertensive treatment generally starts with lifestyle modification such as smoking cessation, moderation of alcohol consumption, regular physical activity, sodium restriction, weight management and healthy eating. If blood pressure is not controlled by lifestyle modification, current guidelines recommend that pharmacologic treatment can start with a single drug at low dose. The decision to start pharmacologic treatment varies depending on the level of blood pressure, age, target organ damage (e.g., left ventricular hypertrophy or CKD) and overall cardiovascular risk. National Institute for Health and Clinical Excellence (NICE) guidance recommends initializing antihypertensive drug treatment to people with stage 2 hypertension or with stage 1 hypertension who have either target organ damage, established CVD, renal disease (RD), DM or a 10-year cardiovascular risk equivalent to 20% or greater[63].

Most guidelines aim for a target clinic blood pressure below 140/90 mmHg in people aged under 80 years, whereas lower targets (below 130/80 mmHg) are set for people with established cardiovascular or RD or DM[8, 10][8, 10] and higher targets (150/90mmHg) are set for people aged over 80 years (see Table ‎4.2)[253, 254]. The ultimate goal of antihypertensive treatment is to reduce cardiovascular and renal morbidity and mortality.

The initial drug should be selected on the basis of the patient’s clinical characteristics, risk factors of CVDs, medical history, possible drug interactions, side effects and cost considerations[8]. NICE guidance recommends A(B)/CD rule initializing treatment to the patients under 55 years with an ACEI or an ARB, and to the patients aged over 55 years with a CCB or a D[63]. This age grouping is based on the capacity of drugs to inhibit (i.e., ACEIs or BBs) or not inhibit (i.e., CCBs or Ds) the components of the renin-angiotensin system (RAS). In general, the RAS is known to be more active in younger patients and less active in older patients. However, it is generally accepted that Thiazide-type Ds (as well as chlorthalidone and indapamide), BBs, CCBs, ACEIs, and ARBs are suitable for the initiation and maintenance of antihypertensive treatment either as monotherapy or in some combinations with each other[8-10, 223, 237]. Nevertheless, the use of BBs for the initial treatment of primary hypertension is controversial because of the outcomes of meta-analyses and other studies that showed poor performance of atenolol based treatment in clinical outcomes[230, 231]. The partial update of the NICE guidelines in 2004 indicated that BBs are no longer preferred as a routine initial therapy for hypertension[238].

If blood pressure is not controlled with a single initial drug low dose, traditionally recommended treatment algorithm for primary hypertension is a stepped-care approach, which titrates to a maximum dose as needed or adds an additional drug as the second step[9, 239]. Currently, a tailored treatment algorithm to individual patient, which allows more treatment options depending on the patient’s risk factors, is also recommended in some clinical guidelines[8]. The variation in the recommendations from major clinical guidelines implies that there is no established standard of evidence-based optimal treatment sequence.

Combination therapy often offers greater blood pressure reduction at lower doses with fewer side effects over monotherapy because of the multiple mechanisms involved in blood pressure[240, 241]. Thus, European Society of Hypertension and European Society of Cardiology (ESH/ESC) considers two-drug treatment as an alternative to monotherapy as a first choice therapeutic approach, not a necessary step after attempting monotherapy[8]. Antihypertensive drugs of different classes can be combined if 1) they have different and complementary mechanisms of action, 2) there is evidence that the antihypertensive effect of the combination is greater than that of either combination component, 3) the combination may have a favourable tolerance profile, the complementary mechanisms of action of the components minimising their individual side effects[8].

Table .. Recommendations from major clinical guidelines of primary hypertension

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Guideline (Country) | Publication  year | Treatment threshold | Treatment goals | First-line treatment |
| NICE (UK)[63] | 2011 | * SBP ≥160/100 mmHg regardless of 10-year CVD risk. * SBP ≥140/90 who have 10-year CVD risk >20%. | * Age<80 years, SBP 140/90 mmHg. * Age≥80 years, SBP 150/90 mmHg. | * Age<55 years, ACEIs/ARBs. * Age ≥ 55 years or black, Ds or CCBs. |
| ESH/ESC (Europe) [8] | 2013 | * Age<80 years, SBP ≥140/90 mmHg. * Age≥80 years, SBP ≥160/100 mmHg. | * SBP ≤140/90 mmHg in all patients with hypertension. * SBP ≤130/80 mmHg in patients with DM and in high-risk. | * Ds, BBs, CCBs, ACEIs/ARBs either as monotherapy or in some combinations. |
| JNC8  (US)[9] | 2014 | * Age<60 years, SBP ≥140/90 mmHg. * Age≥60 years, SBP ≥150/90 mmHg. | * Age<60 years, SBP <140/90 mmHg (same for the hypertensive population with DM or non-diabetic CKD). * Age≥60 years, SBP <150/90 mmHg. | * Ds, CCBs, ACEIs/ARBs either alone or in combination. |
| CHEP (Canada) [10] | 2014 | * Age<80 years, SBP ≥160/100 mmHg or ≥140/90 mmHg with a macrovascular target organ damage. * Age≥80 years, SBP ≥160/100 mmHg. | * Age<80 years, SBP 140/90 mmHg. * Age≥80 years, SBP 150/90 mmHg. | * Ds, BBs (only age <60 years), CCBs, ACEIs/ARBs either as monotherapy or in some combinations. |

1) **NICE** stands for the National Institute for Health and Care Excellence; **ESH/ESC** stands for the European Society of Hypertension (ESH)-European Society of Cardiology (ESC); **JNC8** stands for the Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure published by National Heart and Blood Institute in the US; and **CHEP** stands for the Canadian Hypertension Education Program.

Possible combinations of different classes of antihypertensive drugs are illustrated in Figure ‎4.4. Combining ACEIs and ARBs is not recommended because it does not reduce the risk in the CVD-related outcomes, but increases the risk of hypotension, renal dysfunction and hyperkalaemia[242, 243]. If triple therapy is required, the combination of ACEIs, CCBs and Ds is generally recommended.



1) **Solid lines** stand for the rational combinations considering efficacy, complementarity of action mechanism and tolerance profile. **Dash lines** stand for the less favourable combinations, which should be used carefully for some patients groups or whose effectiveness is not proved yet.

Figure .. Possible combinations of antihypertensive drug classes[8]

For particular patient subgroups having CVD, DM, kidney disease or other high risk factors specific drugs are recommended based on clinical trials demonstrating the benefits of such therapy on the natural disease history of the associated condition. Table ‎4.3 shows the recommendations for the patients having CVD or DM based on the major clinical guidelines; most of them are suitable for patients with CVDs and DM apart from CCBs for HF. Amlodipine is the only CCB with established safety in patients with severe HF[244].

Table .. Recommended drugs for cardiovascular diseases and diabetes[8-10, 245]

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Ds | BBs | CCBs (dihydropyridine) | CCBs  (Non- dihydropyridine) | ACEIs | ARBs |
| Angina pectoris | ∆ | o | o | o | ∆ | ∆ |
| Past MI | ∆ | o | ∆ | o | o | o |
| Past stroke | o | o | o | ∆ | o | o |
| HF | o | o | ∆ (only Amlodipine) | x | o | o |
| DM | o | ∆ | o | ∆ | o | o |

1) **Circle** stands for the recommended drug for the relevant health state, agreed in the clinical guidelines reviewed. **Triangle** stands for the recommended drug for the relevant health state in some guidelines. **Cross** stands for the contraindicated drug for the relevant health state.

## Previous economic evaluations in primary hypertension

Because of the large number of antihypertensive drugs and increasing drug expenditure on hypertension, several countries have conducted economic evaluations on antihypertensive drugs at national level and produced the HTA reports to support the decision-making for an optimal choice, especially for initial drug treatment[63, 223, 246-248]. These studies have generally included an extensive systematic review of existing CEA modelling studies to explore the cost-effectiveness of antihypertensive drugs in primary hypertension. Despite the difference in the depth of search strategy, the included studies (published between 1966 and 2010) overlapped considerably; rather than conducting a new systematic review, this review focused on the included studies in those HTA reports.

### Comparison of cost-effectiveness results

Eight cost-minimisation analyses (CMAs), eight CEAs and three cost-utility analyses (CUAs) were identified. A summary table of the included studies is provided in Appendix 5. Where insignificant differences in blood pressure lowering effect or prevention of CVDs across antihypertensive drugs was assumed, CMAs consistently showed that Ds-based treatments were the least expensive regimen[249-256]. The greater part of the difference in costs was attributed by drug acquisition costs. The differences in other cost components such as the costs for physician visit and laboratory test could not offset the difference in drug acquisition costs because newer drugs such as CCBs and ACEIs were more expensive than Ds by a factor between 4[250] and 73[251]. Although some studies included the costs for treating AEs, the impact on total costs was imperceptible where equal effectiveness across antihypertensive drugs was assumed[249, 256]. This result was robust in a range of sensitivity analyses with varying assumptions of efficacy of ACEIs, utility values and costs associated with potassium supplementation, laboratory tests, clinical visits, compliance and side effects.

In most CEA or CUA studies, Ds or BBs-based regimens also showed greater cost-effectiveness compared with ACEIs or ARBs. However, there were some differences in the rank of cost-effectiveness depending on patient subgroup. For example, Ds were the most cost-effective drug for patients at high risk of HF, but not for patients at a high risk of DM. CCBs were the most cost-effective drug for patients over 55 years, at low risk of HF or at high risk of DM. For patients at high levels of DM risk and intermediate levels of HF risk, ACEIs or ARBs were the most cost-effective alternative to Ds or CCBs because of the difference in relative treatment effect of drugs that act on the risk of CVDs or DM[63]. That is, CCBs are associated with lower rates of stroke and MI, but higher rates of HF, whereas ACEIs or ARBs are associated with lower rates of HF and DM but higher rates of stroke[63].

### Comparison of the disease pathway

The disease pathway of hypertension was constructed to reflect the natural history of hypertension and the relationship with CVDs and death. In Tran et al’s study, a Markov model consisted of six health states: well, unstable angina (UA), MI, HF, stroke and death[246]. All patients without previous CVD history were assumed to transit from the well state to one of CVDs or death every year. Transition probabilities from the well state to a CV event or death were estimated using Framingham equations. Once a patient experienced CVD, the annual risks of subsequent events were affected by the previous disease history.

NICE’s model included an additional state of DM to the disease pathway defined in Tran et al’s model[63, 223]. A cohort of patients, initially in the event-free health state, was assumed to move to one of the other defined health states (i.e., MI, UA, stroke, DM, HF or death) or to stay at the event-free health state every six months. The transition probabilities obtained from clinical trials were adjusted for each subgroup by age, gender, ethnicity, baseline CVD, HF risk and DM risk. Other hypertension-related CVDs, RDs or peripheral vascular diseases were not modelled because of limited data.

### Consideration of drug switches

Richter et al’s study was the only study to address the cost-effectiveness of different sequential treatment strategies over 15 months[257]. A decision tree model was built to explore the effect of adding ARBs (i.e., telmisartan) to the sequential treatment strategies starting with Ds, CCBs, ACEIs, BBs or ARBs. The initial drug was switched to the next drug if a patient failed to control blood pressure every three months. The probability that a specific drug was selected as the second-line therapy was based on physicians’ opinion. The study concluded that adding ARBs could reduce the mean time to control blood pressure and reduce total costs in the short-term.

There were two studies that allowed only one opportunity to switch a drug when a CVD or intolerable AEs occurred. In Stafilas et al’s CMA, which compared the costs of Ds, BBs, CCBs, ACEIs and ARBs, Ds was switched to ACEIs and the other drugs were switched to Ds in the case of AEs or lack of efficacy[254]. For simplicity, they also assumed that only one drug switch from conventional therapy to ACEIs or vice versa could occur if congestive HF developed, blood pressure was not controlled after the first three months of initiation of drug therapy or in response to AEs or non-response.

The other studies focused on the impact of an initial drug on long-term costs and health outcomes assuming that a patient continues with the drug for a defined time period regardless of the health state transitions. Three studies mentioned that they could not consider drug switching because of limited clinical or economic data of each drug and the complexity of modelling the interactive effects between various health states and drug choice over time[42, 246, 258]. Tran et al also stated that they restricted the CEA of antihypertensive drugs to the comparison of initial drugs because there was no clear evidence of optimal secondary drugs after the initial drug fails[246]. The NICE HTA report stated that the impact of drug discontinuation and switching between treatments on effectiveness was implicitly considered in intention-to-treat (ITT) trial data[223].

## Conceptual framework of the hypertension sequential drug decision problem

Figure ‎4.5 graphically represents the sequential drug choice process in primary hypertension. For a patient newly diagnosed with primary hypertension, the initial treatment decision is made depending on the comorbidity, the level of blood pressure and 10-year CVD risk. If the patient has stage 2 or 3 hypertension (i.e., BP ≥ 160/100); or stage 1 hypertension (i.e., 140/90 ≤ BP < 160/100) with a high CVD risk (10-year CVD risk ≥ 20%), pharmacological treatment usually starts with a single drug at low dose; although one of the two drug combinations may be used. For patients with CVD currently or previously, a drug will be selected depending on their medical history and the compelling indications.

As the result of the initial treatment, the patient either achieves the treatment goal or has the same or a worse SBP, CVD, DM or AE due to the drug. In the worst case, the patient may die due to a CVD-related or non-CVD related reason. If the initial drug cannot achieve the treatment goal, then it will be substituted with another single drug or two or three drug combination. In this study, the two or three drug combinations means both adding a second or third-line drug to the current treatment regimen and multiple drugs combined into a single pill. If the patient has a CVD or DM, one of the drugs recommended in clinical guidelines will be given. If the patient achieves the treatment goal, the current treatment regimen usually continues the drug at the same dose or at a lower dose. Depending on the result of second-line treatment, the patient evaluation and treatment decision procedure repeats over the patients’ lifetime.



1) **D** represents thiazide type diuretics; **BB** represents beta-blockers; **CCB** represents calcium channel blockers; **ACEI** represents angiotensin-converting enzyme inhibitors; and **ARB** represents angiotensin II receptor blockers.

Figure .. Graphical display of the sequential drug decision process in primary hypertension

The sequential drug decision process in primary hypertension in Figure 4.5 was conceptualised using the elements of the mathematical description of an SDDP *P(T, H, HS, A, SS, DS, Ω, p, r, f)* in section 2.4.

### The set of time

A cohort of hypertensive patients moves through the model experiencing hypertension-related events at discrete time periods until either death or the patient reaches an age of 100-years. At each time period, the decision maker (i.e., clinician) makes a decision on the choice of drug(s) (e.g., continue with the same drug(s), replace with a new drug or add a new drug into the current treatment regimen) considering the patient’s current blood pressure level, medical history and the risk of the CVD-related health states. In practice, the time to revisit the clinician after treatment initiation and to decide upon treatment success and tolerability is fairly short. If the time interval is too short, however, there is a potential risk of carry-over effect and maximal antihypertensive efficacy is unlikely to have been reached. From a methodological viewpoint, the total drug switching period would be too short to consider the long-term cost and effectiveness of sequential treatment policies. Therefore this study assumes that this decision-making cycle is three months.

It is practically impossible to consider all possible drug switches until 100 years old because of the huge number of possible disease pathways and treatment sequences: thus, this study reduces the size of the problem by restricting the maximum number of drug switches. The NICE clinical guidelines on primary hypertension recommend a 4-step treatment algorithm (i.e., three switches are allowed after the initial drug is prescribed at step 1) including two or three drug combinations[63]. For the untreated hypertension after step 3 (i.e., blood pressure is still not controlled after three types of treatment), the NICE guidelines recommend to consider further Ds-based therapy, adding an AB or BB or seeking specialist advice because it may be associated with secondary hypertension. Depending on the cause of high blood pressure, treatments after step 4 may involve pharmacological treatment, surgery or even renal dialysis, which are beyond the scope of this study. Furthermore, the proportion of hypertensive patients who fail to control blood pressure after step 4 is small in practice[8, 63]. As such, the hypertension SDDP model assumes that the maximum number of drug switches is three, and drug switching beyond step 4 is not included in this analysis.

Markov models are suitable to modelling a long-term disease, which involves an ongoing risk over time[74]. Where a maximum number of drug switches are set, however, the hypertension SDDP model can be structured as a successive decision tree with an add-on Markov model. In this case, drug switching is only considered in the successive decision tree; and the add-on Markov model can be used to calculate the long-term impact of sequential drug use on cost and effectiveness. Therefore, the total follow-up period in the successive decision tree is one year (i.e., three months x four time periods, or *T=(t1,t2,t3,t4)*), whereas the overall cost-effectiveness of the sequential treatment strategy is modelled long-term (i.e., until death or 100 years old). This thesis refers to the successive decision tree as the short-term drug switching model and the add-on Markov model as the long-term CVD model in the following sections 5.4 and 5.5 for description of their structures.

### The set of possible health states and the health state space

As a result of antihypertensive treatment, some patients can successfully achieve the treatment goal (and live), fail to achieve the treatment goal (and live) or die due to CVD or a non CVD-related cause. According to the NICE’s clinical guidelines, the treatment goal of antihypertensive drugs is to reduce SBP<140 mmHg for patients whose 10-year CVD risk≥20%, and SBP<160 if 10-year CVD risk<20%”[63]. In the hypertension SDDP model, treatment failure is defined as the patients who either do not achieve the treatment goal recommended by NICE or have a CVD, DM or other AEs. The inclusion of CVD, DM and other AEs were justified as following:

* ***CVDs***

Modelled CVDs include UA, MI, stroke and HF. The association between blood pressure and the incidence of stroke and CHD is described in section 4.2.

* ***DM***

DM is included to consider the long-term potential impact of diabetics on the cost and clinical effectiveness of antihypertensive drugs. Hypertension is one of the risk factors for the development of DM[259, 260]. Incidence of new-onset DM is 2.5-5 times higher in individuals with elevated blood pressure than normotensive subjects[260-262]. Previous studies have suggested that Ds and BBs may be associated with the development of type 2 DM[261-263]. Some epidemiologic studies and clinical trials also suggested a causal link between the use of Ds or BBs and the development of type 2 DM[264-266]. The reason can be explained by the glucose- and insulin-related negative metabolic effects of Ds[267, 268] and BBs[269-271]. Recently, attention has been moving to the potential metabolic effects of ACEIs and ARBs[272].

Hypertension and DM are independent risk factors for CVDs: patients with both hypertension and DM are particularly vulnerable to CVD. The risk is approximately 2-4 times the CVD risk of the general population[273-275]. While most previous CEAs in primary hypertension excluded the long-term potential impact of DM on the cost and clinical effectiveness of antihypertensive drugs[42, 246, 276], this study includes DM in the model structure to antihypertensive drugs as risk factors for type 2 DM.

* ***Other AEs***

Safety issues are especially important in long-term and asymptomatic diseases such as hypertension[277]; alongside clinical efficacy, clinical guidelines recommend to consider the safety issues when deciding a treatment regimen[8, 9, 63]. Most antihypertensive drugs are associated with increased risk of dizziness, hypotension and drowsiness. Apart from these common reactions, various AEs may happen depending on the type of antihypertensive drugs. For example, cough in patients taking the ACEIs, flushing and/or vasodilation in patients taking the CCBs, breathlessness in patients taking the BBs and metabolic AEs in patients taking Ds[278].

The incidence of AEs varies depending on the study design and the author's definition of an AE: 16-62% in the cross-sectional studies based on survey[279, 280] and 35.4% in a prospective cohort study with patients attending a hypertension outpatient clinic[281]. In clinical trials, the incidence of AEs was lower[278, 282] than those of cross-sectional studies and prospective cohort studies. Most AEs of antihypertensive drugs are minor: a cross-sectional study found that only 7% of the patients have severe AEs that lead to the discontinuation the treatment by physicians[279].

If all those states above are considered individually, i.e., *H={ContBP, UncontBP, UA, MI, Stroke, HF, DM, OtherAEs, Death},* where *ContBP* stands forthe patients who achieve the treatment goal and *UncontBP* stands for the patients who did not achieve the treatment goal without CVDs and DM, the size of health state space *Z(HS)* is 649 excluding 5,912 infeasible health state combinations, which are the branches expanding from death at *t1*, *t2*and *t3*:

*Z(HS)* = 9^4-{(8^0\*9^3+8^1\*9^2+8^3\*9^1)-(8^0+8^1+8^2)} = 649

Equation 4.1.

Where *CVD* combines *UA*, *MI*, *Stroke* and *HF*, i.e., *H={ContBP, UncontBP, CVD, DM, OtherAEs, Death}* and *CVD={UA, MI, Stroke, HF},* the size of health state space *Z(HS)* is 181 excluding 1,115 infeasible health state combinations, which are the branches expanding from death at *t1*, *t2*and *t3*:

*Z(HS)* = 6^4-{(5^0\*6^3+5^1\*6^2+5^3\*6^1)-(5^0+5^1+5^2)}= 181

Equation 4.2.

Where *Failure* combines the patients who do not control the blood pressure, have a CVD, DM or other AEs, i.e., *H={Success, Failure, Death}*, *Success={ContBP}, Failure={UncontBP, CVD, DM, OtherAEs}* and *CVD={UA, MI, Stroke, HF},* the size of health state space *Z(HS)* is 31 excluding 50 infeasible health state combinations, which are the branches expanding from death at *t1*, *t2*and *t3*:

*Z(HS)* =3^4-{(2^0\*3^3+2^1\*3^2+2^2\*3)-(2^0+2^1+2^2)} = 31

Equation 4.3.

The hypertension SDDP model constructs the health state space based on the definition used in Equation 4.3. Where the initial health state is uncontrolled hypertension (i.e., *Failure*), the health state space Z(*HS)* has 31 possible disease pathways as Figure ‎4.6.

|  |  |
| --- | --- |
|  | 1) **d1-d4** represents the drug used for the specific health state in each period, given a policy *π=(d1,d2,d3,d4).*  2) Any patients who have a CVD or DM move to the long-term CVD model and follow the transition rules assumed in the long-term CVD model. At the end of the drug switching period, all alive patients move to the long-term CVD model.  Figure .. Potential treatment pathways and treatment assignment in the short-term drug switching model |

### The set of feasible actions at each stage

For patients newly diagnosed with primary hypertension, it is recommended to start the initial treatment with one of the five major antihypertensive drugs (i.e., Ds, BBs, CCBs, ACEIs and ARBs) if there is no compelling indication. As per the NICE hypertension model, this study integrates ACEIs and ARBs into a single treatment strategy as they are regarded to have equivalent pharmacological mechanism and clinical effectiveness[63]. Hence, it is assumed that there are four single antihypertensive treatment options (i.e., Ds, BBs, CCBs and ACEIs/ARBs) in the hypertension SDDP model. The costs and effects of ACEIs and ARBs are weighted based on the proportions of patients using ACEIs (80%) and ARBs (20%).

Some guidelines say that two or three-drug combinations can be used for initial treatment[8-10]. Despite the proven effectiveness of combination treatment in controlling blood pressure and reducing CVD-related morbidity and mortality, however, there are still concerns on starting treatment with combination drugs because of the risk of hypotension and CHD[240, 241]. For this reason, the hypertension SDDP model restricts initial treatment to single drugs. For the same reason, this study assumes that the second-line drug is selected among single drugs or two-drug combinations. The following shows a set of possible drug alternatives at time *t*:

*A1={Ds, BBs, CCBs, ACEIs/ARBs},* where *t=1,*

*A2={Ds, BBs, CCBs, ACEIs/ARBs, Ds+BBs, Ds+CCBs, Ds+ACEIs/ARBs, BBs+CCBs, BBs+ACEIs/ARBs, CCBs+ACEIs/ARBs},* where *t=2* and

*A3 or A4={Ds, BBs, CCBs, ACEIs/ARBs, Ds+BBs, Ds+CCBs, Ds+ACEIs/ARBs, BBs+CCBs, BBs+ACEIs/ARBs, CCBs+ACEIs/ARBs, Ds+BBs+CCBs, Ds+BBs+ACEIs/ARBs, Ds+CCBs+ACEIs/ARBs, BBs+CCBs+ACEIs/ARBs},* where *t=3* or *4.*

Where the change in the treatment regimen is required, the current drug can be switched to another drug from a different class, which was not previously selected and proven to reduce the risk of CVDs[8, 9]. Thus, it is assumed that there is no return to a previously used drug class. The same drug is only continued for the controlled patients with regular monitoring. This study calls this maintenance therapy henceforth.

Given 14 treatment options and a maximum of three drug switches allowed, the number of potential drug sequences is 24,024 (i.e., 14\*13\*12\*11). With the step-wise treatment assumption (i.e., initial treatment should be a single-drug; and the second-line drug should be a single drug or a two-drug combination, the search space has 4,752 'pre-set' treatment sequences. 624 policies, which move from a single drug to a three-drug combination straight away without trying a two-drug combination, are further excluded because of safety concerns. Therefore, the number of possible treatment sequences in the case study of primary hypertension is 4,128.

*Z(SS)=4\*(10-1)\*(14-2)\*(14-3)-624=4,128* Equation 4.4.

### Transition probability

The SDDP of hypertension follows a semi-Markovian assumption during the drug switching period. The transition probability to the next state *st+1* depends on SBP change and the risk of CVD, DM, other AEs and death, which are time-dependent. The transition probability is also modified depending on which treatment drug is currently in use.

In contrast, the long-term CVD model is a standard Markov model including *Well*, *UA*, *MI*, *Stroke*, *HF*, *DM* and *Death*. During the drug switching period, a proportion of patients in both *Success* and *Failure,* who have CVD or DM, move to the long-term CVD model. After the drug switching periods, all alive patients move to the long-term CVD model. 23 different sub-population groups are defined depending on when they move to the long-term CVD model. Each population has their own baseline risk of CVDs and DM based on the mean SBP and the variance (i.e., SD) when they enter the long-term CVD model. The conventional RR approach is used to consider the treatment effectiveness.

### Reward

The reward in the hypertension SDDP model is the total net benefit, which is the health benefit expressed in the monetary units, minus the total costs associated with sequential treatment. Each drug selected for *s* at time *t* leads to an expected cost or treatment benefit, which is estimated in terms of QALYs. The costs and QALYs assigned to each transition, *r(st+1|st,at,)* can be interpreted as the one-step (or immediate) reward. The global reward for the given policy, *π=(d1,d2,d3,d4),* is the weighted sum of the one-step rewards with the probabilistic structure of the underlying evaluation model; this includes the costs and QALYs, calculated both in the short-term drug switching model and the long-term CVD model.

## Implication for the hypertension SDDP modelling

This chapter conceptualised the hypertension SDDP using 1) the topography of the sequential drug decision process in primary hypertension as in Figure ‎4.5, and 2) the elements of the mathematical description of the SDDP as per section 2.4. Modelling the hypertension SDDP can be overwhelmingly complex because of 1) the long-term follow-up period, 2) the large number of potential combinations of health state transitions, 3) the large number of potential alternative treatment sequences, and 4) the interaction between the treatment sequences and the health state transitions. Therefore, the conceptualisation focused on how to define the scope of the hypertension SDDP and how to reduce the size and computational complexity of the problem.

Firstly, the hypertension SDDP model restricts the maximum number of drug switches to three, as per the treatment algorithm recommend by NICE. As the hypertension is a long-term health condition, it is common to follow-up for lifetime in economic evaluation. However, it is practically impossible to consider all possible drug switches in the long-term because of the huge number of possible combinations of health state and treatment sequences. Setting a limit on the number of drug switches, based on clinical grounds, leads to a reduction in the size of the health state space (see Equation 2.1); this also reduces the size of the search space linearly (see Equation 2.2).

As it is assumed that the drug switching is only allowed in the first four time periods, the hypertension SDDP model is structured in a successive decision tree, which is called the short-term drug switching model, with an add-on Markov model, which is called the long-term CVD model. Drug switching only happens in the short-term drug switching model, whereas the add-on model calculates the long-term impact of sequential drug use on cost and effectiveness. Most of the issues related to the size and computational complexity of this hypertension SDDP model occur within the short-term drug switching model.

Secondly, the size of the health state space is reduced by combining several states that share similarities in terms of transition probability to an aggregate state[58]. *Failure* is an aggregate state that includes the patients who fail to achieve the treatment goal or have a CVD, DM, or other AE. This further reduces the size of the health state space and the computation of matrices for transition probabilities and rewards. To consider the (potentially) higher risk of subsequent CVDs for the patients who have a history of CVD or DM, a proportion of patients who have either a CVD or DM move from the short-term drug switching model to the long-term CVD model in the next period (see Figure ‎4.6). The drug decision rules are also different for those patients who have never had a CVD or DM and those who have, or have previously had, a CVD or DM - this will be further explained in Chapter 5.

Thirdly, excluding drugs or treatment sequences that are not in accordance with the recommendations from major clinical guideline, also reduces the size of search space. For example, the traditionally recommended treatment algorithm for primary hypertension is a stepped-care approach, which starts with a single low-dose drug (usually Ds) and then adds a second-line drug to the current treatment regimen if the initial treatment fails to achieve the treatment goals[9, 63]. The hypertension SDDP model assumes decision rules that follow this stepped-care approach. The hypertension SDDP model does not consider drug switching within the same class and dose-titration. The patients are assumed to take the equivalent dosages of the drugs included in the same class. Due to a sparsity of available data, dose titration is also considered as a single treatment option, where it is assumed that the patients take the average dose of each drug. For the patients currently have, or have had, a CVD or DM, it can be assumed that one of the recommended drugs from major guidelines is used. For those patients with DM, for example, it is well-known that the use of ACEIs is ideal. In the case of stroke, the algorithm can only allow selecting one drug between Ds and ACEIs.

The interaction between the treatment sequences and the health state transitions in the short-term drug switching model is assumed to be semi-Markovian. The main factors in determining the transition probability between health states are the average SBP lowering effect and the average risk of CVD, DM and AEs, which are time and drug dependent for a group of patients in a specific health state at time *t*. Every time disease history and treatment results are saved in memory variables and used for the calculation of transition probabilities and the decision-making in the next period. The reduced computational complexity facilitates the use of the semi-Markov assumption in the hypertension SDDP model.

# Modelling sequential drug decision problem for primary hypertension: evaluation model

## Chapter overview

This chapter describes the evaluation model developed to capture the underlying hypertension disease pathway and the impact of the sequential use of antihypertensive drug(s). The ultimate goal of this evaluation model is to provide the optimisation model with the value of the objective function (i.e., the long-term costs and effectiveness of a candidate sequential treatment strategy in a UK National Health Service (NHS) perspective). The underlying evaluation model is constructed with a short-term drug switching model, which has a form of successive decision tree, and a long-term CVD model, which is a standard Markov model. All the parameters and assumptions used to build the evaluation model are also provided.

## Population

A cohort was defined of patients newly diagnosed with primary hypertension, excluding those with pre-existing CVDs, HF or DM. According to Burke’s retrospective cohort study, which observed 109,454 patients newly diagnosed with hypertension between 1991 and 2001 in the UK, it was assumed that the mean age of the cohort of newly diagnosed primary hypertensive patients was 60.6 years old (standard deviation (SD) 13.4) and the initial SBP was 173.5 mmHg (SD 21.1)[283]. The raw dataset of the Health Survey England (HSE) was analysed to get the mean total cholesterol (TC), high-density lipoprotein cholesterol (HDL) and body mass index (BMI) of the patients with hypertension in the UK (see Table ‎5.1)[284].

Table .. The mean TC, HDL, BMI of the hypertensive patients in the UK[221]

|  |  |  |  |
| --- | --- | --- | --- |
|  | Age groups | Men | Women |
| TC (mg/dl) | 55-64 | 199.96 | 207.68 |
| 65-74 | 185.33 | 206.80 |
| 75-84 | 179.36 | 197.63 |
| 85+ | 159.59 | 185.97 |
| HDL (mg/dl) | 55-64 | 50.55 | 60.61 |
| 65-74 | 50.94 | 60.39 |
| 75-84 | 55.46 | 64.35 |
| 85+ | 66.92 | 63.06 |
| BMI | 55-64 | 32.18 | 31.33 |
| 65-74 | 30.07 | 30.24 |
| 75-84 | 29.01 | 30.75 |
| 85+ | 27.27 | 27.30 |

The patients included in the base-case had the following characteristics:

* 60.6 years old white men.
* SBP 173.5 mmHg (SD 21.1).
* Average TC, HDL, BMI of the patients with hypertension in the UK.
* Non-smoker.
* No CVD family history.
* No chronic renal disease (CRD), atrial fibrillation (AF) or RA.

To test whether the costs and effectiveness of sequential treatment strategies were sensitive depending on the patient’s characteristics, sensitivity analyses were conducted for female, different age groups with mean ages of 50 and 70 years old and the patients having a different SBP (153.5 and 163.5 mmHg) at the initial stage.

## Time

This study assumed that treatment adjustments happen at 3-month intervals. The time to control the level of blood pressure varies depending on a patient’s risk factors: for convenience, it was assumed that the defined time cycle coincided with the unit of time that allows drug switching. As a maximum of three drug switches (four drugs in a sequential treatment strategy) were allowed in the short-term drug switching model, the total drug switching period was one year.

The long-term CVD model calculated the costs and effectiveness over a lifetime horizon after a CV event or DM happens during the drug switching period or the end of the drug switching period. The cycle length was set to one year after the drug switching period to reduce the computational time in the long-term CVD model.

## The structure of the short-term drug switching model

There were three potential health states in the short-term drug switching model as structured in Figure ‎4.6:

* *Success*: including the patients who achieved the treatment goal.
* *Failure:* including
* The patients who did not achieve the treatment goal or
* The patients who had a CVDs, DM or any other AEs.
* *Death*

All patients started from *Failure*, which means uncontrolled hypertension. Every three months, a proportion of patients stayed at 1) *Failure* or moved to either 2) *Success* or 3) *Death*. Treatment success rate, which was the transition probability from *Failure* to *Success*, was dependent on SBP and the risk of CVDs, DM and other AEs. According to the NICE’s clinical guideline, treatment success of antihypertensive drugs was defined as following[63]:

* SBP<140 if 10-year CVD risk is higher than 20%, or
* SBP<160 if 10-year CVD risk is less than 20%,
* without CVD, DM or other AEs.

The treatment success rate was calculated by using a Monte Carlo sampling method. For each health state in each time period, the Monte Carlo simulation randomly generated 1,000 individual patients who have a set of sampled baseline SBP, SBP lowering effect and the risk of CVD, DM and AEs. 1,000 samples of baseline SBPs were generated based on the previous treatment results (i.e., the mean SBP and the SD after previous treatment). 1,000 samples of the level of SBP reductions and the occurrences of AEs including DM were also randomly generated based on the best available data and their distributions of the drug used. SBPs after treatment were calculated by subtracting the levels of SBP reduction from the baseline SBPs. CVD risks were calculated based on the SBPs after treatment, using a reported link between SBP and CVD risk (see discussion in section 5.6.1). The treatment was regarded as being successful if the set of sampled results meet the criteria of treatment success defined above. The treatment success rate was calculated based on the proportion of treatment success in the 1,000 sets of sampled results; and used for the transition probability from the current state to *Success* in the next period. The mean and SD of SBPs after treatment were saved separately for the patients whose treatment were successful and unsuccessful to use them to generate the baseline SBPs in the next time period depending on the health state evaluated.

This model assumed that the controlled patients took an appropriate maintenance therapy with regular check-up and kept their SBP around 128.8 mmHg (SE 0.36) for men and 122.3 mmHg (SE 0.43) for women, which were the mean SBP of general population aged over 60 in England[221].

Total mortality was the sum of CVD mortality and non-CVD mortality. The CVD mortality was estimated by multiplying the CVD risk calculated by QRISK2[285] and the proportion of CVD death of first-onset CVD (see Table ‎5.2)[63, 286]. Therefore CVD mortality was directly dependent on the changes in SBP and patients’ risk factors (e.g., age and gender) over time. On the other hand, non-CVD death, which was defined as the death caused by any other reasons, was calculated based on all-cause mortality estimated from the life tables between 2008 and 2010 in England and Wales (see Table ‎5.3)[287] and the proportion of non-circulatory death of all deaths (see Table ‎5.4)[288].

Table .. Age and gender-specific proportions of first-onset CVD[63, 286]

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Age/Men | UA | MI | Stroke | CVD death | Other | Total |
| 45 | 0.107 | 0.295 | 0.129 | 0.101 | 0.368 | 1 |
| 55 | 0.071 | 0.172 | 0.206 | 0.134 | 0.417 | 1 |
| 65 | 0.083 | 0.173 | 0.270 | 0.160 | 0.314 | 1 |
| 75 | 0.081 | 0.161 | 0.343 | 0.143 | 0.272 | 1 |
| 85 | 0.096 | 0.186 | 0.351 | 0.137 | 0.230 | 1 |
| Age/Women | UA | MI | Stroke | CVD death | Other | Total |
| 45 | 0.117 | 0.080 | 0.229 | 0.091 | 0.483 | 1 |
| 55 | 0.073 | 0.092 | 0.288 | 0.106 | 0.441 | 1 |
| 65 | 0.052 | 0.121 | 0.382 | 0.171 | 0.274 | 1 |
| 75 | 0.034 | 0.102 | 0.464 | 0.152 | 0.248 | 1 |
| 85 | 0.029 | 0.100 | 0.501 | 0.147 | 0.223 | 1 |

Table .. All-cause mortality between 2008 and 2010 in England and Wales[287]

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Age | Men | Women |  | Age | Men | Women |
| 60 | 0.008503 | 0.005451 |  | 81 | 0.069174 | 0.048877 |
| 61 | 0.009045 | 0.005974 |  | 82 | 0.076246 | 0.054728 |
| 62 | 0.009867 | 0.006313 |  | 83 | 0.083825 | 0.061825 |
| 63 | 0.01113 | 0.007036 |  | 84 | 0.095148 | 0.069497 |
| 64 | 0.012319 | 0.007806 |  | 85 | 0.105922 | 0.078345 |
| 65 | 0.013317 | 0.008423 |  | 86 | 0.117177 | 0.087814 |
| 66 | 0.014845 | 0.009294 |  | 87 | 0.127952 | 0.098374 |
| 67 | 0.016206 | 0.010084 |  | 88 | 0.139538 | 0.111449 |
| 68 | 0.018296 | 0.011329 |  | 89 | 0.144657 | 0.118743 |
| 69 | 0.02 | 0.012508 |  | 90 | 0.155582 | 0.13526 |
| 70 | 0.021491 | 0.014067 |  | 91 | 0.164985 | 0.146217 |
| 71 | 0.023871 | 0.015183 |  | 92 | 0.186397 | 0.16876 |
| 72 | 0.026519 | 0.016759 |  | 93 | 0.206562 | 0.187047 |
| 73 | 0.029327 | 0.019023 |  | 94 | 0.227081 | 0.206707 |
| 74 | 0.031908 | 0.021312 |  | 95 | 0.247303 | 0.22523 |
| 75 | 0.035799 | 0.023388 |  | 96 | 0.266587 | 0.244006 |
| 76 | 0.040008 | 0.026653 |  | 97 | 0.283909 | 0.262298 |
| 77 | 0.044184 | 0.029737 |  | 98 | 0.300872 | 0.28506 |
| 78 | 0.049186 | 0.033709 |  | 99 | 0.312745 | 0.302419 |
| 79 | 0.054976 | 0.038206 |  | 100 | 0.341098 | 0.325999 |
| 80 | 0.061857 | 0.043509 |  |  |  |  |

Table .. Age and gender-specific non-circulatory deaths as a proportion of all deaths[288]

|  |  |  |
| --- | --- | --- |
| Age group | Men | Women |
| 55-64 | 0.71 | 0.83 |
| 65-74 | 0.69 | 0.76 |
| 75+ | 0.64 | 0.64 |

During the drug switching period, the proportion of patients who have CVD or DM was calculated using QRISK2[285] (see Section 5.6.1). Assuming that the three-monthly event rate *r* is consistent over 10-years, the 10-year CVD risk was adjusted to three month basis using the following equation[289]:

where *P(t)* is a cumulative probability for t. Equation 5.1.

To calculate the transition probabilities to individual CVDs (i.e., UA, MI, stroke and HF), the composite CVD risk was multiplied by the age and gender-specific distribution of first CVD in the UK (see Table ‎5.2)[63, 286]. The data originally came from the Bromley Coronary Heart Disease Register and Oxfordshire Community Stroke Project[290, 291].

The composite CVD risk calculated by QRISK2 did not include HF risk: therefore the HF risk was estimated by age and gender-dependent HF incidence in the UK (see Table ‎5.5)[288] and the RR of elevated SBP (>140 mmHg) for HF incidence in white population, which was 1.80 (1.27-2.55)[292].

Table .. Incidence per 100,000 of HF in the UK[288]

|  |  |  |
| --- | --- | --- |
| Age group | Men | Women |
| 55-64 | 71.5 | 31.0 |
| 65-74 | 173.1 | 98.7 |
| 75+ | 287.5 | 239.8 |

The risk of new onset type 2 DM came from age and gender-specific type 2 DM incidence in the UK (see Table ‎5.6)[293] and the HR of the new onset DM in patients with hypertension by the class of antihypertensive drugs (see Table ‎5.7)[261]. In order to apply the HR to the transition probability, the annual transition rate was calculated by Equation 5.2, and then the HRs were converted to RRs using Equation 5.3[289]:

Equation 5.2.

Equation 5.3.

Table .. Type 2 DM annual risk per 100,000 population in the UK[293]

|  |  |  |
| --- | --- | --- |
| Age group | Men | Women |
| 60-64 | 1,233 | 915 |
| 65-69 | 1,486 | 1,142 |
| 70-74 | 1,656 | 1,338 |
| 75-79 | 1,625 | 1,380 |
| 80-84 | 1,411 | 1,252 |
| 85-89 | 1,189 | 1,060 |
| 90+ | 538 | 452 |

Table .. Risk of type 2 DM according to category of antihypertensive drug[261]

|  |  |
| --- | --- |
| Antihypertensive drugs | Relative Hazard (95% CI) |
| None | 1 |
| Ds | 0.91 (0.73-1.13) |
| BBs | 1.28 (1.04-1.57) |
| CCBs | 1.17 (0.83-1.66) |
| ACEIs/ARBs | 0.98 (0.72-1.34) |

## The structure of the long-term CVD model

The long-term CVD model is a standard Markov model, which calculates the long-term cost and effectiveness of sequential treatment strategies. The model structure with the following states is identical with the NICE hypertension model[63].

* Well, which has no CVD history and DM
* Four CVDs including UA, MI, stroke and HF
* Four post-CVDs including post-UA, post-MI, post- stroke and post-HF
* DM
* Death

Like the NICE hypertension model, other CVDs such as stable angina, peripheral vascular disease and transient ischemic attacks were not included because data on them were not consistently reported in the trials[63].

During the drug switching period, a proportion of patients in both *Success* and *Failure,* who had CVD or DM, moved to the long-term CVD model. After the drug switching period, all patients alive moved to the long-term CVD model. The initial distribution of health states in the long-term model depended on the final treatment result in the drug-switching period. If a patient had a CVD or DM at the end of the drug switching period, for example, they were allocated to one of CVDs or DM in the long-term model. Otherwise, the patient started the long-term transitions from *Well*.

A cohort of patients with hypertension moved through the long-term CVD model until death or 100-years old. Table ‎5.8 shows the possible transitions between the health states included in the long-term CVD model. Every year patients who had no experience of CVD and DM either stayed in the same state or moved to one of the CVD states, DM or death. Once a CV event happened, it was assumed that a proportion of patients has a recurrent event, moves to another CVD state or moves to the post-CVD states. Same assumption was applied to the post-CVD states. The transition from a post-CVD to *Well* was not allowed because the post-CVD states involved the CVD history. Patients in the DM state were assumed either to stay in the same state or to move to one of CVD states.

Table .. Health states and possible transitions in the long-term CVD model

|  |  |
| --- | --- |
| From | To |
| Well | Well |
| UA |
| MI |
| Stroke |
| HF |
| DM |
| Death |
| UA or post-UA | Post-UA |
| UA |
| MI |
| Stroke |
| HF |
| DM |
| Death |
| MI or post-MI | Post-MI |
| UA |
| MI |
| Stroke |
| HF |
| DM |
| Death |
| Stroke or post-stroke | Post-stroke |
| UA |
| MI |
| Stroke |
| HF |
| DM |
| Death |
| HF or post-HF | Post-HF |
| UA |
| MI |
| Stroke |
| HF |
| DM |
| Death |
| DM | UA |
| MI |
| Stroke |
| HF |
| DM |
| Death |
| Death | Death |

Baseline transition probabilities for the patients having CVD or DM also came from the NICE hypertension model (see Table ‎5.9)[63]. Because the NICE hypertension model calculated the baseline transition probabilities based on a population with 2% CVD risk, those transition probabilities were adjusted to be relative to the patient's final CVD risk in the drug switching period.

Those patients who have never achieved the treatment goal during the drug switching period were assumed to move to *Well* in the long-term CVD model after correcting the underlying cause. They were assumed as resistant hypertension, which was defined as someone whose blood pressure remains above 140/90 mmHg despite the optimal concurrent use of three antihypertensive agents of different classes[63]. The prognosis of resistant hypertension is unclear and the pharmacological treatment for resistant hypertension, which involves three or four-drug combinations, has not been systematically evaluated[294]. Thus there was a difficulty to consider these patients in the framework of the SDDP of primary hypertension. Instead, the average costs and utility decrement of CVDs were used for the negative impact of resistance hypertension on costs and effectiveness.

For patients who have CVD or DM, antihypertensive treatment should be initiated to reduce their CVD risk together with surgical or pharmacological care to treat the underlying disease. There may be a recommended drug for patients with a (history of) specific health state. For example, ACEIs (or ARBs as an alternative) are generally advised for patients with chronic HF[295]. For patients with (a history of) ischemic heart disease, BBs or CCBs are acceptable. For a person on antihypertensive treatment at diagnosis of DM, NICE recommends to initiate pharmacological treatment with ACEIs (or ARBs for a person with continuing intolerance to ACEIs) or CCBs[63]. However, these are recommendation, but not strong compelling indications. In practice, it is possible to use another drug, which is not recommended in the clinical guidelines, but is believed to be the best for the patients without contraindications (Clinician’s opinion). In the base-case, it was assumed that all patients who had or currently have CVD or DM took a recommended antihypertensive drug to treat the underlying disease (i.e., CCBs for UA, BBs for MI and stroke and ACEIs for HR and DM), whereas they were assumed to use a randomly selected drug in a sensitivity analysis apart from CCBs for patients with HF.

Table .. Annual baseline risks of primary and secondary CV events[63]

|  |  |  |
| --- | --- | --- |
| Health state transition | Male | Female |
| Well-UA | 0.0017 | 0.001 |
| Well-MI | 0.0035 | 0.0024 |
| Well-Stroke | 0.0054 | 0.0076 |
| Well-HF | 0.0098 | 0.0098 |
| Well-DM | 0.011 | 0.011 |
| Well-Death | 0.018 | 0.0141 |
| UA-UA | 0 | 0 |
| UA-MI | 0.03 | 0.03 |
| UA-Stroke | 0.0095 | 0.0095 |
| UA-HF | 0.023 | 0.023 |
| UA-DM | 0.0067 | 0.0067 |
| UA-Death | 0.0348 | 0.0307 |
| MI-UA | 0.0078 | 0.0078 |
| MI-MI | 0.072 | 0.0721 |
| MI-Stroke | 0.0095 | 0.0095 |
| MI-HF | 0.023 | 0.023 |
| MI-DM | 0.0067 | 0.0067 |
| MI-Death | 0.0258 | 0.0217 |
| Stroke-UA | 0.0016 | 0.0016 |
| Stroke-MI | 0.0016 | 0.0016 |
| Stroke-Stroke | 0.2875 | 0.2875 |
| Stroke-HF | 0.0115 | 0.0115 |
| Stroke-DM | 0.0067 | 0.0067 |
| Stroke-Death | 0.3548 | 0.3507 |
| HF-UA | 0.023 | 0.023 |
| HF-MI | 0.023 | 0.023 |
| HF-Stroke | 0.0103 | 0.0103 |
| HF-HF | 0.0545 | 0.0545 |
| HF-DM | 0 | 0 |
| HF-Death | 0.0768 | 0.0727 |
| DM-UA | Double the risk of the well population. | |
| DM-MI |
| DM-Stroke |
| DM-HF |
| DM-Death |
| Post-UA | As UA. | |
| Post-MI | As MI. | |
| Post-Stroke | As Stroke. | |
| Post-HF | AS HF. | |

## Treatment effectiveness and costs

### Surrogate outcome modelling based on systolic blood pressure

Surrogate outcome is a laboratory measurement or a physical sign that is intended to substitute for a clinically meaningful patient outcome[296, 297]. The use of surrogate outcomes has the merit of smaller sample size, shorter follow-up period and less cost to dissemination of new treatments, whereas conducting a randomised clinical trial for the final outcomes can be expensive and take a long time. However, there are concerns about the use of surrogate outcomes because many studies showed that the use of surrogate outcome as a final outcome has been misleading for decision-making[298-300]. To validate the surrogate outcome, it must be in the causal pathway of the disease process and all effects of intervention on final outcome should be fully captured by a change in the surrogate outcome.

For HTA, the aim of the use of surrogate outcomes is to predict a clinically important final outcome where data on the final outcomes are not available and the causal relationship between surrogate outcomes and final outcomes is well established[246, 286]. Taylor and Elston recommended that “Ideally, the assessment of clinical effectiveness and cost-effectiveness of a health technology should be based on final patient-related outcomes. When this is not possible, CE analysis based on a surrogate outcome can be considered where there is evidence demonstrating a pathophysiological and clinical consistent association between the surrogate outcome and final patient-related outcome and corresponding treatment effects between them”[297].

In the hypertension SDDP model, SBP was used as the surrogate outcome because of the nature of SDDP. In practice, SBP is an important clinical factor to decide a treatment regimen and to observe whether the treatment is successful or not; clinical guidelines also clearly state the target blood pressure. If a patient’s blood pressure is not reduced to this target blood pressure, a clinician should consider stopping the current drug safely and trying another treatment regimen[63].

There is abundant evidence of a positive and consistent relationship between blood pressure and CV events[224, 227, 301]. Some CEAs in primary hypertension used a risk engine to populate the CV events[258, 302, 303]. The existing risk engines include not just SBP but also various risk factors that are important to address the patient’s CVD risk.

The most widely used Framingham equation was developed based on a large and long-term community-based cohort in the US[304]. The 10-year CVD risk is estimated based on age, gender, SBP, smoking, TC, HDL and DM. However, Cooper et al pointed out that Anderson’s Framingham equation model tends to overestimate the absolute risk of CVD in European populations including the UK, and several risk factors, such as family history, ethnic group, socio-economic status, hypertension treatment and extremes of risk factors, are not included[305]. Hippisley-Cox et al said that D'Agostino’s Framingham model, which is a newer Framingham model (see Table ‎5.10), uses a much broader definition of CVD that is less relevant to UK guidelines[285].

As an alternative, QRISK is a new risk score that has been developed using routine data from UK electronic primary care patient records[285, 306]. It has the advantage that practices and patients on the database are representative of the UK population; hence, QRISK reduces the uncertainty arising from generalising between the variation in population and practice. QRISK also includes ethnicity, BMI, family history of CHD, Townsend deprivation score, treated hypertension, CRD, AF and RA, which are not included in the Framingham equation. The validation of QRISK1 showed a better discriminator of 10-year CVD risk in the UK population compared with the Framingham risk score and the newly developed Scottish score (ASSIGN)[306]. A revised equation for QRISK (QRISK2) was more predictive of CVD risk in the UK cohort compared with the Framingham risk score and the initial version of QRISK[285]. This hypertension SDDP model applies the open sources of QRISK2 to consider the relationship between SBP and CVD risk[307].

Table .. Comparison between Framingham models and QRISK2

|  |  |  |  |
| --- | --- | --- | --- |
| Title | Cardiovascular disease risk profiles[304] | General cardiovascular risk profile for use in primary care The Framingham Heart Study[308] | Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2[285] |
| Author | Anderson | D'Agostino | Hippisley-Cox |
| Year | 1991 | 2008 | 2008 |
| Country | USA | USA | England and Wales |
| Data | The Framingham heart study. | The Framingham heart study. | 531 practices in England and Wales contributing to the national QRESEARCH database. |
| Participants | Persons free of CVD and cancer. | Persons free of CVD and cancer. | Patients aged 35-74, free of CVDs |
| Statistical model | A non-proportional hazards Weibull accelerated failure time model. | Cox proportional hazards model. | Cox proportional hazards model. |
| Risk factors included | Age, gender, SBP (or DBP), smoking, TC, HDL, DM and ECG-LVH. | Age, gender, TC, HDL, SBP, smoking and DM. | Ethnicity, age, gender, smoking, SBP, TC/HDL, BMI, family history of CHD, Townsend deprivation score, treated hypertension, type 2-DM, CRD, AF and RA. |
| Main outcomes | CHD, MI, CHD death, stroke, CVD and CVD death. | CVD, CHD, stroke, CHF and intermittent claudication. | First (incident) diagnosis of CVD (including CHD, stroke, and transient ischemic attack). |
| Definition of CVD | (Silent and unrecognised) MI, (sudden or non-sudden) CHD death, angina pectoris, coronary insufficiency, stroke including transient ischemia, congestive HF and peripheral vascular disease. | CHD (including coronary death, MI, coronary insufficiency and angina), cerebrovascular events (including ischemic stroke, haemorrhagic stroke, and transient ischemic attack), peripheral artery disease (intermittent claudication) and HF. | CHD (angina and MI), stroke or transient ischaemic attacks. |

### Age-dependent systolic blood pressure and blood pressure lowering effect

Age and gender-related changes in SBP were estimated using the regression coefficients developed by Wills et al[309]. Wills et al estimated the life course trajectories of SBP from childhood to elderly by fitting the longitudinal data from eight UK population based cohorts to a non-linear function. Different regression coefficients were estimated for different age groups. The hypertension SDDP model used the regression coefficients in Equation 5.4, which covers the age range between 55 and 77.

137.4+(1.54\*Age)+(-0.046\*Age^2) for men, where the intercept age is 55.

136.7+(1.482\*Age)+(-0.348\*Age^2) for women, where the intercept age is 55. Equation 5.4.

The hypertension SDDP model is based on the assumption that the difference in SBP lowering effect mainly contributes the treatment benefit[310, 311]. However, there are different perspectives to the blood pressure lowering effect between antihypertensive drugs. Some systematic reviews demonstrated that the blood pressure lowering effects of antihypertensive drugs are not significantly different to each other[247, 248]. In contrast, some evidence shows that certain drugs have a significantly better blood pressure lowering effect than others[312, 313]. In order to populate the clinical decision rule based on SBP in SDDP modelling, the hypertension SDDP model accepted the latter even though the difference in the blood pressure lowering effect is small.

Four systematic reviews that conducted a meta-analysis to compare the SBP lowering effect of five major antihypertensive drugs were initially identified (see Table ‎5.11)[282, 313-315]. The SBP lowering effect in the hypertension SDDP model was based on Wright et al’s systematic review, which provides the weighted mean difference and 95% confidence interval (CI) between active drug arm and placebo arm at one year or the earliest time after one year[313], and Wald et al’s systematic review, which presents mean placebo-subtracted SBP reduction (and 95% CI) over a period of 4-12 weeks[315]. Law et al’s review was excluded because of the short time period, which was 24 hours[282]. Baguet et al’s review was also excluded because the final outcome of meta-analysis was not controlled by placebo[314].

Table .. Comparison between systematic reviews on SBP lowering effect of antihypertensive drugs

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | | Law et al, 2003[282] | Baguet et al, 2007[314] | Wald et al, 2009[315] | Wright et al, 2009[313] |
| No of studies included | | 354 trials (56,000 participants) between 1966 and 2000. | 80 trials (10,818 patients) between 1973 and 2007. | 42 trials (10,968 participants) between 1966 and 2008. | 24 trials (58,040 participants) between 1966 and 2008. |
| Types of included studies | | Randomised, placebo-controlled trials followed up more than 2 weeks (Crossover studies were included). | Randomised, double-blinded trials (Crossover studies were excluded). | Randomised-controlled trials (Crossover studies were included). | Randomised-controlled trials followed up at least one year. |
| Participants | | Patients receiving an antihypertensive drug without HF or other CVDs. | Patients with mild or moderate essential hypertension and patient age > 18 years. The average age was around 50. | Hypertensive patients, generally without a history of CHD, stroke, DM or RD. Age range was 46-71. Initial SBP range was 136-173 mmHg. | Patients had elevated blood pressure without angina and congestive HF, but with prior MI or stroke as long as they were not recent. The average age was 62 years old. |
| Interventions | | A specified fixed standard dose of any Ds, BBs, CCBs, ACEIs and ARBs. Trials that in which the dose of the drug was not fixed but titrated were excluded. | Ds, BBs, CCBs, ACEIs, ARBs and the renin inhibitor (Aliskiren) where the drugs were used as monotherapy, either at a fixed daily dosage or in increasing dosages. | Ds, BBs, CCBs, ACEIs and ARBs. | Ds, BBs, CCBs and ACEIs. Initial combined therapies with drug classes not in the defined categories and supplemental drugs from other drug classes of interest were limitedly allowed. |
| Outcome | | The average placebo-adjusted reduction (and 95% CI) in blood pressure over 24 hours and 95% CI. | Weighted average reductions (and 95% CI) in SBP over a period of 8-12 weeks. | Mean (and 95% CI) placebo-subtracted SBP reduction over a period of 4-12 weeks. | The weighted mean difference (and 95% CI) between active drug arm and placebo arm at one year or the earliest time after one year. |
| SBP lowering effect | Ds | 8.8 [8.3 9.4] | 19.2 [18.0 20.3] | 7.3 [6.4 8.2] | 13.04 [12.55 13.53] |
| BBs | 9.2 [8.6 9.9] | 14.8 [13.7 15.9] | 9.3 [8.1 10.4] | 9.51 [8.85 10.16] |
| CCBs | 8.8 [8.3 9.2] | 16.4 [15.8 17.0] | 8.4 [7.2 9.7] | 8.90 [7.66 10.14] |
| ACEIs | 8.5 [7.9 9.0] | 15.6 [13.6 17.6] | 6.8 [6.0 7.7] | 21.14 [19.15 23.13] |

1) Two studies in grey were finally used to estimate the SBP lowering effect over time.

After the initiation of treatment, SBP generally shows a pattern to decrease rapidly in three months and then to stabilize long-term[2, 316, 317]. Based on the observed SBP lowering effects in three months from Wald et al’s review and one year from Wright et al’s review, the gradually reduced SBP lowering effect between three months and one year were assumed using the following logarithmic function (see Table ‎5.12):

*c=(1,2,3,4), where 1=3months, 2=6months, 3=9months and 4=12months.*

*Y=SLE4-SLE1*

*X=EXP(1/Y\*LN(4))*

*SLEc=SLEc-1+LOG(c,X)* Equation 5.5.

Table .. Absolute SBP lowering effects accumulated over one year

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | SLE at three months observed in the Wald’s study | Expected SLEs  at 6 and 9 months | | SLE at 12 months observed in the Wright et al’s study |
| 3 months | 6 months | 9 months | 12 months |
| Ds | 7.3 | 10.17 | 11.85 | 13.04 |
| BBs | 9.3 | 9.41 | 9.47 | 9.51 |
| CCBs | 8.4 | 8.65 | 8.80 | 8.90 |
| ACEIs/ARBs | 6.8 | 13.97 | 18.16 | 21.14 |

1) **SLE** stands for SBP lowering effects.

The current hypertension SDDP model assumes that the BBs and CCBs have little incremental SBP lowering effect after three months, whereas Ds and ACEIs/ARBs gradually drop SBP over one year. Many factors Wald et al’ and Wright et al’s systematic reviews were suspected of causing this difference in the SBP lowering effect at three months and 12 months. Whereas the Wald et al’s systematic review included more trials but short-term with less participants (i.e., 42 trials including 10,968 participants), the Wright et al’s systematic reviews included less trials but long-term with more participants (24 trials with 58,040 participants). Crossover studies were included in the Wald et al’s systematic review, while excluded in the Wright et al’s systematic review, which would have the effect of minimising differences between estimates of treatments. The average initial SBP of participants was 156.14 mmHg in Wald et al’s review and 168.88 mmHg in the Wright et al’s review. No clinical evidence was identified to support the different speed of SBP lowering effect across antihypertensive drugs.

Another way to estimate the time-dependent SBP lowering effects is using the SBP data observed in clinical trials. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) reported the annual change in SBP during the five years of using Ds (chlorthalidone), CCBs (amlodipine) and ACEIs (lisinopril)[317]. The Dutch-TIA trial also provided information about the change in SBP over 5.5 years where an atenolol-based regimen was compared with placebo[318]. These RCTs have the advantage of providing the observed data over a long time in a controlled population, but the result can be sensitive depending on the study design and the characteristics of participants. However, no RCT tested the four single treatment options included in this study at the same study design. Furthermore, the participants in both studies are not similar to the population in the hypertension SDDP model. As both methods had a certain level of uncertainty, the base-model was built using the estimated SBP lowering effects based on the Wald’s and Wright et al’s systematic review and sensitivity analyses were undertaken with the values reported in ALLHAT and Dutch-TIA.

Regardless of the class of antihypertensive drugs, combining two drugs from different classes of antihypertensive drugs has shown an additive effect. Law et al’s review showed that the blood pressure lowering effects of different classes of antihypertensive drugs were independent and additive based on the observed average reductions of two different drugs on blood pressure separately and in combination[282, 319]. Wald et al reconfirmed the additive effect with the ratio of observed to estimated additive SBP lowering effect from combining antihypertensive drugs, which was 1.01 (0.90-1.12) across all classes of antihypertensive drugs[315]. The additive effects between BBs and Ds[320], between CCBs and Ds[321], between CCBs and BBs[322], and between CCBs and ACEIs[116] have been also proved in RCTs. Although there was no clear evidence on the additive effect of three-drug combinations, Law et al suggested that the effect of three-drugs in combination would be not much different with two-drug combinations[282, 319]. This study assumed that the SBP lowering effect of both two and three-drug combinations was additive as following:

, for two-drug combinations

for three-drug combinations Equation 5.6.

Figure ‎5.1 shows the SBP lowering effect over time where the additive effect of two or three-drug combinations was assumed.

Figure .. The absolute SBP lowering effect of single drugs and two or three drug combinations over time

The SBP lowering effect may be different depending on the baseline SBP before treatment. In order to consider the population variation of each treatment effect depending on the baseline SBP, the absolute SBP lowering effect was converted to the relative SBP lowering effect based on pre-treatment SBP as following:

*Relative SLE (%) = (Absolute SLE / pre-treatment SBP)\*100* Equation 5.7.

The average initial SBP of participants was 156.14 mmHg in Wald et al’s review and 168.88 mmHg in the Wright et al’s review; the relative SLE was fitted to the average of the initial SBPs from those two systematic reviews (i.e., 162.51 mmHg). Table ‎5.13 shows the relative SBP lowering effects where a single drug, two-drug combination or three-drug combination is used consistently over one year.

As the SBP reduction due to the previous drugs were considered in the baseline SBP of each period, it was assumed that the SBP lowering effect of the first drug was not counted towards the effect of the second, third or fourth-line drug once a drug was switched. As the first-line drug was taken away and moved to the second, third and fourth-line drug, the SBP reduction due to the first drug should not remain over the next period because of the effect of stopping the first drug. Therefore, those values in the second column in Table ‎5.13 were used as the SBP lowering effect of the newly selected drug(s) and the incremental SBP lowering effects were used as the SBP lowering effect where the same drug was continuously used in the next cycle.

Table .. Relative SBP lowering effects (%) accumulated over one year

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | 3 months | 6 months | 9 months | 12 months |
| Ds | 4.5 (9.7) | 6.3 (12.4) | 7.3 (12.4) | 8.0 (15.0) |
| BBs | 5.7 (10.3) | 5.8 (12.5) | 5.8 (12.5) | 5.9 (14.6) |
| CCBs | 5.2 (13.9) | 5.3 (14.1) | 5.4 (14.1) | 5.5 (14.4) |
| ACEIs/ARBs | 4.2 (13.4) | 8.6 (12.2) | 11.2 (12.2) | 13.0 (11.1) |
| Ds+BBs | 10.2 (14.1) | 12.0 (17.6) | 13.1 (17.6) | 13.9 (21.0) |
| Ds+CCBs | 9.7 (16.9) | 11.6 (18.9) | 12.7 (18.9) | 13.5 (20.8) |
| Ds+ACEIs/ARBs | 8.7 (16.5) | 14.9 (17.6) | 18.5 (17.6) | 21.0 (18.7) |
| BBs+CCBs | 10.9 (17.3) | 11.1 (18.9) | 11.2 (18.9) | 11.3 (20.5) |
| BBs+ACEIs/ARBs | 9.9 (16.9) | 14.4 (17.6) | 17.0 (17.6) | 18.9 (18.4) |
| CCBs+ACEIs/ARBs | 9.4 (19.3) | 13.9 (18.7) | 16.6 (18.7) | 18.5 (18.2) |
| Ds+BBs+CCBs | 15.4 (19.8) | 17.4 (22.6) | 18.5 (22.6) | 19.4 (25.4) |
| Ds+BBs+ACEIs/ARBs | 14.4 (19.5) | 20.6 (21.6) | 24.3 (21.6) | 26.9 (23.7) |
| Ds+CCBs+ACEIs/ARBs | 13.8 (21.6) | 20.2 (22.6) | 23.9 (22.6) | 26.5 (23.6) |
| BBs+CCBs+ACEIs/ARBs | 15.1 (21.9) | 19.7 (22.6) | 22.4 (22.6) | 24.3 (23.3) |

1) SDs are given in parentheses. Appendix 6 provides the SDs of the individual studies included in the Wald et al’s and Wright et al’s systematic reviews. The pooled SDs are the weighted average of the individual SDs by the number of participants in each study. They were adjusted to a relative value based on the mean initial SBPs of the Wald et al’s and Wright et al’s systematic reviews (i.e., 162.51 mmHg) .

### Conventional RR approach for the long-term CVD model

The conventional RR approach was used for the CVD prevention effect of antihypertensive drugs in the long-term CVD model. The RRs of antihypertensive drugs to UA, MI, Stroke and death were taken from the NICE hypertension models[63, 223]. The RRs to HF and DM were replaced with the up-to-date meta-analyses for the treatment effects of antihypertensive drugs on DM and HF[323, 324]. The same RRs were applied to patients with prior CVD identified (see Table ‎5.14).

The overall treatment effectiveness of combination treatment was calculated based on the multiplicative effect, as done in previous similar studies[276, 325, 326] (see Equation 5.8). For the joint effects of combination treatment, the RRs of each drug in the combination were assumed to be independent.

, for two-drug combinations

, for three-drug combinations Equation 5.8.

Table .. Relative risks to CVDs, DM and death depending on antihypertensive drug

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | UA | MI | Stroke | HF | DM | Death |
| Ds | 0.893 | 0.78 | 0.69 | 0.6 | 0.985 | 0.91 |
| BBs | 0.984 | 0.855 | 0.851 | 0.88 | 0.887 | 0.939 |
| CCBs | 0.881 | 0.796 | 0.656 | 0.84 | 0.739 | 0.883 |
| ACEIs/ARBs | 1.01 | 0.85 | 0.69 | 0.728 | 0.64 | 0.9 |
| Ds+BBs | 0.879 | 0.667 | 0.587 | 0.528 | 0.874 | 0.854 |
| Ds+CCBs | 0.787 | 0.621 | 0.453 | 0.504 | 0.728 | 0.804 |
| Ds+ACEIs/ARBs | 0.902 | 0.663 | 0.476 | 0.437 | 0.630 | 0.819 |
| BBs+CCBs | 0.867 | 0.681 | 0.558 | 0.739 | 0.655 | 0.829 |
| BBs+ACEIs/ARBs | 0.994 | 0.727 | 0.587 | 0.641 | 0.568 | 0.845 |
| CCBs+ACEIs/ARBs | 0.890 | 0.677 | 0.453 | 0.612 | 0.473 | 0.795 |
| Ds+BBs+CCBs | 0.774 | 0.531 | 0.385 | 0.444 | 0.646 | 0.755 |
| Ds+BBs+ACEIs/ARBs | 0.887 | 0.567 | 0.405 | 0.384 | 0.559 | 0.769 |
| Ds+CCBs+ACEIs/ARBs | 0.795 | 0.528 | 0.312 | 0.367 | 0.466 | 0.723 |
| BBs+CCBs+ACEIs/ARBs | 0.876 | 0.578 | 0.385 | 0.538 | 0.420 | 0.746 |

### Adverse effects

Two systematic reviews that quantified the occurrence of AEs of antihypertensive drugs in primary hypertension were identified (see Table ‎5.15). The primary interest of Ross’s systematic review was the prevalence of discontinuations due to AEs (DAEs)[278]. Compared with placebo, only CCBs had higher frequency of DAEs in treated patients, although the difference 0.0055 (95% CI -0.012 to 0.022) was not statistically significant. AE was also examined as the secondary outcome and categorised according to the World Health Organization Adverse Reaction Dictionary (WHOARD). Across drug classes, the occurrence of AEs was not significantly different to each other.

Law et al’s systematic review examined the placebo-adjusted probability of the symptoms that might be plausibly caused by the antihypertensive drug[282]. The symptoms included dizziness, impotence, nausea, muscle cramp, skin rash, fatigue, cold extremities, dyspnoea, cough, back pain, flushing, ankle oedema and so on. At the standard dose, the percentages of persons with the undesirable symptoms attributable to Ds, BBs, CCBs, ACEIs and ARBs were 9.9%, 7.5%, 8.3%, 3.9% and 0% respectively. The placebo-adjusted prevalence of severe symptoms that stopped treatment with the drug were 0.1%, 0.8%, 1.4%, 0.1% and -0.2%, respectively.

Compared with Ross et al’s review, Law et al’s review provided more comprehensive information including the AEs of combination treatment and adverse metabolic change. Law et al’s review showed that in 33 trial arms two drugs together caused the undesirable symptoms in 7.5% (95% CI 5.8-9.3%), which is significantly lower than the value of 10.4% (twice 5.2%) expected with an additive effect (p=0.03). Various metabolic changes such as abnormalities in glucose and lipid metabolism also have been examined: any adverse metabolic change in TC and its sub-fractions was negligible. This study selected the Law et al’s study by priority for the risk of AEs or DAEs for antihypertensive drugs.

The reported incidence of AEs can be various depending on the definition and the thresholds for reporting AEs. It is also common that a patient has more than one AE. On the other hand, DAEs counts only one case per patient, whereas the actual timing of DAEs is rarely reported[278]. As DAEs are more explicit to capture the cases, the incidence of DAEs reported in Law et al’s study was used for the risk of AE in the base model, and the prevalence of AEs reported in the same study were tested in a sensitivity analysis.

Table .. Comparison between Ross et al’s and Law et al’s systematic reviews

|  |  |  |  |
| --- | --- | --- | --- |
|  | | Law et al, 2003[282] | Ross et al, 2001[278] |
| Participants | | Persons receiving an antihypertensive drug. Trials in which patients were recruited because of HF or other cardiovascular disorders were excluded. | Adults with essential hypertension. Hypertensive patients who might have DM were accepted, but any other complicating illness (e.g., congestive HF or renal failure) were not accepted. |
| Interventions | | A specified fixed dose of any D, BBs, CCBs or ACEIs/ARBs. | Ds, BBs, CCBs, ACEIs, ARBs and AAB. Studies using within-group dose titrations were acceptable. |
| Included studies | | Randomised, placebo-controlled trials followed up at least 2 weeks. Cross-over trials were accepted if they met the inclusion criteria. | Randomised, parallel and controlled trials, which followed up at least 1 week and enrolled at least 10 patients. |
| Database | | MEDLINE, the Cochrane collaboration and Web of Science databases. | MEDLINE, Current Contents CD-ROM and Cochrane Library. |
| Search period | | 1966–2000 | 1990-1999 |
| No of included trials | | 354 trials, 791 treatment groups comprised 39,879 participants. | 190 trials, 409 treatment groups comprised 28,922 participants. |
| Duration | | The median duration was 4 weeks; the range was 2–15 weeks. Nine trials lasted 5–36 months. | Ranged from 1.4 weeks–2 years; 22 studies lasted 1 month or less, and 4 continued for longer than one year. |
| Meta-analysis | | The difference in the proportions of AEs between the treated and placebo groups were weighted by the numbers of participants. Parallel group and cross-over trials yielded similar results, so they were combined. | Treatment group frequencies divided by the number of patients analysed for safety in each group were pooled across studies and grouped by category of antihypertensive drug, using fixed effects models and random effects models. |
| AEs  (%) | Definition | The prevalence of symptoms recorded that the authors considered might plausibly be caused by the drug in the treated and placebo groups (placebo-adjusted). | Any anxious, unintended effect occurring at doses administered to humans for therapy that is not attributable to therapeutic failure or drug abuse (not adjusted by placebo). |
| Ds | 9.9 (6.6 to 13.2) | 39.3 |
| BBs | 7.5 (4.0 to 10.9) | 32.3 |
| CCBs | 8.3 (4.8 to 11.8) | 34.3 |
| ACEIs | 3.9 (-0.5 to 8.3) | 36.1 |
| ARBs | 0 (-5.4 to 5.4) | 38.8 |
| Placebo | - | 37.3 |
| DAEs  (%) | Definition | The prevalence of symptoms severe enough for the patients to stop taking the tablets in the treated and placebo groups. | The difference in the risk of DAEs between the active drug group and placebo. |
| Ds | 0.1 (-0.7 to -0.9) | -0.027 (-0.053 to -0.001) |
| BBs | 0.8 (0.3 to 1.4) | -0.0018 (-0.044 to 0.008) |
| CCBs | 1.4 (0.4 to 2.4) | 0.0055(-0.012 to 0.022) |
| ACEIs | 0.1 (-0.3 to 0.6) | -0.014 (-0.029 to 0.002) |
| ARBs | -0.2 (-0.5 to 0.2) | -0.02 (-0.038 to -0.001) |

Based on the Law et al’s study, it was assumed that the AEs of two or three-drug combinations were less than an additive effect as following:

Equation 5.9.

It was assumed that this equation considers the interaction between the drugs combined implicitly. Depending on the combined drugs, the ratio may be various. Antihypertensive drugs from different classes may offset AEs from each other (e.g., Ds decrease edema occurring from CCBs[327]), or aggravate a specific AE (e.g., BBs, together with verapamil or diltiazem, may produce marked bradycardia and AV block, and may precipitate HF[328]; and ACEIs given together with a potassium-sparing D may cause the marked hyperkalemia[329]). However, these positive or negative interactions between the combined drugs were limited to be quantified.

### Quality of life

Health outcomes were estimated in terms of QALYs. The age-dependent baseline utility was estimated using the utility function developed based on the data used in the NICE statin appraisal[330]:

*Baseline utility by age = 1.060-0.004\*Age , where Age>15* Equation 5.10.

Hypertension is asymptomatic for many years: thus, hypertension in itself has a negligible impact on the QoL. Even considering the possible side effects, financial costs of long-term treatment and any inconvenience of regular check-ups, the negative impact on QoL from hypertension or taking an antihypertensive drug was negligible[247, 331, 332]. As such, existing CEAs in primary hypertension often excluded the disutility due to hypertension or taking an antihypertensive drug[63, 246, 333, 334]. This hypertension SDDP model also assumed that there is no disutility associated with hypertension and antihypertensive treatment.

Multiplicative utility weights for various types of CVDs and DM came from the NICE hypertension model, which conducted an extensive literature review to identify the best available utility estimates by health state[63] (see Table ‎5.16). All utility weights for health states were adjusted for different age groups by the age-dependent baseline utility. Discount rate, 3.5%, was applied to QALYs.

Table .. Annual costs and utility weights by CVD and DM

|  |  |  |
| --- | --- | --- |
| Health states | Utility weights | Annual costs (£) |
| No event | 1 | 59.57 |
| UA | 0.77 | 579.61 |
| Post-UA | 0.8 | 225.26 |
| MI | 0.76 | 5,859.36 |
| Post-MI | 0.88 | 225.26 |
| Stroke | 0.63 | 10,599.02 |
| Post-stroke | 0.88 | 2,849.33 |
| HF | 0.71 | 3,564.58 |
| Post-HF | 0.88 | 225.26 |
| DM | 0.9 | 1,190.03 |

### Costs

As antihypertensive treatment is lifelong treatment, it was assumed that the patients took antihypertensive drugs for the remainder of their lives. Annual drug costs came from the NICE hypertension model[63]. NICE calculated the drug costs per year based on the prices quoted in the British National Formulary 60 (September 2010). The optimal doses were provided by clinical members of the Guideline Development Group (GDG). The costs of base-case represent the cost for the most commonly used drug in each class based on the 2008 NHS Prescription Cost Analysis.

As recommended in the NICE guideline, it was assumed that both the controlled and uncontrolled patients had an annual GP check-up, which included physical examination, routine laboratory tests and other diagnostic procedures[63]. The estimated cost for the annual check-up in the NICE hypertension model, which was £56, was converted to 2011/12 value using the Personal Social Services Research Unit (PSSRU) 2011 inflation indices[335].

Table .. Antihypertensive drug costs per year

|  |  |  |  |
| --- | --- | --- | --- |
|  | Base-case (£) | Cheapest drug (£) | Most expensive drug (£) |
| Ds | 11.86 | 11.86 | 50.74 |
| BBs | 13.17 | 13.17 | 485.45 |
| CCBs | 18.64 | 18.64 | 431.22 |
| ACEIs | 20.73 | 20.71 | 163.08 |
| ARBs | 25.94 | 25.94 | 263.71 |

Annual costs of each CVD estimated in the ScHARR statin model were also adjusted to 2011/2012 value using the Unit Costs of Health and Social Care 2011 inflation indices[286, 335]. Those costs include the overall expenses related to drug, GP contact, hospitalisation and surgical procedure for appropriate patients. Subsequent year costs of each CVD were applied to the post-CVD states (see Table ‎5.16).

As the costs for HF and DM were not included in the ScHARR statin model[286], they came from the financial analysis of HF community services of South London Cardiac and Stroke Network[336] and Currie et al’s study, which estimated primary care treatment costs for people with type 1 and type 2 DM in the United Kingdom[337]. All the annual costs were converted to 3-month basis. 3.5% of discount rate was applied to costs. The threshold of the incremental cost-effectiveness ratio (ICER) was assumed to be £30,000.

### Uncertainty

PSA was conducted, where probability distributions were assigned as per Table ‎5.8. The normal distribution was used to model the patient-level variation in the pre-treatment SBP in each period and the SBP during the maintenance therapy. The HR of DM by drug was characterised by a lognormal distribution. The uncertainty in the occurrence of AEs was accounted for by using a beta distribution.

A lognormal distribution was assumed for the SBP lowering effect. For each drug, the SD of the SBP lowering effects was calculated by the weighted sum of the individual SDs, from the included studies in Wald et al’s and Wright et al’s reviews, and the number of participants (see Appendix 6). Assuming the SDs in the placebo arm and the active drug arm were independent and their variances were equal, the pooled SD of the mean difference between the placebo arm and the active drug arm was approximated using Equation 5.11[338]. Equation 5.11 was also used to calculate the SD of two or three combinations, which assumed that the SBP lowering effect had an additive effect of two or three single drugs.

*SD = SQRT (SD1^2+ SD2^2)* Equation 5.11.

Where 95% CIs or standard errors (SEs) were provided, they were transformed to SD using Equation 5.12, and then combined using Equation 5.11.

*SE = (Upper limit –Lower limit)/3.92,* where a normal distribution of SE is assumed.

*SD = SE\*SQRT(N)* Equation 5.12.

As the hypertension SDDP model included randomness, the simulation produced results that changed randomly with each run. Therefore the final value of the objective function, *f(π,)* was estimated by the average total net benefit from 100 PSA runs for a specific policy π (i.e., *G(π,ωi))* :

Equation 5.13.

where *ω1, ω2, ..., ω100* is a random sample of *100* independent, identically distributed realizations of the random vector *ω*.

In principle, the simulation should average out the randomness after many runs; however, multiple runs for each sequential treatment policy increase the computation time considerably. Considering the given computational resources and time to implement all tests planed in this thesis, the number of replications was set to 100.

Table .. Parameters of key variables for PSA

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Key parameters | | | Distribution | Parameters | | | Reference |
| Mean | SD | |
| LB | UB |
| Population characteristics | | Initial SBP | Lognormal | 173.5 | 21.1 | | Burke et al, 2006[283] |
| TC, HDL, BMI | Fixed | Table ‎5.1 | . | . | HSE, 2011 (Raw dataset) [284] |
| Distribution of first-onset CVD | | | Fixed | Table ‎5.2 | . | . | ScHARR, 2007[286]; NICE, 2011[63] |
| Death | | All-cause mortality | Fixed | Table ‎5.3 | . | . | ONS, 2011[287] |
| Non-circulatory death | Fixed | Table ‎5.4 | . | . | BHF, 2012[288] |
| Maintenance SBP | | Male | Normal | 134.89 | 16.85 | | HSE, 2011 (Raw dataset) [284] |
| Female | Normal | 134.99 | 18.94 | | HSE, 2011 (Raw dataset)[284] |
| Baseline risk of primary and secondary CV events | | | Fixed | Table ‎5.9 | . | . | NICE, 2011[63] |
| HR of type 2 DM | | Ds | Lognormal | 0.91 | 0.73 | 1.13 | Gress et al, 2000[261] |
| BBs | Lognormal | 1.28 | 1.04 | 1.57 |
| CCBs | Lognormal | 1.17 | 0.83 | 1.66 |
| ACEIs/ARBs | Lognormal | 0.98 | 0.72 | 1.34 |
| AEs | | Ds | Beta | . | 1 | 999 | Law et al, 2003[282] |
| BBs | Beta | . | 8 | 992 |
| CCBs | Beta | . | 14 | 986 |
| ACEIs/ARBs | Beta | . | 0 | 1000 |
| RRs in the long-term CVD model | | | Fixed | Table ‎5.14 | . | . | NICE, 2011[63] |
| Drug costs | Ds | | Gamma | 11.86 | 11.86 | 50.74 | NICE, 2011[63] |
| BBs | | Gamma | 13.17 | 13.17 | 485.45 |
| CCBs | | Gamma | 18.64 | 18.64 | 431.22 |
| ACEIs/ARBs | | Gamma | 21.77 | 21.76 | 183.21 |
| CVD costs | | | Fixed | Table ‎5.16 | . | . | NICE, 2011[63]; ScHARR, 2007[286]; Currie et al, 2010[337]; http://www.slcsn.nhs.uk/cardiac-hf.html |
| Utility weight | | | Fixed | Table ‎5.16 | . |  | NICE, 2011[63] |

### Other assumptions and limitations

#### (1) Interaction between drugs

Clinical interaction between antihypertensive drugs can result in either additive, greater than additive or less than additive effects. Two different types of interactions exist in the framework of the hypertension SDDP: one is the SBP lowering effect of combining two drugs, and the other is the SBP lowering effect depending on the drug ordering. Based on the given evidence, this hypertension SDDP model assumed that the drugs combined were independent and had an additive SBP lowering effect, whereas the AEs were slightly less than the value estimated under the additive assumption. The CVD prevention effectiveness of combination treatment was assumed to be multiplicative.

The clinical interaction between the current drug and the next drug is also important to capture the sequential treatment effect. For example, the SBP lowering effect of Ds may be different depending on whether they are used initially or as a second, third or fourth-line treatment and which drug was used previously. The difference is possibly attributable to not just the patient’s characteristics (i.e., whether the patient is naïve or not), but also the impact of drug ordering. If someone starts treatment with a D and then adds a BB to the D as the second-line therapy, the clinical interaction between those drugs used in sequence is more complex to explain. Additional randomised intervention is not preferred in clinical trials because the efficacy would be confounded by the effects of the other treatments[339]. Furthermore, most existing evidence on the interactions between drugs used in sequence were described in terms of pharmacokinetic or pharmacodynamics, rather than clinical outcomes[340, 341]. Law et al showed that the blood pressure-lowering effect of a second-line drug was approximately 1 mm Hg less for each 10 mm Hg decrement in pre-treatment blood pressure[282]. The change of SBP lowering effect due to pre-treatment blood pressure was considered in this study by using the relative SBP lowering effect to the baseline SBP. However, the hypertension SDDP model was limited to consider the further incremental or decremented impact associated with the second, third or fourth-line drug in patients who have not controlled by the previous drug(s).

#### (2) Compliance

Hypertension is largely asymptomatic and is not a sufficiently serious disease to cause death directly; for this reason, compliance with antihypertensive treatment is generally poor. Some studies have found that more than half of all persons being treated by antihypertensive drugs did not take their drug properly[342-346]. This is one of the possible reasons that the patient may not respond to antihypertensive treatment[347, 348].

Good compliance is associated with better blood pressure lowering effect[349]. The relationship between better compliance and better clinical outcomes such as CHD and survival also has been confirmed[350, 351]. Regardless of the type of disease, however, the lack of reliable data is a common problem in CEAs when trying to consider the expected change in costs and health benefits resulting from compliance. Thus, the potential impact of compliance has been largely neglected in previous CEAs or relied on clinical opinions or assumptions[352]. With the same reason, this hypertension SDDP model did not consider the relationship between compliance and health outcomes (i.e., SBP lowering effect and CVD risk reductions).

#### (3) Lifestyle modification and other treatments

Lifestyle modification is recommended to patients with primary hypertension either before the start of pharmacological treatment or during the pharmacological treatment[8, 9, 63]. There is considerable evidence suggesting that lifestyle modification, such as smoking cessation, exercise, diet and relaxation, can reduce blood pressure and CVD risk[353-356]. Clinical guidelines also recommend the consideration of additional therapy, such as lipid-lowering drugs and antiplatelet therapy, for the patients at higher risk (i.e., with target organ damage, established CVD, DM, CKD or an estimated 10-year CVD risk ≥20%)[8, 9, 63]. The benefit of adding these drugs to antihypertensive treatment was well established[357-360]. To exclude the confounding effect and to reduce the complexity, however, the hypertension SDDP model assumed that the proportions of patients who adopted lifestyle modification or took lipid-lowering drugs and antiplatelet therapy were the same in each treatment option.

### Comparison between the hypertension SDDP model and the NICE hypertension model

The underlying evaluation model of the hypertension SDDP model was constructed based on the NICE hypertension model, which has been regularly updated since it was developed in 2006; therefore, both models share similarities in terms of the population’s characteristics, single treatment options and the structure of CVD model. However, the ultimate goals of the two models are very different. The objective of the NICE hypertension model is to identify the most cost-effective initial drug for the management of hypertension in primary care, whereas the objective of this hypertension SDDP model is to identify the optimal sequential treatment strategy in primary hypertension. Accordingly, the comparators in the NICE hypertension model are single antihypertensive drugs, whereas the comparators in the hypertension SDDP model are all possible combinations of single drugs and two or three-drug combinations. While the NICE hypertension model assumed that the initial drugs were used continuously over the follow-up period, the hypertension SDDP model allowed changing treatment regimen depending on the patient’s health state (i.e., the result of previous treatment) during the drug switching period.

Although the included health states are the same in both the NICE hypertension model and the hypertension SDDP model, the structures are different. While the NICE hypertension model is a conventional Markov model, the hypertension SDDP model has a successive decision tree with an add-on Markov model. The clinical drug switching rules were incorporated into the successive decision tree. To populate the clinical drug switching rules, the surrogate outcome modelling based on SBP was used. The CVD risk was calculated using QRISK2, which is a validated risk engine for the UK population. A shorter time cycle of three months, compared with the NICE hypertension model of six months, was selected to better reflect the time to revisit the clinician after treatment initiation and to decide whether the drug is well-responded and needs to be switched.

In addition to the novel underlying evaluation model, the hypertension SDDP model has an additional outer loop that inputs potential sequential treatment policies to the underlying evaluation model and assesses the optimality of the current policy based on the treatment net benefit. Due to the computational complexity and the size of the problem, Matlab (version 8.1, R2013a) was used to develop the model, whereas the NICE hypertension model was built by using Microsoft Excel.

Table .. Comparison between the SDDP hypertension model and the NICE hypertension model

|  |  |  |
| --- | --- | --- |
|  | SDDP model in primary hypertension | NICE hypertension model[63] |
| Objective | * To identify the optimal treatment sequence, which maximises the total net benefit. | * To identify the initial drug, which is the most cost-effective compared with competing major antihypertensive drugs. |
| Perspective | * UK NHS perspective. | * UK NHS perspective. |
| Time | * Total follow-up period: Lifetime Cycle: 3months. | * Total follow-up period: Lifetime Cycle: 6 months. |
| Population | * Patients newly diagnosed with primary hypertension excluding those with pre-existing CVD, HF or DM. | * Essential hypertension seen in primary care, excluding those with pre-existing CVD, HF or DM. |
| Cohort | * Different cohorts, defined by age (50, 60 and 70), gender and initial level of SBP (153.5, 163.5 and 173.5 mmHg). * Base-case population is 60-year old men with the SBP of 173.5 mmHg. | * Different cohorts defined by age (55, 65, 75 and 85), gender, CVD risk (0.5-5% per year), HF risk (0-5% per year) and DM risk (0-5% per year). * Base-case population is 65-year-old men and women with 2% CVD risk, 1% HF and 1.1% DM risk. |
| Modelling method | * Successive decision tree with an added-on Markov model (built by Matlab). | * Semi-Markov model (built by Excel). |
| Model structure | 1. Success.  2. Failure.   * Uncontrolled SBP without CVD. * UA. * MI. * Stroke. * HF. * DM.   3. Death. | * Well. * MI. * HF. * Stroke. * UA. * DM. * Death. |
| Treatment options | 4,128 combinations of:  •  Ds. •  BBs. •  CCBs. •  ACEIs/ARBs. | •  Do nothing. •  Ds. •  BBs. •  CCBs. •  ACEIs/ARBs. |
| Treatment effectiveness | * A surrogate outcome modelling based on SBP lowering effect. | * The conventional RR approach. |
| Outcome | * Total net benefit. | * Cost-effectiveness and total net benefit. |

# Modelling sequential drug decision problem for hypertension: Implementation

## Chapter overview

This chapter includes an overview of the developed simulation-based optimisation model. Particularly, this chapter describes how various optimisation methods including enumeration, GA, SA and RL are implemented alongside the underlying evaluation model described in the previous chapter. The summary of the functions and pseudo-codes of optimisation algorithms used in the hypertension SDDP model are provided.

## Overview of the hypertension SDDP optimisation model

The hypertension SDDP optimisation model consists of a set of functions written in m-files, which is the name of script file in Matlab (see Table ‎6.1). It starts with ‘OptModel’, which allows selecting different scenarios to test using one of the optimisation methods selected for implementation. The base model is designed to simulate a cohort of 60 year old male patients whose mean SBP was 173.5 mmHg. Every three months they experience one of three health states (i.e., *Success*, *Failure* or *Death)*. There are 14 potential active treatment options including four single drugs and their two or three drug combinations. No treatment is included only for the purpose of model validation, but not included in sequential treatment strategies. The number of drugs used for the drug switching period is four (i.e., the maximum number of drug switches is three). The applied decision rule restricted the first-line drug to a single drug and the second-line drug to either a single or two-drug combination. Three-drug combinations were only allowed after the use of two-drug combinations.

Table .. Summary of the functions included in the hypertension SDDP model

|  |  |
| --- | --- |
| Functions | Description |
| OptModel | Selects the scenario to test |
| TreeGenerator | Generates the health state space (i.e., a set of possible disease pathways). |
| PolicyGenerator | Generate the search space (i.e., a set of possible sequential drug treatment policies). |
| VasGenerator | Generates a matrix indicating which lines of drug treatment are used for a specific health state. |
| MTGenerator | Generates a matrix indicating whether the maintenance therapy is used and if so, how long it has been used. |
| TrtGenerator | Generates a treatment scenario for CVDs and DM. |
| Combinator | Performs permutation and combination with/without repetition. |
| EvModel | Calculates the value of the objective function where the decision space is not decomposed (i.e., where enumeration, SA or GA is used). |
| EvModelDC | Calculates the value of the objective function where the decision space is decomposed (i.e., where RL is used). |
| SBPmodelling | Simulates the SBP change after treatment using Monte Carlo sampling. |
| CVDmodelling | Computes CVD-related costs and effectiveness in long-term. |
| QRISK2 | Predicts the 10-year CVD risk using the QRISK2 equation. |
| Data | Provides the relevant data. |
| Enu | Solves the problem using enumeration. |
| SA | Solves the problem using simulated annealing. |
| GA | Solves the problem using genetic algorithm. |
| RL | Solves the problem using reinforcement learning. |
| Validation | Runs the validation model, which assumes a drug is used continuously over the follow-up period. |
| PostHoc | Implements descriptive cluster analysis and statistical analyses (including t-test, ANOVA and multiple comparison) based on the enumeration results. |

Different scenarios are tested depending on the selection of the parameters described in Table ‎6.2. The options for the optimisation algorithm includes enumeration, GA, SA and RL. The objective function can be either to maximise total benefit in the long-term or treatment success rate in the short-term. The number of drug switching period is modifiable: however, it is not recommended to extend more than eight periods because of the computational time. The hypertension SDDP model also allows solving the decision problem in different gender and age groups with various level of SBP at the beginning. Two data sets of SBP lowering effect are included. Treatment scenarios for UA, MI, stroke, HF and DM can be either a set of recommended drugs (i.e., using CCBs, BBs, BBs, ACEIs, ACEIs for UA, MI, stroke, HF and DM, respectively) or randomly selected. AEs can be defined by either the discontinuation due to AEs or the prevalence of any unfavourable symptoms that might be caused by the antihypertensive drug. The number of PSA runs is modifiable; it was set to 100 in the base-case. Both costs and QALYs were discounted at 3.5%. Willingness-to-pay for a unit of QALY was assumed to be £30,000.

The purpose of the function ‘TreeGenerator’ is to generate a decision tree, which includes a set of possible disease pathways for the drug switching period. The number of possible disease pathways is dependent on the number of potential health states (i.e., three health states including *Success*, *Failure* and *Death*) and the selected drug switching period (i.e., four periods in the base-case). Where infeasible disease pathways (i.e., *Success* or *Failure* followed *Death*) are excluded, a total number of 31 possible disease pathways are generated as per Table ‎6.3.

The function ‘PolicyGenerator’ generates a search space that includes a set of sequential treatment policies having the fixed length of four (see Table ‎6.4). The number of potential sequential treatment policies is dependent on the number of treatment options in each line of drug treatment (i.e., four options for the first-line, 10 options for the second-line and 14 options for subsequent lines of use), the maximum number of drug switching allowed (i.e., fixed to three in this study) and additional step-wise drug decision rules (e.g., three-drug combinations are only allowed after the use of two-drug combinations). 4,128 sequential treatment policies were generated with a combination of four integer numbers between 2 and 15 (see Table ‎6.4). For example, a specific treatment policy using “Ds-BBs-CCBs-ACEIs/ARBs” was coded as “2-3-4-5”. Then, a policy number from 1 to 4,128 was assigned to the 4,128 policies, which were sorted in ascending order based on the coded number for the first-line drug (i.e., policy number 1 denotes “2-3-4-5” and policy number 4,128 denotes “5-11-15-14”). The complete list of 4,128 treatment sequences is presented in Appendix 7.

The function ‘VasGenerator’ returns a 31 by 4 matrix, where 31 is the number of possible disease pathways and 4 is the number of selected drug switching period (see Table ‎6.5). The values in the matrix are an integer number between 1 and 4, which indicate what line of drug should be used on a specific health state. They are directly associated with the decision tree encoded like Table ‎6.3. For example, for the disease pathway of “1-1-1-1-1” in the first row of the decision tree in Table ‎6.3, the values in the matrix generated by ‘VasGenerator’ will be “1-2-3-4”, where the first-line drug is replaced with second, third and then fourth-line drugs for the patient who failed to achieve the treatment goal successively during the drug switching period. 0 was used for *Death*.

The purpose of the function ‘MTGenerator’ is to create a 31 by 4 matrix that indicates whether the maintenance therapy is used and if so, how long it is used (see Table ‎6.6). This matrix is also associated with the decision tree in Table ‎6.3. ‘MTGenerator’ assigns 0 for *Failure* and an integer number between 1 and 3 for *Success* depending on the previous health states. If a patient achieves the treatment goal with the initial drug (i.e., second column and sixteenth row in Table ‎6.3), the value in the same location of Table ‎6.6 is 1. If the patient consistently achieves the treatment goal in the third and fourth periods (i.e., 3rd column and 23th rows and 4th column and 26th row in Table ‎6.3), the values in the same location of Table ‎6.6 are 2 and 3, respectively. These numbers facilitates the use of different levels of SBP lowering effect depending on the period in which a specific drug is used. If the current drug is replaced with a new drug in the second period, the SBP change in that period is determined based on the SBP lowering effect of the new drug in three months; otherwise, the SBP lowering effect is cumulative at 6, 9 or 12 months, depending on how long the current drug has been used.

Table .. Scenario selection to implement the hypertension SDDP model

|  |  |
| --- | --- |
| Parameter | Scenario selection |
| Fixed parameters | |
| The length of drug sequence | 4 |
| Cycle length | 3 (months) |
| The number of health states | 3 |
| The number of potential treatment options | 14 |
| Additional decision rule | Stepwise drug selection |
| Variable parameters | |
| Optimisation method | NaN = Validation model  'Enu' = Enumeration, which provides the exact solution.  'SA' = Simulated annealing, which provides an approximate solution.  'GA' = Genetic algorithm, which provides an approximate solution.  'RL' = Reinforcement learning, which provides an approximate solution. |
| The objective of the model | 1 = To maximise the total treatment net benefit in long-term (until 100 years-old)\*  2 = To maximise the treatment success rate in short-term (only in the drug switching period) |
| The number of drug switching period | 4 = Total drug switching period is one year (i.e., 3 months x 4)\*  6 = Total drug switching period is 1.5 year (i.e., 3 months x 6)  8 = Total drug switching period is 2 year (i.e., 3 months x 8) |
| Gender | 1 = Male\* and 2 = Female |
| Initial age | 50, 60\* and 70 |
| Initial SBP | 173.5 (SD 21.1) |
| SBP lowering effect | 1 = Based on Wald’s and Wright et al’s systematic reviews\*  2 = Based on ALLHAT and Dutch-TIA |
| Treatment scenario for UA, MI, Stroke, HF and DM | 1 = A set of recommended drugs\*  2 = Random selection |
| The risk of AEs | 1 = Discontinuation due to adverse effects\*  2 = Any unfavourable symptoms, which might be caused by the drug |
| The number of PSA repetitions | 100 |
| Discount rate | 3.5% |
| Willingness-to-pay | £30,000 |

1) The values with \* were used in base-case.

Table .. Matrix of the decision tree generated by ‘TreeGenerator’

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Number | The combinations of potential health states | | | | |
| t=1 | t=2 | t=3 | t=4 | t=4 |
| 1 | 1 | 1 | 1 | 1 | 1 |
| 2 | 1 | 1 | 1 | 1 | 2 |
| 3 | 1 | 1 | 1 | 1 | 3 |
| 4 | 1 | 1 | 1 | 2 | 1 |
| 5 | 1 | 1 | 1 | 2 | 2 |
| 6 | 1 | 1 | 1 | 2 | 3 |
| 7 | 1 | 1 | 1 | 3 | 3 |
| 8 | 1 | 1 | 2 | 1 | 1 |
| 9 | 1 | 1 | 2 | 1 | 2 |
| 10 | 1 | 1 | 2 | 1 | 3 |
| 11 | 1 | 1 | 2 | 2 | 1 |
| 12 | 1 | 1 | 2 | 2 | 2 |
| 13 | 1 | 1 | 2 | 2 | 3 |
| 14 | 1 | 1 | 2 | 3 | 3 |
| 15 | 1 | 1 | 3 | 3 | 3 |
| 16 | 1 | 2 | 1 | 1 | 1 |
| 17 | 1 | 2 | 1 | 1 | 2 |
| 18 | 1 | 2 | 1 | 1 | 3 |
| 19 | 1 | 2 | 1 | 2 | 1 |
| 20 | 1 | 2 | 1 | 2 | 2 |
| 21 | 1 | 2 | 1 | 2 | 3 |
| 22 | 1 | 2 | 1 | 3 | 3 |
| 23 | 1 | 2 | 2 | 1 | 1 |
| 24 | 1 | 2 | 2 | 1 | 2 |
| 25 | 1 | 2 | 2 | 1 | 3 |
| 26 | 1 | 2 | 2 | 2 | 1 |
| 27 | 1 | 2 | 2 | 2 | 2 |
| 28 | 1 | 2 | 2 | 2 | 3 |
| 29 | 1 | 2 | 2 | 3 | 3 |
| 30 | 1 | 2 | 3 | 3 | 3 |
| 31 | 1 | 3 | 3 | 3 | 3 |

1) **1, 2** and **3** represent *Failure* , *Success* and *Death*, respectively.

Table .. Matrix of the search space generated by ‘PolicyGenerator’

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Policy number | Treatment sequence. | | | |
| First-line | Second-line | Third-line | Fourth-line |
| 1 | 2 | 3 | 4 | 5 |
| 2 | 2 | 3 | 4 | 6 |
| 3 | 2 | 3 | 4 | 7 |
| 4 | 2 | 3 | 4 | 8 |
| 5 | 2 | 3 | 4 | 9 |
| 6 | 2 | 3 | 4 | 10 |
| 7 | 2 | 3 | 4 | 11 |
| 8 | 2 | 3 | 5 | 4 |
| 9 | 2 | 3 | 5 | 6 |
| 10 | 2 | 3 | 5 | 7 |
| 11 | 2 | 3 | 5 | 8 |
| 12 | 2 | 3 | 5 | 9 |
| 13 | 2 | 3 | 5 | 10 |
| 14 | 2 | 3 | 5 | 11 |
|  | .  .  . | | | |
| 4118 | 5 | 11 | 15 | 2 |
| 4119 | 5 | 11 | 15 | 3 |
| 4120 | 5 | 11 | 15 | 4 |
| 4121 | 5 | 11 | 15 | 6 |
| 4122 | 5 | 11 | 15 | 7 |
| 4123 | 5 | 11 | 15 | 8 |
| 4124 | 5 | 11 | 15 | 9 |
| 4125 | 5 | 11 | 15 | 10 |
| 4126 | 5 | 11 | 15 | 12 |
| 4127 | 5 | 11 | 15 | 13 |
| 4128 | 5 | 11 | 15 | 14 |

1) **1** represents no treatment; **2** represents Ds; **3** represents BBs; **4** represents CCBs; **5** represents ACEIs/ARBs; **6** represents Ds+BBs; **7** represents Ds+CCBs; **8** represents Ds+ACEIs/ARBs; **9** represents BBs+CCBs;**10** represents BBs+ACEIs/ARBs; **11** represents CCBs+ACEIs/ARBs; **12** represents Ds+BBs+CCBs; **13** represents Ds+BBs+ACEIs/ARBs; **14** represents Ds+CCBs+ACEIs/ARBs and **15** represents BBs+CCBs+ACEIs/ARBs.

Table .. Matrix of the actual drug use generated by ‘VasGenerator’

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Number | The position of the drug used at *t* in the treatment sequence. | | | |
| t=1 | t=2 | t=3 | t=4 |
| 1 | 1 | 2 | 3 | 4 |
| 2 | 1 | 2 | 3 | 4 |
| 3 | 1 | 2 | 3 | 4 |
| 4 | 1 | 2 | 3 | 3 |
| 5 | 1 | 2 | 3 | 3 |
| 6 | 1 | 2 | 3 | 3 |
| 7 | 1 | 2 | 3 | 0 |
| 8 | 1 | 2 | 2 | 3 |
| 9 | 1 | 2 | 2 | 3 |
| 10 | 1 | 2 | 2 | 3 |
| 11 | 1 | 2 | 2 | 2 |
| 12 | 1 | 2 | 2 | 2 |
| 13 | 1 | 2 | 2 | 2 |
| 14 | 1 | 2 | 2 | 0 |
| 15 | 1 | 2 | 0 | 0 |
| 16 | 1 | 1 | 2 | 3 |
| 17 | 1 | 1 | 2 | 3 |
| 18 | 1 | 1 | 2 | 3 |
| 19 | 1 | 1 | 2 | 2 |
| 20 | 1 | 1 | 2 | 2 |
| 21 | 1 | 1 | 2 | 2 |
| 22 | 1 | 1 | 2 | 0 |
| 23 | 1 | 1 | 1 | 2 |
| 24 | 1 | 1 | 1 | 2 |
| 25 | 1 | 1 | 1 | 2 |
| 26 | 1 | 1 | 1 | 1 |
| 27 | 1 | 1 | 1 | 1 |
| 28 | 1 | 1 | 1 | 1 |
| 29 | 1 | 1 | 1 | 0 |
| 30 | 1 | 1 | 0 | 0 |
| 31 | 1 | 0 | 0 | 0 |

1) Where a specific drug sequence is given, **1** represents that the first-line drug is used for the corresponding health state; **2** represents that the second-line drug is used for the corresponding health state; **3** represents that the third-line drug is used for the corresponding health state; **4** represents that the fourth-line drug is used for the corresponding health state; and **0** represents that no drug is used for death.

Table .. Matrix of the maintenance therapy generated by ‘MTGenerator’

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Number | The time period that maintenance therapy is applied. | | | |
| t=1 | t=2 | t=3 | t=4 |
| 1 | 0 | 0 | 0 | 0 |
| 2 | 0 | 0 | 0 | 0 |
| 3 | 0 | 0 | 0 | 0 |
| 4 | 0 | 0 | 0 | 1 |
| 5 | 0 | 0 | 0 | 1 |
| 6 | 0 | 0 | 0 | 1 |
| 7 | 0 | 0 | 0 | 0 |
| 8 | 0 | 0 | 1 | 0 |
| 9 | 0 | 0 | 1 | 0 |
| 10 | 0 | 0 | 1 | 0 |
| 11 | 0 | 0 | 1 | 2 |
| 12 | 0 | 0 | 1 | 2 |
| 13 | 0 | 0 | 1 | 2 |
| 14 | 0 | 0 | 1 | 0 |
| 15 | 0 | 0 | 0 | 0 |
| 16 | 0 | 1 | 0 | 0 |
| 17 | 0 | 1 | 0 | 0 |
| 18 | 0 | 1 | 0 | 0 |
| 19 | 0 | 1 | 0 | 1 |
| 20 | 0 | 1 | 0 | 1 |
| 21 | 0 | 1 | 0 | 1 |
| 22 | 0 | 1 | 0 | 0 |
| 23 | 0 | 1 | 2 | 0 |
| 24 | 0 | 1 | 2 | 0 |
| 25 | 0 | 1 | 2 | 0 |
| 26 | 0 | 1 | 2 | 3 |
| 27 | 0 | 1 | 2 | 3 |
| 28 | 0 | 1 | 2 | 3 |
| 29 | 0 | 1 | 2 | 0 |
| 30 | 0 | 1 | 0 | 0 |
| 31 | 0 | 0 | 0 | 0 |

1) **0** represents no maintenance therapy (i.e., where either a new drug is started or death); **1** represents the start of maintenance therapy (i.e., a drug is continuously used in the next period); **2** represents the second period of maintenance therapy (i.e., a drug is continuously used in the next two subsequent periods); and **3** represents the third period of maintenance therapy (i.e., a drug is continuously used in the next three subsequent periods).

The function ‘TrtGenerator’ generates a 1 by 5 array that indicates which drug is used to treat patients with UA, MI, stroke, HF and DM. Depending on the scenario selected, it may generate a set of recommended drugs for each health state, which are [CCB, BB, BB, ACEI, ACEI] for UA, MI, Stroke, HF and DM; or randomly selected drugs excluding CCBs for HF.

The function ‘Combinator’ performs basic permutation and combination with/without repetition. Any function that involves numerical permutations or combinations such as ‘TreeGenerator’, ‘PolicyGenerator’, ‘VasGenerator’ and ‘MTGenerator’, employs the function ‘Combinator’. The m-file function developed by Matt Fig (2009) was modified for the hypertension SDDP[361].

The function ‘EvModel’ (or ‘EvModelDC’) is the underlying evaluation model, which calculates the total net benefit of the sequential treatment policies. Given a specific sequential treatment policy generated by ‘PolicyGenerator’, this function provides total net benefit in the long-term or treatment success rate in the short-term. Where the decision space is decomposed, ‘EvModelDC’ provides the immediate reward from the transition between the current state and the next state. A number of sub-functions are implemented for ‘EvModel’ (or ‘EvModelDC’), which are ‘SBPmodelling’, ‘CVDmodelling’, ‘QRISK2’ and ‘Data’. Pseudo-code is provided in Figure ‎6.3.

For a group of patients who were in *h* at *t*, the function ‘SBPmodelling’ performs a Monte Carlo simulation to generate 1,000 random samples of baseline SBPs and treatment results after the consideration of SBP lowering effect. Given the mean SBP (and SD), which is the treatment result(s) in the previous period, and the drug used for the current state, this function returns the information required to decide the transition probabilities to the health states in the next period, which include the treatment success rate and the percentage of CVDs and AEs. The mean SBPs after treatment are saved for the controlled and uncontrolled, separately, and then used to generate the baseline SBPs depending on the health state in the next period. Pseudo-code is provided in Figure ‎6.4.

The function ‘CVDmodelling’ is the add-on Markov model, which calculates the CVD and DM related cost and effectiveness of each sequential treatment policy in the long-term. During the drug switching period, this function only considers those patients who have CVD or DM, whereas after the drug switching period, the function is applied to all surviving patients. Key data comes from the function ‘Data’. The 10-year CVD risk is calculated by the function ‘QRISK2’. Pseudo-code is provided in Figure ‎6.5.

‘Enu’, ‘SA’, ‘GA’ and ‘RL’, which represent enumeration, simulated annealing, genetic algorithm and reinforcement learning, were tested in this model. The following sub-sections describe the implementation of each method in detail. ‘Validation’ is included to validate the hypertension SDDP model internally and externally against the NICE hypertension model. ‘PostHoc’ implements various statistical analyses to provide a better understanding of the enumerated results.



1) Information about each functions and the full names for abbreviations are provided in Table ‎6.1.

Figure .. The structure of the hypertension SDDP model built by m-files

## Enumeration

The total net benefit of 4,128 sequential treatment policies was examined through the underlying evaluation model (see Figure ‎6.2). The outer loop generated a sequential treatment policy, Policy, and sent the policy to the underlying evaluation model ‘EvModel’ consecutively. The inner loop repeated 100 times to produce the total net benefits, TNB, of each policy. The optimal solution was determined based on the mean of the 100 sampled total net benefits. Due to the computational burden to run 4,128 policies for 100 times, enumeration was implemented through Iceberg, which is the Linux based High Performance Computing Cluster at the University of Sheffield. 100 samples, which were independent of each other, were run in parallel using two of Intel X5650 6-core processors (12 cores in total).

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| matlabpool open12 % Open 12 workers.  **FOR** Policy = 1:4128 % Policy generation.  % Repeat PSAs for 100 times in parallel using 12 workers.  **PARFOR** n = 1:100  [TNB(Policy)] = EvModel(Policy,Scenario); % Calculate the total net benefit of the inputted policy, given a scenario.  **END**  **END**  % Average the sampled total net benefits and determine the optimal solution.  [OptV,OptSol] = max(mean(TNB(:)));  matlabpool close |

Figure .. Pseudo-code of the enumeration used for the hypertension SDDP model

Given a specific scenario defined by the variables in Table ‎6.2, the underlying evaluation model ‘EvModel’ calculated the total net benefit of the policy generated by enumeration, SA or GA (see Figure ‎6.3). The decision tree as in Table ‎6.3 was generated by ‘TreeGenerator’ (i.e., dTree). The matrices indexing the actual drug use of a specific sequential treatment policy, DrugIdx, and the maintenance therapy, Maintenance, were also generated as in Table ‎6.5 and Table ‎6.6. Memory variables defined by time t and health state h were used to store treatment success rate, SBP and the variation of SBP, the probabilities of AEs, CVDs, HF and DM for each health state h at t(i.e., pTrtSux, SBP, SBPSD, pAE, pCVD, pHF and pDM) .

The transition probabilities between the health states included in the decision tree were saved in pDizPath. As the patients who had a CVD or DM moved to the long-term CVD model straight away, pDizPath only included the patients who have never had a CVD or DM during the drug switching period. The state transition probabilities for the patients who moved to the long-term model were saved in the long-term state transition matrix called CumLTProb.

The outer loop t is the time period and the inner loop h is the possible health states in each time period. For each health state h at t, the baseline SBP and the SD of SBP were updated based on the information saved in SBP and SBPSD. The cohort of patients was initialized to use the first-line drug of the given sequential treatment policy for the initial health state. Treatment failure invoked change from the first-line drug to the second, third, and fourth-line drugs according to DrugIdx, which is the matrix generated by ‘VasGenerator’. If a patient used all four drugs in the sequential treatment policy, where the selected drug switching period was longer than four time periods, the next drug was selected randomly among the drugs, which were not previously used. If treatment was successful, the same drug was continued in the next period. The period of maintenance therapy was considered by Maintenance.

Given the information about SBP, drug and maintenance therapy, ‘SBPmodelling’ returned the treatment success rate, the level of SBPs after treatment (separately for the controlled and uncontrolled patients) and the risk of CVDs, HF, DM and AEs (see Figure ‎6.4 for the pseudo-code). The outputs of ‘SBPmodelling’ were used to calculate the transition probabilities to the health states in the next period. The SBPs after treatment and the variations for the controlled and the uncontrolled patients were also saved separately for the use in the next period. The short-term costs included the costs for the regular GP check-up and drug use for the time period. The short-term QALYs were calculated based on the age-dependent utility assuming there was no disutility from hypertension or antihypertensive treatment.

‘CVDmodelling’ calculates the long-term costs and QALYs for a group of patients who have a CVD or DM during the drug switching period; and for all patients alive after the drug switching period (see Figure ‎6.5 for the pseudo-code). 23 cohorts were defined by when they moved to the long-term CVD model. For each cohort including the patients who move to the long-term CVD model from h at t, the outputs are the matrices including the state transition probabilities from the time they had a CVD or DM to 100 years old (i.e., LTProb) and the long-term costs and QALYs occurred with the state transitions (i.e., LTCost and LTQaly). Those matrices were added up into the cumulated long-term transition matrices (i.e., CumLTProb, CumLTCost and CumLTQaly), which included the transition probabilities and the long-term costs and QALYs from all patients who had a CVD or DM until t, and updated as a new cohort of patients moved into the long-term CVD model.

Total costs and QALYs for h at t are the sum of the costs and QALYs from the short-term drug switching model and the long-term CVD model. The long-term costs and QALYs only referred to the costs and QALYs occurred from h at t during the drug switching period. At the last stage of the drug switching period (i.e., t=4), the long-term costs and QALYs included all the costs from the end of the drug switching period to 100 years old.

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| % For the selected scenario, the function ‘EvModel’ provides the total net benefit of the inputted policy.  **Function** [TNB] = EvModel(Policy,Scenario)  % Redefine the key variables from the scenario.  T = Scenario.drug\_switching\_period; % Drug switching period.  Age = Scenario.initial\_age; % Initial age.  iSBP = Scenario.initial\_SBP; % Initial SBP.  cLength = Scenario.cycle\_length; % Cycle length.  Sample = Scenario.number\_of\_repetitions; % The no. of PSA runs.  WTP = Scenario.WTP; % Willingness-to-pay.  % Generate the decision tree by the scenario defined.  dTree = TreeGenerator(Scenario);  % Generate the index of the location of the drug used for h at t, where a specific policy is given.  DrugIdx = VarsGenerator(dTree);  % Generate whether a maintenance therapy is used, if so, how long the maintenance therapy has been used.  Maintenance = MTGenerator(dTree);  % Defined the memory variables for the use in the next period.  pTrtSux = zeros(size(dTree,1),T); % Treatment success rate.  SBP = zeros(size(dTree,1),T); SBP(1,1) = iSBP; % SBP  SBPSD = zeros(size(dTree,1),T); SBPSD(1,1) = 21.1; % The SD of SBP.  pCVD = zeros(size(dTree,1),T+1); % The probability of CVDs.  pHF = zeros(size(dTree,1),T+1); % The probability of HF.  pDM = zeros(size(dTree,1),T+1); % The probability of DM.  pAE = zeros(size(dTree,1),T); % The probability of AEs.  % Initialise the state transition matrix for the patients who stay in the short-term drug switching model.  pDizPath = zeros(size(dTree,1),T+1); pDizPath(1,1) = 1;  % Initialise the matrices for the short-term costs and QALYs calculated from h at t.  STCosts = zeros(size(dTree,1),T);  STQALYs = zeros(size(dTree,1),T);  % Each group of patients who move to the long-term CVD model from h at t has their own matrices for the long-term state transition probabilities, costs and QALYs.  LTProb = cell(t,h);  LTCost = cell(t,h);  LTQaly = cell(t,h);  % The cumulated state transition probabilities, costs and QALYs for all those patients who moved to the long-term model.  CumLTProb = zeros((104-Age)+1,11);  CumLTCost = zeros((104-Age)+1,11);  CumLTCQALY = zeros((104-Age)+1,11);  % Call datasets.  [cEvent,cDrug,distCVD,pNonCVDd] = Data(Scenario);  **FOR** t = 1:T % Repeat for the drug switching period.  % Go through all possible health states at t one by one.  **FOR** h = 1:size(dTree)  **IF** dTree(h,t)==3 % For the patients died.  TotalCosts(h,t) = 0; TotalQALYs(h,t) = 0;  **ELSE** % Otherwise, carry on the following calculations.  % Assign the baseline SBP and SD.  bSBP = SBP(h,t); bSBPSD = SBPSD(h,t);  % For the given policy, select the actually used drug for h at t.  **IF** DrugInx(h,t) <= size(Policy)  Drug = Policy(DrugIdx(h,t));  % If the patients used all drugs in the given policy, randomly generate a drug, which has not been used.  **ELSE**  RdOpt = 1:NoTrtOpt+1; % All possible treatment options.  RdOpt(:,Policy) = []; % Exclude the drugs, which was used.  Drug = datasample(RdOpt,1); % Randomly generated a drug.  **END**  % Decide whether a maintenance therapy is applied, and if so, how long the patient has been under the maintenance therapy.  MT = Maintenance(h,t);  % With the given t, Drug, MT, bSBP and bSBPSD, run the function ‘SBPmodelling’(see Figure 6.4). The outputs are the treatment success rate, the mean SBP and SD for the controlled and the uncontrolled and the probability of CVD, HF, DM and AEs.  [rTrtSux,UncontSBP,UncontSBPSD,ContSBP,ContSBPSD,rCVD,rHF, rDM,rAE] = SBPmodelling(t,Drug,MT,bSBP,bSBPSD);  % Calculate the following parameters with the outputs of ‘SBPmodelling’.  pCVD(h,t) = pDizPath(h,t)\*rCVD(h,t); % Prob. of CVDs.  mortCVD = pCVD(h,t)\*distCVD(Age,4); % CVD mortality.  mortNonCVD = pDizPath(h,t)\*(pNonCVDd(Age,1)); % Non-CVD mortality.  pDeath = mortCVD+mortNonCVD; % Prob. of total death.  pSurv = pDizPath(h,t)-pDeath; % Prob. of survivors.  pHF(h,c) = pSurv\*rHF; % Prob. of HF.  pDM(h,c) = pSurv\*rDM; % Prob. of DM.  pAE(h,c) = pSurv\*rAE; % Prob. of AE.  otherCVDs = pQRISK(h,t)\*(1-sum(distCVD(Age,1:4)); % Prob. of other CVDs.  % Calculate the transition probabilities to *Success* and *Failure*.  pCont = pSurv\*rTrtSux; pUncont = pSurv\*(1-rTrtSux);  % Save the one-step transition probabilities to the health states in the next period.  pDizPath(Uncont,t+1) = (pUncont-(pCVD(h,t)+pHF(h,t)+pDM(h,t)-otherCVD-mortCVD+pHF(h,t)));  pDizPath(Cont,t+1) = pCont;  pDizPath(Death,t+1) = pDeath;  % Save the mean SBP and the SD after treatment depending on the health state in the next period.  SBP(Uncont,t+1) = UncontSBP;  SBP(Cont,t+1) = ContSBP;  SBPSD(Uncont,t+1) = UncontSBPSD;  SBPSD(Cont,t+1) = ContSBPSD;  % Calculate the short-term costs and QALYs.  STCosts(h,t) = (cEvent(Well)+cDrug(Drug))\*pDizPath(h,t);  STQALYs(h,t) = AgeDepUtility\*pDizPath(h,t);  % With the given t, Drug, pCVD(h,t), pHF(h,t), pDM(h,t), SBP(h,t) and pDeath, run the function ‘CVDmodelling’ to calculate the long-term costs and QALYs for a cohort of patients who move to the long-term CVD model from h at t. Each cohort had a 44x11 matrix including the CVD and DM related costs and QALYs from the time moved to the long-term CVD model to 100 years old.  [LTCost{t}{h},LTQaly{t}{h},LTProb{t}{h}]  = CVDmodelling(t,Drug,pCVD(h,t),pHF(h,t),pDM(h,t),SBP(h,t),  pDeath);  % Incorporate the long-term costs and QALYs from 23 cohorts.  CumLTProb = CumLTProb(:,:)+LTProb{t}{h}(:,:);  CumLTCost = CumLTCost(:,:)+LTCost{t}{h}(:,:);  CumLTQaly = CumLTQaly (:,:)+LTQaly{t}{h}(:,:);  % Calculate the total costs and QALYs for h at t.  **IF** t~=T  TotalCosts(h,t) = STCosts(h,t)+sum(CumLTCost(t,:);  TotalQALYs(h,t) = STQALYs(h,t)+sum(CumLTQaly(t,:);  **ELSE**  TotalCosts(h,t) = STCosts(h,t)+sum(CumLTCost(t:end,:);  TotalQALYs(h,t) = STQALYs(h,t)+sum(CumLTQaly(t:end,:);  **END**  **END**  **END** % End of loop h.  **END** % End of loop t.  % Calculate the total net benefit.  TNB = sum(TotalQALYs(:,:))\*WTP-sum(TotalCosts(:,:)); |

Figure .. Pseudo-code of the function ‘EvModel’ included in the hypertension SDDP model

Given the treatment regimen used for h at t and the mean SBP with the variation before treatment, the function ‘SBPmodelling’ provided the treatment success rate, the mean SBP and SD after treatment (separately for the controlled and the uncontrolled), the probability of CVD, HF, DM and AE for a group of patients who were in h at t.

An individual Monte Carlo modelling method was used for the function ‘SBPmodelling’. Assuming there are 1,000 individual entrants in this cohort, the simulation randomly generated 1,000 samples of baseline SBPs (i.e., SBP\_Before) and the SBP lowering effects (i.e., SBP\_Rdt) using a lognormal distribution. The SBPs after treatment (i.e., SBP\_After) were calculated based on the baseline SBP, age-dependent SBP change and the SBP lowering effect. For each SBP result after treatment, the 10-year CVD risk (i.e., TenYearCVD) was calculated using QRISK2, which considers a set of variables including gender, age, treatment history, DM, BMI, ethnicity, family history and other comorbidities. The 10-year CVD risk was adjusted to the three month basis (i.e., ThreeMonthCVD).

For the AEs, a beta distribution was used to generate a probability of AEs including DM. Given the probability of the patients who have an AE (i.e., pAE), 1,000 samples of AE occurrence were randomly generated by assigning 1 for the patients having an AE and 0 for the patients having no AE (i.e., Sampled\_AE).

If a set of the sampled SBP, CVD and AE results met the criteria of treatment success, it was assumed that the treatment was successful for the individual patient. For the rest it was assumed that the treatment failed. The proportions of treatment success/failure, CVD, HF, DM and AE were the output of the function ‘SBPmodelling’ and used to calculate the transition probabilities to *Success*, *Failure*, *Death* and the long-term CVD model in the next period. The mean SBP and SD of the entrants were used to extrapolate forward their long-term costs and health outcomes.

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| % Given the treatment regimen, the mean SBP and the variation of the patients who are in h at t, the function ‘SBPmodelling’ provides the treatment success rate, the SBP and SD for the controlled patients and the uncontrolled patients, the probability of CVD, HF, DM and AE.  **Function** [rTrtSux,UncontSBP,UncontSBPSD,ContSBP,ContSBPSD,rCVD,rHF, rDM,rAE] = SBPmodelling(t,Drug,MT,bSBP,bSBPSD);  % Call datasets.  [mSLE,vSLE,RiskHF,RiskDM,hrDM,RiskAE] = Data(Scenario);  % Generate 1,000 random samples of baseline SBP using a lognormal distribution.  SBP\_Before(1000,1) = lognrnd(mu\_bSBP,sigma\_bSBPSD,1,1000);  % Generate 1,000 random samples of SBP lowering effect using a lognormal distribution.  SBP\_Rdt(1000,1) = lognrnd(mu\_mSLE,sigma\_vSLE,1,1000);  % SBP after treatment is a function of the baseline SBP, age-dependent SBP change and SBP lowering effect.  SBP\_After(1000,1) = SBP\_Before(:,1)+AgeDepSBP-(SBP\_Before(:,1).\* SBP\_Rdt(:,1));  % Generate the probability of AEs including DM using a beta distribution.  pAE = betarnd((rAE+rDM)\*1000,1000-((rAE+rDM)\*1000));  % Randomly generate 1,000 samples of AEs using pAE and assign 1 for the proportion of the patients with AE and 0 for the proportion of the patients without AE.  AEs = round(pAE\*1000); NoAEs=round((1-pAE)\*1000);  TempAE = [zeros(NoAEs,1), ones(AEs,1)];  Sampled\_AE(1000,1) = TempAE(randperm(1000));  % Estimate the 10-year CVD risks using the QRISK2.  TenYearCVD(1000,1) = QRISK2(Gender,Age,AF,RA,RD,TreatHist, Type1DM,Type2DM,BMI,Ethnicity,FamilyHist,SBP\_After(:,1),Smoking,11, TownsendScore)+(TenYearHF\*100);  % Adjust the 10-year CVD risk to the 3 month basis.  ThreeMonthCVD(1000,1) = 1-power((1-TenYearCVD(:,1)/100), 0.1\*CycleLength);  % Decide whether the treatment is successful or not.  **FOR** n=1:1000  **IF** (SBP\_After(n,1)<140 && Sampled\_AE(n,1)==0) || (SBP\_After(n,1)>=140 && SBP\_After(n,1)<160 &&  TenYearCVD(n,1)<20 && Sampled\_AE(n,1)==0)  TreatResult(n,1) = 1; % Treatment success.  **ELSE**  TreatResult(n,1) = 0; % Treatment failure.  **END**  **END**  % Calculate the treatment success rate.  pTreatSux = (sum(TreatResult(:,1))/1000);  % Classify the SBPs after treatment depending on whether the treatment was successful or not.  CombinedTable = [SBP\_After(1000,1),TreatResult(1000,1)];    **FOR** n = 1:1000  **IF** CombinedTable(n,2)==1,  ContSBPs = [ContSBPs;CombinedTable(n,1)];  **ELSE** UncontSBPs = [UncontSBPs;CombinedTable(n,1)];  **END**  **END**  % Save the mean SBP and the SD, separately, for the treatment success and failure.  ContSBP = mean(ContSBPs(:)); ContSBPSD = std(ContSBPs(:));  UncontSBP = mean(UncontSBPs(:)); UncontSBPSD = std(UncontSBPs(:)); |

Figure .. Pseudo-code of the function ‘SBP modelling’ included in the hypertension SDDP model

Given the time to enter ‘CVDmodelling’, the last drug used in the drug switching model, the proportion of patients who have a CVD, HF and DM and their mean SBP, the function ‘CVDmodelling’ calculated the CVD and DM related cost and effectiveness in the long-term. Once a group of patients entered ‘CVDmodelling’, they probabilistically went through the health states included in ‘CVDmodelling’, which are well, UA, post-UA, MI, post-MI, stroke, post-stroke, HF, post-HF, DM and death, until 100 years old. The time cycle was set to 3 months between 60 and 61 years old so that the long-term CVD model had the same time cycle with the short-term drug switching model. The annual cycle was used afterwards. The state transition probabilities were saved in StateTransit, which is a 44x11 matrix in the base-case. The same size matrices were used to save the costs and QALYs obtained from each health state in each period. The distribution of the initial health states in ‘CVDmodelling’ (i.e., pUA, pMI, pStroke, pHF, pDM and pDeath) were assigned based on the inputted percentage of the patients who have a CVD, HF or DM.

The initial distribution of health states transferred to the health states in the next period according to the 11x11 transition matrix (i.e., TransMtrix), which was based on the baseline risk of CVD and DM and the RR reduction depending on the type of antihypertensive drugs used. The baseline CVD and DM risk (i.e., BaseCVDrisk), which came from the NICE hypertension model, were adjusted based on the mean CVD risk of the current population, AnnualCVD.

The long-term costs, LTCost, were calculated by the health state costs and the drug costs depending on the drugs selected for each health state. The long-term QALYs, LTQALY, considered the age-dependent utility and the disutility due to the CVD or DM. Where a three-month cycle was used, the state transition probability and the long-term costs and QALYs were adjusted accordingly.

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| % The function ‘CVDmodelling’ provides the long-term state transition probabilities, mean costs and QALYs for a group of patients who enter ‘CVDmodelling’ from h at t. The inputs are the time to enter ‘CVDmodelling’, the last drug used before enter ‘CVDmodelling’, the percentage of the patients having a CVD, HF and DM and their mean SBP and the SD.  **Function** [LTCost,LTQaly,LTProb]  = CVDmodelling(t,LastDrug,pCVD,pHF,pDM,SBP,pDeath);  % Call datasets.  [TotalMort,CostEvent,CostDrug,DistCVD,BaseCVDrisk,TrtRR] = Data(Scenario);  % Initialize the key parameters.  StateTransit = zeros(104-Age,11); % State transition matrix.  LTCost = zeros(104-Age,11); % Long-term cost matrix.  LTQaly = zeros(104-Age,11); % Long-term QALY matrix.  % StateTransit, LTCost and LTQaly have a matrix as following:  % ----------------------------------------------------------------  % Well UA p-UA MI p-MI Stroke p-stroke HF post-HF DM Death  % ------:----:--:----:--:----:------:--------:--:-------:--:------  % 60  % 60.25  % 60.50  % 60.75  % 61  % 62  % ...  % ...  % 100  % ----------------------------------------------------------------  % Initial distribution for the health states.  pUA = pCVD\*DistCVD(Age,1);  pMI = pCVD\*DistCVD(Age,2);  pStroke = pCVD\*DistCVD(Age,3);  StateTransit(t,:) = [pWell,pUA,0,pMI,0,pStroke,0,pHF,0,pDM,pDeath];  % Initialize the transition matrix as following:  TransMatrix = zeros(11,11);  % ------------------------------------------------------------------  % Well UA p-UA MI p-MI Stroke p-stroke HF post-HF DM Death  % --------:----:--:----:--:----:------:--------:--:-------:--:-----  % Well  % UA  % p-UA  % MI  % p-MI  % Stroke  % p-Stroke  % HF  % p-HF  % DM  % Death  % --------:----:--:----:--:----:------:--------:--:-------:--:-----  % Calculate the 10-year CVD risk using QRISK2.  TenYearCVD = QRISK2(Gender,Age,AF,RA,RD,TreatHist, Type1DM,Type2DM,BMI,Ethnicity,FamilyHist,SBP,Smoking,11,Townsend);  % Adjust the 10-year CVD risk to the annual risk.  AnnualCVD = 1-power((1-TenYearCVD(:,1)/100),0.1);  % Adjust the baseline CVD risks, which came from the NICE hypertension model, based on the current population’s annual CVD risk.  AdjCVDrisk(:,:) = BaseCVDrisk(:,:)\*(AnnualCVD/0.02);  % Generate a treatment scenario for CVD and DM.  DrugForCVDDM = TrtGenerator(Scenario.drug\_CVD);  % Given the treatment scenario for CVD and DM, generate a 1x11 matrix including the drug costs for each health states.  cDrug = [CostDrug(LastDrug), ...  CostDrug(DrugForCVDDM(1)), CostDrug(DrugForCVDDM(1))...  CostDrug(DrugForCVDDM(2)), CostDrug(DrugForCVDDM(2))...  CostDrug(DrugForCVDDM(3)), CostDrug(DrugForCVDDM(3))...  CostDrug(DrugForCVDDM(4)), CostDrug(DrugForCVDDM(4))...  CostDrug(DrugForCVDDM(5)), 0];  % Calculate the state transition probabilities and the long-term costs and effectiveness.  **FOR** c = t:104-Age  **IF** c<4, AdjAge = Age; **ELSE** AdjAge = Age+c; **END**  % Calculate TransMatrix from the health states in the first column to the health states in the first row. This depends on the drug selected for each health state.  TransMatrix(1,1:10) = AdjCVDrisk(1,1:10).\*TrtRR(LastDrug,1:10);  TransMatrix(1,11) = TotalMort(AdjAge)\*TrtRR(LastDrug,11);  TransMatrix(1,1) = 1-sum(TransMatrix(1,:));  .  .  .  TransMatrix(10,1:10) = AdjCVDrisk(10,1:10).\*TrtRR(DrugForCVDDM(5),1:10);  TransMatrix(10,11) = TotalMort(AdjAge)\*TrtRR(DrugForCVDDM(5),11);  TransMatrix(10,1) = 1-sum(TransMatrix(10,:));  % Calculate the state transition probabilities in the next period.  StateTransit(c+1,:) = StateTransit(c,:)\*TransMatrix (:,:);  LTCost(c+1,:) = (StateTransit(c+1,:).\*(cEvent(:)+cDrug(:)))/ ((1+DC)^(c-1));  LTQALY(c+1,:) = StateTransit(c+1,:).\*(Ustate(:)\*Uage)/((1+DC)^(c-1));  % Adjust the transition probabilities to three month basis.  **IF** c<4,  StateTransit(c+1,:)=1-power(StateTransit(c+1,:),0.25);  LTCost(c+1,:) = LTCost(c+1,:)\*0.25;  LTQALY(c+1,:) = LTQALY(c+1,:)\*0.25;  **END**  **END** |

Figure .. Pseudo-code of the function ‘CVD modelling’ included in the hypertension SDDP model

## Simulated annealing

The SA started with the heuristically selected initial solution that had the smallest total net benefits in enumeration. A random choice was made between available moves from the neighbourhood of the current solution N(x,σ) (i.e., a set of solutions that can be reached from the current solution x by a simple operation σ). For a discrete parameter, such an operation σ might be swapping, replacing, moving or combining two or more objects in a solution[102, 209, 210, 362]. The operator σ used in the hypertension SDDP model allowed moving to a new solution based on the randomly generated policy number within the neighbourhood of the current solution. As there was no information about the most appropriate size of the neighbourhood for the hypertension SDDP, different sizes of the neighbourhood (i.e., ±25, 50 and 100 from the current solution) were tested in the prior tests and found that the final solutions of SA were not sensitive to the size of the neighbourhood in the range between ±25 and ±100, whereas the number of total iteration was smallest where the size of the neighbourhood was ±50 (see Appendix 8). Therefore the hypertension SDDP model defined the neighbourhood ±50 from the current solution.

In order to avoid premature convergence, a random jump to another area was allowed after 30% of the neighbourhood was searched. This happened approximately every 30 iterations. The whole search space can be divided into four sub-spaces having 1,032 policies depending on the initial drug. The range of allowing the random jump was set to ±1000 so that the areas having a different initial drug were searched. The process re-started from the new solution and continued to iterate in this way until the following stopping criteria were met:

* Temperature at which to stop is 1e-8.
* Maximum number of consecutive rejections is 1,000.

If the incremental reward between the new candidate solution and the current solution was greater than £1e-6 of total net benefit, the current solution was replaced with the new solution. SA also allowed moving to worse solutions with a probability obtained from the Equation 3.3. That is, if a random number was greater than the probability to accept the worse solutions, the current solution was replaced with the new solution despite the current solution being better than the new solution: this is one of the key mechanisms of SA to avoid getting trapped in a local optimum.

The temperature parameter T was controlled by the initial temperature and cooling rate. It is generally accepted that the initial temperature should be high enough to allow a gradual annealing procedure and to avoid getting trapped into the local optimum. In the hypertension SDDP model, the initial temperature, InitTemp, was set to 1.

The initial temperature slowly and gradually decreased during the search process by a temperature reduction function Q(β,Tc-1). The cooling rate β was assumed to be constant (i.e., the temperature Tc-1 was decreased linearly by β*)* during the search like many other studies[60, 102, 209, 363]. A careful annealing through a series of temperature levels is desirable to reach a stationary distribution before temperature reduction. This model tested different combinations of cooling rates (β= 0.5, 0.7 and 0.9) and the maximum number of attempts within one temperature (MaxTries = 10, 30 and 50). As the initial temperature decreased, the probability of accepting worse solutions also decreased.

During the search process, the evaluation function ‘EvModel’ described a trajectory of the total net benefit of the optimal solution identified in each temperature. The total net benefit of the optimal solution was estimated based on the mean of 100 replications of the underlying evaluation model. Parallel computation was implemented to allow multiple replications to be tested at the same time. When the searching stopped, the SA algorithm provided a solution with its associated expected total net benefit.

The SA algorithm written in Matlab by Vandekerckhove[364] was modified for the hypertension SDDP model. Modifications were made for the neighbourhood structure and parallel computation. Key parameters for SA were also altered so that they were appropriated to the context of the hypertension SDDP. Figure ‎6.6 illustrates the pseudo-code for the SA algorithm used in this study.

|  |
| --- |
| % Select the parameters for simulated annealing.  Def = struct(  ‘CoolSched’, @(T) (β\*T), % Cooling schedule (*β*=0.5, 0.7 or 0.9).  ‘Generator’, @(x) randi([x-50,x+50]), % Definition of the neighbourhood of the current solution x.  ‘InitTemp’, 1, % Initial temperature.  ‘MaxConsRej’, 1000, % Maximum no. of consecutive rejections.  ‘MaxSuccess’, 100, % Maximum no. of successes within one temperature.  ‘MaxTries’, 100, % Maximum number of tries within one temperature.  ‘StopTemp’, 1e-8, % Temperature at which to stop.  'k', 1); % Boltzmann constant.  T = InitTemp; % Initialize the temperature.  Parent = Policy(3257,:); % Select the initial solution.  OldReward = EvModel(Parent); % Evaluate the initial solution.  **WHILE** ~Finished; % Repeat until the following stopping rules are satisfied.  **IF** itry >= MaxTries || Success >= MaxSuccess;  **IF** T <StopTemp || Consec >= MaxConsRej; **Break;**  **ELSE**  T = CoolSched (T); % Update T according to cooling schedule.  **END**  NewParam = Generator (Parent); % Generate a new solution.  **IF** pertc == 30 % Every 30 repetitions, jump to another area.  NewParam = NewParam + randi([-1000,1000]);  **END**  NewReward = EvModel(NewParam); % Evaluate the new solution.  incNewReward = NewReward - OldReward;  % If the new solution is better than the old solution, accept the new solution.  **IF** (incNewReward > 1e-6)  Parent = NewParam; OldReward = NewReward;  % Otherwise, accept the new solution with a probability obtained from the Boltzman distribution.  **ELSE**  **IF** (rand > exp(-incNewReward/(k\*T) ));  Parent = NewParam; OldReward = NewReward;  **END**  **END**  **END**  % Decide the optimal solution and the reward where the optimal solution is used.  OptSol = Parent; OptV = OldReward; |

Figure .. Pseudo-code of the SA used for the hypertension SDDP model

## Genetic algorithm

In the context of the hypertension SDDP, a chromosome, mChrom, represents a sequential treatment policy. For convenience, all chromosomes (i.e., sequential treatment policy numbers from 1 to 4,128) were stored as 2^13 binary data, which uses a string of 0s and 1s. For example, the policy number 1, which is the combination of Ds, BBs, CCBs and ACEIs/ARBs, was converted to ‘0-0-0-0-0-0-0-0-0-0-0-0-1’; and the policy number 4,128, which is the combination of ACEIs/ARBs, CCBs+ACEIs/ARBs, BBs+CCBs+ACEIs/ARBs and Ds+CCBs+ACEIs/ARBs, was represented as ‘1-0-0-0-0-0-0-1-0-0-0-0-0’. To evaluate the objective function, the individual strings were decoded by phenotypes (i.e., mPhen), which were the policy numbers included in the population.

Whereas SA moves from one solution to another, GA works by maintaining a population of solutions whose fitness values (i.e., the value of the objective function) are better. Small populations have the risk of seriously under-covering the solution space, whereas large populations require increased computational time. In the hypertension SDDP model, various combinations of the number of generations (nGeneration = 25, 50 and 100) and population size (nInitPop = 10, 30, 50 and 100) were tested to determine the best set of the number of generations and the population size for the SDDP in primary hypertension. The size of the population was assumed to be fixed, whereas some studies assumed a variable population size[365, 366].

The hypertension SDDP model selected the initial population using a random number generator that uniformly distributes numbers between 1 and 4,128. During every iteration, the individuals (i.e., sequential treatment policies) included in the population were evaluated in terms of the fitness function, ObjVal, which is the mean total net benefit based on 100 replications from the underlying evaluation model.

The applied GA used the roulette wheel selection method, which selects individuals probabilistically based on their fitness (see Figure ‎6.7). An individual’s slice of a Monte Carlo-based roulette wheel is an area proportional to its fitness[217, 218]. The fittest individual has the largest share of the roulette wheel, whereas the weakest individual has the smallest share of the roulette wheel. To select an individual, a random number is generated from a uniform distribution in the interval [0, the sum of the *N* fitness values] and the individuals are chosen based on where the pointer stops. This process is repeated until the desired number of individuals has been selected. It was assumed that 90% of the fittest parents will remain in the future generation.



1) The numbers in each area represent the number of chromosome (i.e., the number of policy) and the fitness (i.e., total net benefit)

Figure .. Roulette wheel selection operator applied to the GA

After the parents were selected on a fitness basis, two or more of the parent chromosomes were recombined to produce new individuals. This model used the double-point crossover operator, which exchanges the bits in both parents where two crossover points are selected randomly (see Figure ‎6.8). The probability that crossover happens at a particular couple (i.e., crossover rate) was assumed to be 70%.



Figure .. Double-point crossover operator applied to the GA

Mutation was performed on a bit-by-bit basis where one or more bits chosen were flipped from 0 to 1 or vice versa with the probability of 10% for an individual (see Figure ‎6.9). The infeasible offspring was rejected, whereas the feasible offspring was evaluated and reinserted into the general population.



Figure .. Mutation operator applied to the GA

The GA was terminated after repeating for the number of generations selected. The population-based GA itself involves parallel processing (i.e., the individuals in the current population are evaluated at the same time). In addition to the parallelisation of fitness evaluations, the hypertension SDDP model also allowed parallel computation in 100 replications in calculating the objective function through the underlying evaluation model.

The GA toolbox developed in the department of Automatic Control and Systems Engineering at the University of Sheffield[367] was modified for the hypertension SDDP model. Modifications were mainly made to generate the initial population and the feasible individuals in the next generations in the context of the hypertension SDDP. The pseudo-code of the applied GA is presented in Figure ‎6.10.

|  |
| --- |
| % Select the parameters for genetic algorithm.  nGeneration = 50; % The number of generations.  nInitPop = 30; % The size of initial population.  % Select an initial population randomly.  InitPop = randi(4128, nInitPop));  mChrom = dec2bin(InitPop); % Encoded InitPop into binary vectors.  mPhen = bin2dec(mChrom); % Convert chromosomes into real values.  % Evaluate the initial population via the underlying evaluation model. This provides the set of total net benefits of the policies included in the initial population.  [ObjVal(:)] = EvModel(mPhen(:))  % Repeat for the number of generations selected.  **WHILE** iGeneration < nGeneration  % Assign fitness values to the population based on the total net benefits.  vFitVal = ranking(ObjVal(:,:));  % Select individuals for breeding using the roulette wheel selection 'rws'. 90% of the fittest patents are selected for bleeding.  [mSelChrom] = select('rws',mChrom,vFitVal 0.9);  % Recombine the selected individuals using the double-point 'xovdp'. The probability of crossover at a particular parent is 70%.  [mSelChrom] = recombin('xovsh',mSelChrom,0.7);  % Perform mutation on the offspring with the probability of 10% for an individual.  [mSelChrom] = mut(mSelChrom,0.1);  % Convert the offspring chromosomes into real values and then evaluate them via the underlying evaluation model.  mSelPhen = bin2dec(mSelChrom);  [mSelObjVal(:)] = EvModel(mSelPhen(:));  % Reinsert offspring into the general population.  [mChrom,mObjVal] = reins(mChrom,mSelChrom,mObjVal,mSelObjVal);  % Save the best solution and the maximum reward in each generation.  [MaxV(iGeneration),MaxIdx(iGeneration)] = max(mObjVal);  % Update the generation number.  iGeneration = iGeneration+1;  **END**  % Decide the optimal solution and the reward where the optimal solution was used.  OptSol = Policy(MaxIdx(end)); OptV = MaxV(end); |

Figure .. Pseudo-code of the GA used for the hypertension SDDP model

## Reinforcement learning: Q-learning

The hypertension SDDP model applied the Q-learning method, which is a simple incremental learning method that repeatedly updates Q-values based on the new cases until it converges upon the optimal solution. The decision space was decomposed by consecutive time cycles as Figure ‎6.11. The health space *HS* had five sub-health state spaces HS1-HS5, which had 2^(t-1) health sates. *Death* was not included in the decomposed *HS* because it is the absorbing state and no decision or further update is made. As the transition probabilities and the drug decision rule depended on the disease history, all possible health states in each sub health state space included the information about the previous health states. The search space *SS* was also decomposed by consecutive time cycles SS1-SS5. Each search space included the treatment options as defined in Chapter 4.

Five Q-tables were defined by the number of possible health states and the number of possible drugs in each time period (i.e., 1x4 for Q1, 2x10 for Q2, 4x14 for Q3, 8x14 for Q4and 16x14 for Q5). The Q-values were set to 0 initially and gradually updated as the simulator went through the corresponding state and action at t. The outer loop repeated 1,000 times in minimum and 1,000,000 times in maximum so as to observe the performance and convergence depending on the number of cases. The inner loop repeated for the number of drug switching period. Starting from the initial health state (i.e., cState), the algorithm generated the subsequent trajectories of drugs (i.e., cDrug) and health states (i.e., nState) until a terminal state at t4. As the subsequent drugs and health states were generated, the treatment history (i.e., tHist), and the disease history (i.e., dHist), were updated. The probability of the initial health state was set to 1 because the hypertension model assumed that all patients started from the same initial health state. The initial SBP was 173.5 and the SD was 21.1.

A drug was selected using a ε-greedy method, which is often the method of first choice because of the practical effectiveness[200]. With the ε-greedy method, the simulator selects a drug greedily at each time step, with an increasing probability determined by ε*=*1-(1/log(n+2)). At the beginning of learning, a drug is likely to be selected randomly. As more learning is achieved, the action, which maximises the Q-value for the current health state, has a higher probability to be selected.

For the patients alive, EvModelDC calculates the one-step reward for the transition from cState to nState where cDrug is used at t. The underlying evaluation model ‘EvModel’ used for enumeration, SA and GA was slightly modified so that ‘EvModelDC’ provided the one-step net benefit observed in a decomposed period rather than the whole follow-up period. IR is a single value, which represents the one-step reward for the transition from cState to nState where cDrug is used at t. fProb is a 1x3 matrix including the transition probabilities from cState to the next possible health states. fSBP and fSBPSD are 1x2 matrices including the mean SBPs and the SD of the patients whose treatment is successful and unsuccessful. They were used to update the baseline information (i.e., cProb, cSBP and cSBPSD) in the next period.

The target to maximise is the Q-value for the current health state, which is the sum of the one-step reward IR from the current state and the maximum Q-value from the next health state (i.e., max(Q{t+1}(nStateIdx,:))). In sensitivity analyses, Q-learning considering a two or three-step future reward was also implemented to compare the performance; in this case, the feedback is the sum of the immediate rewards and the mean total net benefit from two or three transitions in the future. Where the time to the end of the drug switching period is shorter than the time to be considered in Q-learning (e.g., decision-making in the third period where a two-step future reward was considered), the feedback was made based on the immediate reward and any future reward that would occur until the end of the drug switching period.

As mentioned earlier, all the values in the Q-tables are 0 until the simulator passes the corresponding health state and drug. If there is a Q-value, which has been calculated previously, the old Q-value is updated with the difference between the old Q-value and the new Q-value (i.e., delta). All the differences between the old Q-values and the new Q-values were saved in Discrepancy with the learning rate ɑ=1/sqrt(n+2), which gradually decreased over iterations. Their mean discrepancy every 100 cases were saved in mDiscrepancy and used to check the convergence of the Q-values. The discount rate of 0.8 determined the importance of the future rewards in decision-making.

All the updated Q-values were stored in a look-up table, where rows represent the possible health states and columns represent the possible drugs. At the end of the learning, the optimal drug, which provides the highest Q-value at t, was selected for each state h at t. A feasibility test was included to check whether the selected action was feasible under the given drug switching rules (i.e., a drug cannot be used if it has been previously used for treatment; initial treatment should be one of single drugs; and three-drug combinations are only accepted after the use of any two-drug combinations).



1) ***HSt*** represents the health state space at *t*; ***SSt***represents the search space at *t*, **1** represents *Failure* and **2** represents *Success*.

Figure .. Possible health states and treatment options, where the decision space is decomposed

|  |
| --- |
| % Select the key parameters for reinforcement learning.  T = 4; % The number of drug switching period.  DR = 0.8; % Discount rate.  N = 1000000; % The number of cases (1000, 10000 and 100000 were also tested).  FR = 1; % Future reward considered (from one to three steps).  % Define the health state space decomposed by the time period. The possible health states include the previous disease history.  HS1 = 1;  HS2 = [1,1;1,2];  HS3 = [1,1,1;1,1,2;1,2,1;1,2,2];  HS4 = [1,1,1,1;1,1,1,2;1,1,2,1;1,1,2,2;...  1,2,1,1;1,2,1,2;1,2,2,1;1,2,2,2];  HS5 = [1,1,1,1,1;1,1,1,1,2;1,1,1,2,1;1,1,1,2,2;...  1,1,2,1,1;1,1,2,1,2;1,1,2,2,1;1,1,2,2,2;...  1,2,1,1,1;1,2,1,1,2;1,2,1,2,1;1,2,1,2,2;...  1,2,2,1,1;1,2,2,1,2;1,2,2,2,1;1,2,2,2,2];  HS = {HS1,HS2,HS3,HS4,HS5};  % Define the search space decomposed by the time period.  SS1 = (1:1:4); % Possible treatment options 1-4 at t1.  SS2 = (1:1:10); % Possible treatment options 1-10 at t2.  SS3 = (1:1:14); % Possible treatment options 1-14 at t3.  SS4 = (1:1:14); % Possible treatment options 1-14 at t4.  SS5 = (1:1:14); % Possible treatment options 1-14 at t5.  SS = {SS1,SS2,SS3,SS4};  % Initialise the Q-tables for each time period to 0.  Q1 = zeros(size(HS1,1),size(SS1,2)); % 1x4 matrix at t1.  Q2 = zeros(size(HS2,1),size(SS2,2)); % 2x10 matrix at t2.  Q3 = zeros(size(HS3,1),size(SS3,2)); % 4x14 matrix at t3.  Q4 = zeros(size(HS4,1),size(SS4,2)); % 8x14 matrix at t4.  Q5 = zeros(size(HS5,1),size(SS5,2)); % 16x14 matrix at t5.  Q = {Q1,Q2,Q3,Q4,Q5};  % Initialise the parameters to check convergence.  Discrepancy = []; mDiscrepancy = [];  % Initialise the solution tables storing the optimal solutions and the maximum reward where the optimal solutions were used.  OptSeq = zeros(2^(T-1),T); MaxV = zeros(2^(T-1),T);  % Repeat calculating Q-values for N times.  **FOR** n = 1:N  cState = 1; % Initial state.  cStateIdx = 1; % Location of the current state in the Q-table.  dHist = 1; % Memory variable to save the disease history.  tHist = []; % Memory variable to save the treatment history.  cMT = 0; % Maintenance therapy.  cProb = 1; % The probability of the initial state.  cSBP = 173.5; cSBPSD = 21.1; % Initial SBP and SD.  % For each time period, generate a subsequent states from cState to a terminal state.  **WHILE** t < T+1    % Select a drug using the ε-greedy method with increasing 1-(1/log(n+2)).  pn = rand(1);  **IF** (pn < (1-(1/log(n+2))))  [nil,cDrug] = max(Q{t}(cState,:));  **ELSE** cDrug = randi([1,size(SS{t},1)]); **END**  % Update the treatment history.  tHist = [tHist;cDrug];    % Simulate a next state and reward associated to R(s,a,s’).  nState = randi([1,3]);  **IF** nState ~= 3 % For the alive patients,  dHist = [dHist,nState]; % Update the disease history.  [~,nStateIdx] = ismember(dHist,HS{t+1},'rows');    % Evaluate the one-step reward for the transition from cState to nState where cDrug is used at t, using EvModelDC. fProb is a 1x3 matrix including the transition probabilities from cState to the next health states; and fSBP and fSBPSD are 1x2 matrices including the mean SBPs for the controlled and uncontrolled patients after treatment.  [IR,fProb,fSBP,fSBPSD] = EvModelDC...  (Scenario,t,dHist,cDrug,cProb,cSBP,cSBPSD,cMT,DrugForCVDDM);  % Generate the subsequent health states depending on the future transitions to be considered.  **IF** FR == 1 || (FR > 1 && t == 3)  delta = IR + DR \* max(Q{t+1}(nStateIdx1,:)) - Q{t}(cStateIdx,cDrug);  **ELSEIF** FR == 2 || (FR > 2 && t == 2)  nState2 = randi([1,2]); fdHist=[dHist,nState2];  [~,nStateIdx2] = ismember(fdHist,HS{t+2},'rows');  delta = IR + DR \* (max(Q{t+1}(nStateIdx1,:))+ max(Q{t+2}(nStateIdx2,:)))/2 - Q{t}(cStateIdx,cDrug);  **ELSE**  nState2 = randi([1,2]); fdHist1=[dHist,nState2];  nState3 = randi([1,2]); fdHist2=[fdHist1,nState3];  [~,nStateIdx2] = ismember(fdHist1,HS{t+2},'rows');  [~,nStateIdx3] = ismember(fdHist2,HS{t+3},'rows');  delta = IR + DR \* (max(Q{t+1}(nStateIdx1,:))+ max(Q{t+2}(nStateIdx2,:))+max(Q{t+3}(nStateIdx2,:)))/3 - Q{t}(cStateIdx,cDrug);  **END**  % Compute the value function and update the Q-value. Learning rate α = (1/sqrt(n+1)).  dQ = (1/sqrt(n+2))\*delta;  Q{t}(cStateIdx,cDrug) = Q{t}(cStateIdx,cDrug)+dQ;  % Computing and saving maximal values of the Q variation  Discrepancy = [Discrepancy,abs(dQ)];    % Computing means all over Q variations values.  **IF** size(Discrepancy,2) == 100  mDiscrepancy{t} = [mDiscrepancy,mean(Discrepancy,2)];  Discrepancy = [];  **END**  % Update the probability, SBP and SBPSD for the next state.  t = t+1;  cState = fdHist(1,end);  cStateIdx = nStateIdx;  cProb = fProb(1,nState);  cSBP = fSBP(1,nState);  cSBPSD = fSBPSD(1,nState);  cMT = Maintenance(nState,t+1);  **ELSE** t=5; **END** % For the patients died.  **END** % Reach a terminal state.  **END** % The end of learning in time t.  % Determine the best drug for each health state in t based on the Q-values.  **FOR** t = 1:T  **FOR** h = 1:size(Q{t},1)  [v,idx] = sort(Q{t}(h,:),'descend');  **FOR** a = 1:size(v,2)  **IF** The feasibility assumptions is satisfied,  **Break**  **END**  [OptV(:,:),OptSol(:,:)] = max(Q{t},[],2);  **END**  **END**  **END** |

Figure .. Pseudo-code of the Q-learning used for the hypertension SDDP model

# Modelling sequential drug decision problem for hypertension: Results

## Chapter overview

This chapter starts with the sub-section of model validity, which describes how the hypertension SDDP model was checked for technical errors and validated internally and externally. The rest of this chapter consists of the outcomes of the hypertension SDDP model depending on the optimisation method applied, which are enumeration, SA, GA and RL. The main outcomes include the optimal solution, the total net benefit where the optimal solution is used and the time or computational expense. Sensitivity analyses present whether the optimal or near optimal solutions are robust to changing the value of key parameters in each method.

## Model validity

The model structure corresponded to a widely accepted underlying disease process of primary hypertension[63]. Clinically and economically relevant events were selected based on the causal linkages between major CV events and antihypertensive treatment. To ensure that the model structure was well designed on a clinically intuitive level, key modelling assumptions relating to clinical and practical issues (such as the cycle of regular check-up, key considerations to change the treatment regimen, the selection of the next drug and the maximum number of drugs sequenced and maintenance therapy) were advised by two clinical experts: Dr. Paul Morris who is a cardiologist in Sheffield Teaching Hospitals NHS Foundation Trust and Eunhee Lee who is a pharmacist working for the National Health Insurance Review Agency in South Korea.

Checks for technical errors were undertaken throughout the entire model development process. In the early stage of model development, two separate models were built in Excel and Matlab and double checked whether the results were agreed each other. The final Matlab model was designed to print key time-dependent parameters on the screen and to alert any errors within the model (e.g., whether the minimum and maximum values of key parameters are acceptable and whether the sum of rows of transition probabilities equals to 1) by popping up an error message box. Validation was also implemented for the randomly generated distributions of key parameters by comparing the mean of the generated distributions against the point estimates. Certain programming errors were automatically checked by ‘Code Analyzer’, which is built in Matlab.

The validation process included examining the relationship between key parameters and comparing the outputs with those of previously published models and studies. A validation scenario, which assumed a treatment regimen is continuously used over the follow-up period like the conventional CEAs, was used to test the internal consistency and external validity of the hypertension SDDP model. Table ‎7.1 represents the predicted outcomes of 14 treatment options (including no treatment, four single drugs, six two-drug combinations and four three-drug combinations), where they were assumed to be used continuously over the follow-up period. ‘No treatment’ was included as a comparator to test whether the base model makes preconceived expectations of future events.

Under the validation scenario the treatment success rate, which was defined as the cumulative percentage of the patients who achieve the treatment goal every three months, was gradually increased over time for all treatment options apart from no treatment (see Table ‎7.1). The treatment regimens using a three-drug combination reached the peak treatment success rate the fastest (in 6 months), followed by the treatment regimens using a two-drug combination and a single drug. For the single drugs, the treatment success rate was 96.1% for ACEIs/ARBs, 70.2% for Ds, 44.0% for BBs and 36.3% for CCBs at one year. Considering that the treatment success rates of single antihypertensive drugs were around 30~60% at one year in the RCTs[317, 368, 369], the estimated treatment success rates of BBs and CCBs were within the bounds, whereas the treatment success rate of Ds was slightly over the upper bound and the treatment success rate of ACEIs/ARBs was considerably over the upper bound. In the hypertension SDDP model, however, this high treatment success rate in ACEIs/ARBs at one year was only applied for a small proportion of patients who consistently achieved the treatment goal for one year with the initial drug being ACEIs/ARBs.

The increase in the treatment success rate was mostly due to the time-dependent SBP lowering effects, which were assumed to decrease over time (see Table ‎5.12). This pattern was found in the cumulative treatment success rate and the mean levels of SBP in Table ‎7.1. The mean levels of SBP after using a single drug for one year were 144.98 mmHg for ACEIs/ARBs, 153.23 mmHg for Ds, 155.15 mmHg for BBs and 156.14 mmHg for CCBs. These levels were slightly higher than the SBPs in patients using a single antihypertensive drug after one year in major clinical trials, which were between 135 and 157 mmHg[316, 317, 370, 371]. One possible reason for this difference is that the patient’s initial SBP used in the hypertension SDDP model, which came from the Burke’s retrospective cohort study[283], was higher than the initial SBP of the participants in the clinical trials. Most patients in the Burke’s study had moderate or severe hypertension (32.0% and 32.7%, respectively), whereas patients with mild hypertension or controlled hypertension were only 12.4%.

The 10-year risk of CVD was calculated by QRISK2 and then adjusted to a three month basis. The slight increase in the CVD risk between three months and six months was due to the treatment history included as a risk factor in QRISK2. It was assumed that the patients had a treatment history after three months, whereas they had no treatment history at the beginning of simulation. The minor fluctuation in the CVD risk between six months and 12 months was because of the population variation in their baseline SBPs and SBP lowering effect.

The annual CVD incidence rate per 100,000 persons was estimated by the model at 1112.49 where no treatment was used. According to the CHD statistics published in 2012[288] and the Stroke Statistics published in 2009[372], the CVD incidence (including acute MI, angina, stroke and HF) per 100,000 was approximately 437.20 for a male population aged between 55 and 64. Considering that the CVD risk more than doubles at SBP≥160 mmHg compared with the optimal BP (SBP<120 mmHg)[373, 374], the estimated annual CVD incidence rate in the hypertension SDDP model seems to be plausible.

In the long-term, the percentage of patients without either CVD or DM history steadily decreased and reached 0 at the end of the simulation (see Figure ‎7.1). The slope of the prevalence was steepest for no treatment, followed by single drugs, two-drug combinations and three-drug combinations. The opposite occurred for the percentage of death where patients receiving no treatment died the fastest, and in three-drug combinations the slowest (see Figure ‎7.2). The percentage of patients in a CVD state, which reached the peak at around 75 years old and then gradually declined, was also highest in no treatment across the whole follow-up period, followed by single drugs, two-drug combinations and three-drug combinations (see Figure ‎7.3). The jump between 61 and 62 years old was due to the different mechanism to calculate the transition probability to a CVD between the short-term drug switching model and the long-term CVD model. Whereas the surrogate outcome modelling based on QRISK2 was used to calculate the transition probabilities to a CVD between 60 and 61 years old (i.e., during the drug switching period), the transition probabilities to a CVD afterward came from the NICE hypertension model and propagated through the long-term CVD model.

The occurrence of DM was highest in no treatment until 70 years old, followed by single drugs, two-drug combinations and three-drug combinations (see Figure ‎7.4). Although some of antihypertensive drugs were assumed to increase the risk of DM in the hypertension SDDP model, the same pattern was found in Figure ‎7.3 and Figure ‎7.4 because of another assumption, which doubles the baseline CVD risk in patients with DM risk over patients without DM. The percentage of patients in the DM state gradually declined after 70 years old.

Table .. Treatment effectiveness predicted from the validation scenarios where the same treatment is applied in the follow-up period

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Total net benefits (£) | Treatment success rate | | | | Mean SBP (mmHg) | | | | CVD risk per three months | | | | Annual CVD incidence rate per 100,000 persons1) |
| 3m | 6m | 9m | 12m | 3m | 6m | 9m | 12m | 3m | 6m | 9m | 12m |
| No treatment | 285,474 | 0.001 | 0.001 | 0.001 | 0.004 | 174.47 | 172.63 | 170.74 | 168.57 | 0.0033 | 0.0045 | 0.0044 | 0.0046 | 1112.49 |
| Ds | 305,596 | 0.061 | 0.270 | 0.487 | 0.702 | 166.70 | 161.23 | 157.01 | 153.23 | 0.0032 | 0.0042 | 0.0041 | 0.0042 | 1034.80 |
| BBs | 297,516 | 0.122 | 0.255 | 0.356 | 0.440 | 164.91 | 161.04 | 158.18 | 155.15 | 0.0031 | 0.0042 | 0.0041 | 0.0043 | 1049.20 |
| CCBs | 302,177 | 0.107 | 0.203 | 0.282 | 0.363 | 165.48 | 162.50 | 159.27 | 156.14 | 0.0032 | 0.0042 | 0.0042 | 0.0043 | 1060.23 |
| ACEIs/ARBs | 313,163 | 0.054 | 0.546 | 0.909 | 0.961 | 167.26 | 157.32 | 150.53 | 144.98 | 0.0032 | 0.0041 | 0.0039 | 0.0040 | 1025.71 |
| Ds+BBs | 315,347 | 0.751 | 0.964 | 0.979 | 0.979 | 156.84 | 151.27 | 145.58 | 141.44 | 0.0030 | 0.0040 | 0.0039 | 0.0040 | 1000.26 |
| Ds+CCBs | 321,510 | 0.700 | 0.947 | 0.974 | 0.975 | 157.79 | 151.52 | 147.38 | 142.96 | 0.0030 | 0.0040 | 0.0039 | 0.0040 | 1003.96 |
| Ds+ACEIs/ARBs | 326,497 | 0.540 | 0.977 | 0.977 | 0.977 | 159.53 | 146.53 | 138.16 | 132.52 | 0.0030 | 0.0039 | 0.0037 | 0.0037 | 969.76 |
| BBs+CCBs | 316,485 | 0.817 | 0.945 | 0.962 | 0.965 | 155.83 | 151.00 | 146.34 | 143.85 | 0.0030 | 0.0040 | 0.0039 | 0.0040 | 1010.65 |
| BBs+ACEIs/ARBs | 320,533 | 0.720 | 0.980 | 0.980 | 0.980 | 157.32 | 147.52 | 140.43 | 135.04 | 0.0030 | 0.0039 | 0.0037 | 0.0038 | 956.67 |
| CCBs+ACEIs/ARBs | 325,448 | 0.629 | 0.973 | 0.980 | 0.980 | 158.48 | 148.36 | 140.64 | 134.47 | 0.0030 | 0.0039 | 0.0037 | 0.0038 | 980.51 |
| Ds+BBs+CCBs | 329,290 | 0.981 | 0.983 | 0.983 | 0.983 | 147.76 | 142.14 | 137.86 | 134.18 | 0.0028 | 0.0038 | 0.0037 | 0.0038 | 953.95 |
| Ds+BBs+ACEIs/ARBs | 334,604 | 0.976 | 0.984 | 0.984 | 0.984 | 149.36 | 136.53 | 129.19 | 123.17 | 0.0029 | 0.0036 | 0.0035 | 0.0036 | 913.81 |
| Ds+CCBs+ACEIs/ARBs | 334,370 | 0.941 | 0.970 | 0.970 | 0.970 | 150.49 | 135.53 | 127.04 | 120.29 | 0.0029 | 0.0037 | 0.0034 | 0.0035 | 925.11 |
| BBs+CCBs+ACEIs/ARBs | 333,854 | 0.973 | 0.980 | 0.980 | 0.980 | 148.46 | 137.64 | 130.30 | 125.50 | 0.0029 | 0.0037 | 0.0035 | 0.0036 | 931.58 |

1) Annualised rate when modelled over a lifetime.

Figure .. The percentage of patients without either CVD or DM history by age

Figure .. The percentage of death by age

Figure .. The percentage of patients in a CVD state by age

Figure .. The percentage of patients in the DM state by age

The total costs and effectiveness derived from the validation scenario were compared against the NICE hypertension model[63] (see Table ‎7.2 - Table ‎7.5). For this, the age of the initial population in the hypertension SDDP model was set to 65 years old, which is same as the NICE hypertension model. The model repeated 1,000 times for both men and women. Uncertainty in the costs and effectiveness was reported by SD. PSA was not undertaken because the NICE hypertension SDDP model did not conduct this in the latest version. Please note the objective and structure of the NICE hypertension model was very different from the hypertension SDDP model, so the comparison should be interpreted accordingly.

Where a certain drug was assumed to be continuously used over time for the newly diagnosed hypertensive patients aged 65 years, the costs estimated in the hypertension SDDP model were lower than the cost estimated from the NICE hypertension model. While the total costs estimated in the NICE hypertension model ranged from £3,910 to £4,690 in men, the total costs estimated in the hypertension SDDP model were between £2,611 and £3,857 in men (see Table ‎7.2). For women, the total costs estimated in the NICE hypertension model ranged from £4,310 to £5,230, while the total costs estimated in the hypertension SDDP model were between £2,985 and £3,857 (see Table ‎7.4). The average difference in the total costs between the NICE hypertension model and the hypertension SDDP model was £1,069 in men and £1,320 in women.

The QALYs estimated in the hypertension SDDP model were also lower than those from the NICE hypertension model. While the total QALYs estimated in the NICE hypertension model ranged from 9.57 to 10.28 in men, the total QALYs estimated in the hypertension SDDP model were between 7.90 and 8.57 in men. For women, the total QALYs estimated in the NICE hypertension model ranged from 9.96 to 10.71, while the total QALYs estimated in the hypertension SDDP model were between 8.92 and 9.77. The average difference in the total QALYs between the NICE hypertension model and the hypertension SDDP model was 1.8 in men and 0.97 in women.

The difference in the total costs and QALYs between the hypertension SDDP model and the NICE hypertension model is possibly because the type 2 DM risk at 65 years old in the hypertension SDDP model (1.38% for men and 1.14% for women in average) was higher than DM risk assumed in the NICE hypertension model (1.1%). Another potential reason is the difference in the annual CVD risk between the hypertension SDDP model and the NICE hypertension model. The annual CVD risk estimated in the hypertension SDDP model was 2.08% for 65 year old men and 1.98% for 65 years old women, whereas the NICE hypertension model assumed 2% for both men and women in the same age.

In the NICE hypertension model, CCBs were the most cost-effective initial treatment option, whereas ACEIs/ARBs were the most cost-effective initial treatment option in the hypertension SDDP model. This result arose from the SBP lowering effect used in the hypertension SDDP model. The hypertension SDDP model includes the surrogate outcome modelling based on the time-dependent SBP lowering effect over one year. Although CCBs had a higher SBP lowering effect than ACEIs/ARBs in three months, the cumulative SBP lowering effect was higher in ACEIs/ARBs after three months. This also has an effect on the long-term cost and effectiveness because the transitions between health states in the long-term CVD model depends on the final treatment result in the drug switching period. BBs and no treatment were dominated and ruled out in both studies.

Table .. Comparison of the CE results from the hypertension SDDP and the NICE hypertension models in men

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Total net benefit1)  (£) | Total cost2)  (£) | Total effectiveness2)  (QALYs) | ICER  (cost per QALY) |
| The hypertension SDDP model | | | | |
| ACEIs/ARBs | 254,607 (221.98) | 2,611 (9.80) | 8.57 (0.01) | Lowest cost option |
| Ds | 244,243 (177.78) | 2,981 (7.31) | 8.24 (0.01) | Dominated3) |
| CCBs | 246,086 (229.28) | 3,067 (12.41) | 8.31 (0.01) | Dominated |
| BBs | 241,046 (199.88) | 3,328 (12.12) | 8.15 (0.01) | Dominated |
| No treatment | 233,366 (18.89) | 3,857 (2.81) | 7.90 (0.00) | Dominated |
| The NICE hypertension model | | | | |
| Ds | 302,690 | 3,910 | 10.22 | Lowest cost option |
| ACEIs/ARBs | 302,290 | 4,010 | 10.21 | Dominated |
| CCBs | 304,370 | 4,030 | 10.28 | £1,960 |
| BBs | 292,150 | 4,550 | 9.89 | Dominated |
| No treatment | 282,410 | 4,690 | 9.57 | Dominated |

1) Willingness-to-pay for a unit of QALY was assumed £30,000.

2) The total costs and effectiveness represents the total costs and QALYs per person over a lifetime. A discount rate of 3.5% was applied to both costs and effectiveness.

3) The treatment options, which were less effective but cost more than the lowest cost option, were excluded from the calculation of the ICERs.

4) SD is presented in parenthesis.

Table .. Breakdown of the costs and QALYs of the hypertension SDDP model in men

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Costs (£) | | QALYs | |
| BP control | CVD and DM treatment | BP control | CVD and DM treatment |
| ACEIs/ARBs | 372.52 (8.87) | 2,238.10 (5.46) | 6.24 (0.02) | 2.33 (0.01) |
| Ds | 617.07 (6.78) | 2,364.09 (3.72) | 5.76 (0.01) | 2.48 (0.01) |
| CCBs | 627.04 (10.96) | 2,439.64 (9.04) | 5.73 (0.02) | 2.58 (0.02) |
| BBs | 585.10 (11.28) | 2,742.98 (6.17) | 5.39 (0.02) | 2.76 (0.01) |
| No treatment | 687.86 (0.45) | 3,090.84 (2.79) | 5.03 (0.00) | 2.88 (0.00) |

1) SD is presented in parenthesis.

2) BP stands for blood pressure.

Table .. Comparison of the CE results from the hypertension SDDP and the NICE hypertension models in women

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Total net benefit1) (£) | Total cost2)  (£) | Total effectiveness2)  (QALYs) | ICER  (cost per QALY) |
| The hypertension SDDP model | | | | |
| ACEIs/ARBs | 290,099 (327.34) | 2,985 (10.77) | 9.77 (0.03) | Lowest cost option |
| Ds | 284,793 (51.05) | 3,135 (3.32) | 9.60 (0.00) | Dominated3) |
| CCBs | 286,379 (136.23) | 3,193 (9.15) | 9.65 (0.00) | Dominated |
| BBs | 280,610 (94.89) | 3,611 (8.62) | 9.47 (0.00) | Dominated |
| No treatment | 262,922 (160.01) | 3,857 (7.10) | 8.92 (0.01) | Dominated |
| The NICE hypertension model | | | | |
| Ds | 315,190 | 4,310 | 10.65 | Lowest cost option |
| CCBs | 316,910 | 4,390 | 10.71 | £1,520 |
| ACEIs/ARBs | 314,500 | 4,400 | 10.63 | Dominated |
| BBs | 303,650 | 5,050 | 10.29 | Dominated |
| No treatment | 293,570 | 5,230 | 9.96 | Dominated |

1) Willingness-to-pay for a unit of QALY was assumed £30,000.

2) The total costs and effectiveness represents the total costs and QALYs per person over a lifetime. A discount rate of 3.5% was applied to both costs and effectiveness.

3) The treatment options, which were less effective but cost more than the lowest cost option, were excluded from the calculation of the ICERs.

4) SD is presented in parenthesis.

Table .. Breakdown of the costs and QALYs of the hypertension SDDP model in women

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Costs (£) | | QALYs | |
| BP control | CVD and DM treatment | BP control | CVD and DM treatment |
| ACEIs/ARBs | 204.67 (4.98) | 2,780.80 (9.59) | 7.19 (0.02) | 2.58 (0.01) |
| Diuretics | 188.61 (2.20) | 2,945.97 (2.65) | 6.84 (0.01) | 2.76 (0.00) |
| CCBs | 206.79 (7.03) | 2,986.07 (6.28) | 6.81 (0.02) | 2.84 (0.01) |
| BBs | 186.24 (7.48) | 3,424.99 (4.50) | 6.40 (0.01) | 3.08 (0.01) |
| No treatment | 635.39 (5.74) | 3,900.14 (3.08) | 5.65 (0.01) | 3.26 (0.00) |

1) SD is presented in parenthesis.

2) BP stands for blood pressure.

## Markov model-based optimisation: Enumeration

### Base-case

#### 1) Enumeration results

The total computational time to enumerate 4,128 sequential treatment policies in parallel was 12.20 hours where 12 Intel X5650 processors were used. The evaluation of one sequential policy was 10.64 seconds on average (note each evaluation of a policy option includes 100 Monte Carlo simulation replications to estimate the mean and CIs of the objective function). The maximum total net benefit was achieved by the sequential treatment policy starting with ACEIs/ARBs, followed by Ds+ACEIs/ARBs, Ds+CCBs+ACEIs/ARBs and Ds+BBs+ACEIs/ARBs as second, third and fourth-line treatments. The total expected net benefit for this optimal sequential treatment policy was £330,080 (95% CI £330,013-£330,147). The estimated total net benefits of the top seven policy options were not significantly different at the 5% significance level (see Table ‎7.6).

Table .. Optimal solutions using enumeration in the base-case

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| No. | Solutions | | | | TNB | SD | (p-value) |
| 1st | 2nd | 3rd | 4th |
| 3720 | ACEIs/ARBs | Ds+ACEIs/ARBs | Ds+CCBs+ACEIs/ARBs | Ds+BBs+ACEIs/ARBs | 330,080 | 342.58 |  |
| 621 | Ds | Ds+ACEIs/ARBs | Ds+CCBs+ACEIs/ARBs | BBs+ACEIs/ARBs | 330,000 | 371.88 | (p=0.15) |
| 622 | Ds | Ds+ACEIs/ARBs | Ds+CCBs+ACEIs/ARBs | CCBs+ACEIs/ARBs | 329,990 | 359.81 | (p=0.09) |
| 623 | Ds | Ds+ACEIs/ARBs | Ds+CCBs+ACEIs/ARBs | Ds+BBs+CCBs | 330,030 | 374.12 | (p=0.34) |
| 624 | Ds | Ds+ACEIs/ARBs | Ds+CCBs+ACEIs/ARBs | Ds+BBs+ACEIs/ARBs | 330,020 | 349.05 | (p=0.27) |
| 625 | Ds | Ds+ACEIs/ARBs | Ds+CCBs+ACEIs/ARBs | BBs+CCBs+ACEIs/ARBs | 329,990 | 310.92 | (p=0.05) |
| 3719 | ACEIs/ARBs | Ds+ACEIs/ARBs | Ds+CCBs+ACEIs/ARBs | Ds+BBs+CCBs | 330,020 | 411.57 | (p=0.28) |
| 3721 | ACEIs/ARBs | Ds+ACEIs/ARBs | Ds+CCBs+ACEIs/ARBs | BBs+CCBs+ACEIs/ARBs | 330,030 | 343.33 | (p=0.40) |

1) The optimal solution, which had the highest total net benefit, is in grey.

Figure ‎7.5 graphically shows the estimated mean total net benefits of 4,128 policies. The range of the total net benefits was between £296,250 (policy number 3257, treatment sequence starting with ACEIs/ARBs, followed by CCBs, Ds and BBs) and £330,080, which is the total net benefit of the optimal solution as shown in Table ‎7.6 (policy number 3720, treatment sequence starting with ACEIs/ARBs, followed by Ds+ACEIs/ARBs, Ds+CCBs+ACEIs/ARBs and Ds+BBs+ACEIs/ARBs). The difference in total net benefit between the best solution and the worst solution was over £30,000, which is more than one full QALY gained. The enumeration results are also shown in Figure ‎7.6 as four separate figures by initial drug. Regardless of the initial treatment, Figure ‎7.6 shows that the total net benefits can vary substantially depending on the choice of subsequent treatments. The estimated total net benefits of the sequential treatment policy appear to be considerably associated with the additive effect of the four single drugs.

Figure ‎7.7 shows that the percentage of the patients who used the third or fourth-line drug at the end of the drug switching period was low, where the percentage of the patients who used the second-line drug was high. The percentage of the patients who used only the first-line drug during the drug switching period was very low from a minimum of 0.06% (policy number 767, whose total net benefit was £320,760) to a maximum of 0.28% (policy number 2007, whose total net benefit was £320,820). The percentage of the patients who used the second-line drugs at the end of the drug switching period was from a minimum of 0.65% (policy number 3143, whose total net benefit was £324,520) to a maximum of 67.68% (policy number 1725, whose total net benefit was £316,570). The percentage of the patients who used the third-line drugs at the end of the drug switching period was from a minimum of 13.44% (policy number 1691, whose total net benefit was £313,160) to a maximum of 80.07% (policy number 209, whose total net benefit was £314,670). The percentage of the patients who used all four lines of treatments during the drug switching period (also used forth-line drug at the end of the drug switching period) was from a minimum of 0.08% (policy number 2795, whose total net benefit was £320,070) to a maximum of 76.95% (policy number 170, whose total net benefit was £315,900).

Figure .. Total net benefit of 4,128 policies where enumeration was used

|  |  |
| --- | --- |
|  |  |
|  |  |

Figure .. Total net benefits of 4,128 sequential treatment policies depending on the initial drug

|  |  |
| --- | --- |
|  |  |
|  |  |

Figure .. The percentage of the patients who were using first, second, third or fourth-line drug at the end of the drug switching period

#### 2) Cluster analysis depending on the first, second, third and fourth-line drug

Cluster analyses were conducted for better understanding on the nature of the estimated total net benefits of the 4,128 policies. Firstly, all possible treatment sequences were divided into four groups depending on the initial drug and named Group 1 for the policies starting with Ds, Group 2 for the policies starting with BBs, Group 3 for the policies starting with CCBs and Group 4 for the policies starting with ACEIs/ARBs. If there was a significant difference between group means by the Analysis of Variance (ANOVA), a multiple comparison test using the Tukey’s Honestly significant difference criterion (Tukey’s HSD) was performed[375].

ANOVA showed that there was no significant difference between the means of the four defined groups (see Figure ‎7.8). The mean of Group 1 was £319,410, Group 2 was £ 319,180, Group 3 was £ 319,160 and Group 4 was £ 319,310 (p=0.51705).



1) X-axis represents the groups divided by initial drugs (1: Ds, 2: BBs, 3: CCBs and 4: ACEIs/ARBs).

Figure .. Graphical summary of the mean and CIs for each group classified by initial drug

All possible treatment sequences were also divided into 10 groups depending on the second-line drug, and named from Group 1 to Group 10 for the groups whose second-line drug was Ds, BBs, CCBs, ACEIs/ARBs, Ds+BBs, Ds+CCBs, Ds+ACEIs/ARBs, BBs+CCBs, BBs+ACEIs/ARBs and CCBs+ACEIs/ARBs (see Figure ‎7.9). ANOVA found that there was a significant difference in total net benefit between 10 groups defined by the second-line drug (p<0.05). The result from Tukey’s HSD analysis in Figure ‎7.9 shows the significant different in total net benefit between, where single drugs were used and where two-drug combination drugs were used as the second-line drug. The average total net benefit was highest where CCBs+ACEIs/ARBs was used as the second-line drug (£321,999) followed by where Ds+ACEIs/ARBs or Ds+CCBs were used as the second-line drug (£321,361 and £ 321,056). The rest groups had means significantly lower than those three groups.

Cluster analyses also found significant differences between 14 groups defined by the third or fourth-line drug (p<0.05 for both). In both cases, the group means were greater where three-drug combinations were used as the third or fourth-line drug followed by two-drug combinations and single drugs (see Figure ‎7.10 and Figure ‎7.11). In the comparison between 14 groups divided by the third-line drug, the group of sequential treatment policies using Ds+CCBs+ACEIs/ARBs as the third-line drug had the significantly greater mean than the other 13 policies (£325,797). In contrast, no significant difference was found between the policies using three-drug combinations as the fourth-line treatment.

|  |  |  |
| --- | --- | --- |
|  | | 1) Group 1 to Group 10 represent the set of treatment sequences whose second-line drug is Ds, BBs, CCBs, ACEIs/ARBs, Ds+BBs, Ds+CCBs, Ds+ACEIs/ARBs, BBs+CCBs, BBs+ACEIs/ARBs and CCBs+ACEIs/ARBs, respectively.  2) Cycle represents the mean of total net benefits; horizontal line represents the comparison intervals; the blue colour represents the group, which has the highest average total net benefit; the grey colour represents the group whose average total net benefit is not significantly different with the group, which has the highest average total net benefit; and the red colour represents the group whose average total net benefit is significantly different with the group, which has the highest average total net benefit.    Figure .. Graphical summary of the mean and comparison intervals for each group classified by second-line drug |
|  | 1) Group 1 to Group 14 represent the set of treatment sequences whose third-line drug is Ds, BBs, CCBs, ACEIs/ARBs, Ds+BBs, Ds+CCBs, Ds+ACEIs/ARBs, BBs+CCBs, BBs+ACEIs/ARBs, CCBs+ACEIs/ARBs, Ds+BBs+CCBs, Ds+BBs+ACEIs/ARBs, Ds+CCBs+ACEIs/ARBs and BBs+CCBs+ACEIs/ARBs, respectively.  2) Cycle represents the mean of total net benefits; horizontal line represents the comparison intervals; the blue colour represents the group, which has the highest average total net benefit; the grey colour represents the group whose average total net benefit is not significantly different with the group, which has the highest average total net benefit; and the red colour represents the group whose average total net benefit is significantly different with the group, which has the highest average total net benefit.  Figure .. Graphical summary of the mean and comparison intervals for each group classified by third-line drug | |
|  | 1) Group 1 to Group 14 represent the set of treatment sequences whose third-line drug is Ds, BBs, CCBs, ACEIs/ARBs, Ds+BBs, Ds+CCBs, Ds+ACEIs/ARBs, BBs+CCBs, BBs+ACEIs/ARBs, CCBs+ACEIs/ARBs, Ds+BBs+CCBs, Ds+BBs+ACEIs/ARBs, Ds+CCBs+ACEIs/ARBs and BBs+CCBs+ACEIs/ARBs, respectively.  2) Cycle represents the mean of total net benefits; horizontal line represents the comparison intervals; the blue colour represents the group, which has the highest average total net benefit; the grey colour represents the group whose average total net benefit is not significantly different with the group, which has the highest average total net benefit; and the red colour represents the group whose average total net benefit is significantly different with the group, which has the highest average total net benefit.  Figure .. Graphical summary of the mean and comparison intervals for each group classified by fourth-line drug | |

#### 3) Cluster analysis depending on the combination of initial and second-line drugs

Cluster analysis was also implemented to compare the average total net benefits depending on the combination of initial and second-line drugs. Full list of groups tested by ANOVA and Tukey’s HSD is provided in Table ‎7.7.

Figure ‎7.12 shows that there was a significant difference in total net benefit between the 36 groups defined by the initial and second-line drug (p<0.05). Regardless of the initial drug, using CCBs+ACEIs/ARBs as the second-line treatment provides higher total net benefits than other second-line treatment options: that is, Group 9 (£322,141 where Ds were used initially, followed by CCBs+ACEIs/ARBs), Group 18 (£321,945 where BBs were used initially, followed by CCBs+ACEIs/ARBs), Group 27 (£321,900 where CCBs were used initially, followed by CCBs+ACEIs/ARBs) and Group 36 (£322,009 where ACEIs/ARBs were used initially, and then adding CCBs to ACEIs/ARBs).

The average total net benefits of the policies using Ds+CCBs (Group 5, 14, 23 and 32) or Ds+ACEIs/ARBs (Group 6, 15, 24 and 33) as a second-line drug were also high regardless of the initial drug. These policies were significantly better than using a single drug (Group1, 2, 3, 10, 11, 12, 19, 20, 21, 28, 29 and 30) and using Ds+BBs (Group 4, 13, 22 and 31) or BBs+CCBs (Group 7, 16, 25 and 34) as the second-line drug.

Table .. The list of tested groups divided by the combination of initial and second-line drugs

|  |  |  |
| --- | --- | --- |
|  | 1st drug | 2nd drug |
| Group 1 | Ds | BBs |
| Group 2 | Ds | CCBs |
| Group 3 | Ds | ACEIs/ARBs |
| Group 4 | Ds | Ds+BBs |
| Group 5 | Ds | Ds+CCBs |
| Group 6 | Ds | Ds+ACEIs/ARBs |
| Group 7 | Ds | BBs+CCBs |
| Group 8 | Ds | BBs+ACEIs/ARBs |
| Group 9 | Ds | CCBs+ACEIs/ARBs |
| Group 10 | BBs | Ds |
| Group 11 | BBs | CCBs |
| Group 12 | BBs | ACEIs/ARBs |
| Group 13 | BBs | Ds+BBs |
| Group 14 | BBs | Ds+CCBs |
| Group 15 | BBs | Ds+ACEIs/ARBs |
| Group 16 | BBs | BBs+CCBs |
| Group 17 | BBs | BBs+ACEIs/ARBs |
| Group 18 | BBs | CCBs+ACEIs/ARBs |
| Group 19 | CCBs | Ds |
| Group 20 | CCBs | BBs |
| Group 21 | CCBs | ACEIs/ARBs |
| Group 22 | CCBs | Ds+BBs |
| Group 23 | CCBs | Ds+CCBs |
| Group 24 | CCBs | Ds+ACEIs/ARBs |
| Group 25 | CCBs | BBs+CCBs |
| Group 26 | CCBs | BBs+ACEIs/ARBs |
| Group 27 | CCBs | CCBs+ACEIs/ARBs |
| Group 28 | ACEIs/ARBs | Ds |
| Group 29 | ACEIs/ARBs | BBs |
| Group 30 | ACEIs/ARBs | CCBs |
| Group 31 | ACEIs/ARBs | Ds+BBs |
| Group 32 | ACEIs/ARBs | Ds+CCBs |
| Group 33 | ACEIs/ARBs | Ds+ACEIs/ARBs |
| Group 34 | ACEIs/ARBs | BBs+CCBs |
| Group 35 | ACEIs/ARBs | BBs+ACEIs/ARBs |
| Group 36 | ACEIs/ARBs | CCBs+ACEIs/ARBs |

|  |  |
| --- | --- |
|  | 1) The full list of tested groups divided by initial and second-line drugs is provided in Table ‎7.7.  2) Cycle represents the mean of total net benefits; horizontal line represents the comparison intervals; the blue colour represents the group, which has the highest average total net benefit; the grey colour represents the group whose average total net benefit is not significantly different with the group, which has the highest average total net benefit; and the red colour represents the group whose average total net benefit is significantly different with the group, which has the highest average total net benefit.  Figure .. Graphical summary of the mean and comparison intervals for each cluster classified by the combination of initial and second drugs |

#### 4) Cluster analysis of top 10 % solution

Cluster analyses were conducted to explore the characteristics of the top 10% of policy options regarding mean total net benefit. Figure ‎7.13 shows the distributions (%) of each drug or drug combination included in the top 10% policies, depending on the position of the drug or drug combination in the drug sequence. Of 413 top 10% policies, 27.1% had Ds as the initial drug, 26.9% were ACEIs/ARBs, 24.7% were CCBs and 21.3% were BBs. The second-line drugs distribution mainly comprised of CCBs+ACEIs/ARBs of 41.4%, Ds+ACEIs/ARBs of 40.9% and Ds+CCBs of 15.0%. For the third-line drug, three drug combinations such as Ds+CCBs+ACEIs/ARBs (32.0%), BBs+CCBs+ACEIs/ARBs (25.7%), Ds+BBs+CCBs (21.3%) and Ds+BBs+ACEIs/ARBs (18.4%) took a greater proportion than other drugs. The fourth-line drugs were more evenly distributed across 14 treatment options with Ds+CCBs+ACEIs/ARBs (8.96%) and Ds+ACEIs/ARBs (5.08%) being the highest and lowest.

Figure .. Distribution of the drugs included in the top 10% policies

A similar pattern was found in the second, third and fourth-line drugs where the top 10% of policy options were divided by initial drug (see Figure ‎7.14 - Figure ‎7.17). For example, where a Ds was used initially (Figure ‎7.14), the second-line drugs of the top 10% solutions mainly comprised of Ds+ACEIs/ARBs (42.7%) and CCBs+ACEIs/ARBs (42.7%). For the third-line drug, three drug combinations such as Ds+CCBs+ACEIs/ARBs (32.0%), BBs+CCBs+ACEIs/ARBs (22.3%), Ds+BBs+CCBs (21.4%) and Ds+BBs+ACEIs/ARBs (21.4%) took a greater proportion than other drugs. The fourth-line drugs were evenly distributed across the remaining 13 treatment options.

Figure .. Distribution of the drugs included in the top 10% policies, where Ds are used initially

Figure .. Distribution of the drugs included in the top 10% policies, where BBs are used initially

Figure .. Distribution of the drugs included in the top 10% policies, where CCBs are used initially

Figure .. Distribution of the drugs included in the top 10% policies, where ACEIs/ARBs are used initially

### Sensitivity analysis

#### 1) Population characteristics

Sensitivity analyses were conducted to examine whether the base-case enumeration results were sensitive to gender, age and initial SBP. Table ‎7.8 summarises the optimal solutions and their net benefits depending on age, gender and initial SBP.

The total net benefit decreased as the age increased. It was higher in women than men across all age groups because women had a lower CVD risk so lived longer than men in the hypertension SDDP model. Despite the different baseline risks depending on the age and gender, most optimal treatment sequences were not out of the optimal solution identified in enumeration and the seven policies that were not statistically different with the optimal policy. The optimal initial drug was either ACEIs/ARBs or Ds across all age and gender groups. For both men and women whose initial treatment fails, optimal second-line treatment was either adding Ds to ACEIs/ARBs, where ACEIs/ARBs is used initially, or adding ACEIs/ARBs to Ds, where Ds is used initially. For the third-line treatment, Ds+CCBs+ACEIs/ARBs were optimal in most age and gender groups, which was identical with the NICE guidelines. For the fourth-line treatment, Ds+CCBs+ACEIs/ARBs or BBs+CCBs+ACEIs/ARBs were optimal, depending on the optimal drugs selected in the previous cycles. The computational time was longer in the patient group aged 50 initially (14.58 hours for men and 18.90 hours for women) than the patient group aged 70 initially (8.39 hours for men and 8.56 hours for women) due to how long the patients live.

The total net benefit was lower where the initial SBP was lower (i.e., 163.5 or 153.5 mmHg) than the base-case (173.5 mmHg). This result corresponds with MacMahon et al and Collins et al’ s studies, which showed the greater treatment benefit for an individual having a greater CVD risk at any age[224, 225]. For the patients with a lower initial SBP than the base-case, the optimal initial drug was ACEIs/ARBs, which was same with the base-case. The optimal second-line drug was sensitive to the change in patients’ initial SBP. Where the initial SBP was 163.5 or 153.5 mmHg, the optimal second-line drug was CCBs+ACEIs/ARBs, whereas Ds+ACEIs/ARBs was the optimal second-line drug in other scenarios. This can be explained by the relative (rather than absolute) SBP lowering effect assumed in the hypertension SDDP model because, with the same relative effect, the difference in the absolute SBP reduction between Ds+ACEIs/ARBs and CCBs+ACEIs/ARBs was reduced if the initial SBP becomes lower. This could reduce the difference in total net benefit between the policies using Ds+ACEIs/ARBs and CCBs+ACEIs/ARBs as the second-line drug.

#### 2) Other parameters

Sensitivity analyses were undertaken to find out whether the optimal solution identified using enumeration in the base-case is sensitive when the objective of SDDP is to maximise the treatment success rate rather than total net benefit. In practice, costs might be of secondary concern to clinicians, who primarily seek to optimise clinical outcomes for individual patients.

There was significant uncertainty in the time-dependent SBP lowering effect based on Wald’s and Wright et al’s systematic reviews. The assumptions in the base-case of the hypertension SDDP model is that the BBs and CCBs drop SBP quickly in the first three months and then have little incremental SBP lowering effect after three months, whereas Ds and ACEIs/ARBs gradually drop SBP over one year. In sensitivity analysis, all single antihypertensive drugs were assumed to decrease SBP gradually over one year. The long-term SBP lowering effect of Ds, CCBs and ACEIs/ARBs was derived from ALLHAT[317] and those of BBs was derived from Dutch-TIA[318]. In this case, the SBP lowering effect is highest in Ds, followed by CCBs, ACEIs/ARBs and BBs consistently over time. Three-monthly SBP change was calculated based on Equation 5.5. The same assumption with the base-case was used for the SBP lowering effect of both two and three-drug combinations (see Equation 5.6). The absolute SBP lowering effect was converted to the relative SBP lowering effect using Equation 5.7.

Table .. Optimal treatment sequences and total net benefit depending on gender and initial age

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Policy number | Optimal solution | | | | Optimal value (£) | Computation  time (h) |
|  | 1st | 2nd | 3rd | 4th |
| Male | | | | | | | |
| 50 years old | 625\* | Ds | Ds+ACEIs/ARBs | Ds+CCBs+ACEIs/ARBs | BBs+CCBs+ACEIs/ARBs | 435,950 | 14.58 |
| 60 years old  (base-case) | 3720\* | ACEIs/ARBs | Ds+ACEIs/ARBs | Ds+CCBs+ACEIs/ARBs | Ds+BBs+ACEIs/ARBs | 330,080 | 12.20 |
| 70 years old | 602 | Ds | Ds+ACEIs/ARBs | Ds+BBs+CCBs | Ds+CCBs+ACEIs/ARBs | 211,530 | 8.39 |
| Female | | | | | | | |
| 50 years old | 625\* | Ds | Ds+ACEIs/ARBs | Ds+CCBs+ACEIs/ARBs | BBs+CCBs+ACEIs/ARBs | 462,270 | 18.90 |
| 60 years old | 3718 | ACEIs/ARBs | Ds+ACEIs/ARBs | Ds+CCBs+ACEIs/ARBs | CCBs+ACEIs/ARBs | 356,300 | 13.75 |
| 70 years old | 3721\* | ACEIs/ARBs | Ds+ACEIs/ARBs | Ds+CCBs+ACEIs/ARBs | BBs+CCBs+ACEIs/ARBs | 247,030 | 8.56 |
| Initial SBP1) | | | | | | | |
| 163.5 mmHg | 4105 | ACEIs/ARBs | CCBs+ACEIs/ARBs | Ds+BBs+ACEIs/ARBs | Ds+CCBs+ACEIs/ARBs | 320,420 | 13.32 |
| 153.5 mmHg | 4117 | ACEIs/ARBs | CCBs+ACEIs/ARBs | Ds+CCBs+ACEIs/ARBs | BBs+CCBs+ACEIs/ARBs | 318,690 | 12.99 |

1) The different levels of initial SBP were only applied to the base-case, which included a cohort of 60 year old male patients.

2) The policy numbers with \* are included in the top eight policies identified from the enumeration in Table ‎7.6.

Figure .. SBP lowering effect calculated based on ALLHAT and Dutch-TIA

Sensitivity analyses investigated the impact of the changes in the drug switching period on the optimal solution and computational complexity. The analyses tested whether the drug switching period used in the base model (i.e., three months x four periods = one year) could provide sufficient scope for the long-term effects of the sequential drug decision-making. Also, there were a proportion of patients who did not use all four lines of drugs in some treatment sequences in the base-case. This sensitivity analysis tried to extend the time frame from four periods to six and eight periods (i.e., three months x six periods = 1.5 year and three months x eight periods = two years) so that more patients used all four lines of drugs during the drug switching period. The patients who used all four lines of drugs before the end of the given drug switching period were assumed to use a randomly selected treatment option until a CV event or DM happened. This study did not try to extend the drug switching period beyond two years because the change in treatment regimen is more likely to occur in the early stage of primary hypertension (i.e., before 18 months)[4], and drug switching after two years from initial diagnosis is likely to be due to a complication, rather than lack of SBP lowering effect.

The uncertainties in AEs were also explored in sensitivity analyses. Whereas DAEs, which were used in the base-model, only include serious AEs that cause treatment discontinuation, AEs include any symptoms that might plausibly be caused by antihypertensive drugs. Law et al provided comprehensive information on the AEs of antihypertensive drugs[282, 319]. Furthermore, considering that the prevalence of AEs may be higher in a clinical setting than RCTs, it was expected that using AEs, which have higher rates of incidence than DAE, could provide more realistic results[281].

Lastly, sensitivity analysis was conducted to explore the uncertainties in treatment scenarios for CVD. In the base-case it was assumed that all patients who had a CV event or DM took a recommended antihypertensive drug to treat the underlying disease. In practice, however, it is possible to use another drug that is not recommended in the clinical guidelines, but is believed by the clinicians to be the best for the patients without contraindications (clinician’s opinion)[4]. In sensitivity analysis, patients, who had a history of a CV event or DM, were assumed to use a randomly selected drug. The exception was CCB for patients with HF as CCB is contraindicated in these patients[8-10, 245].

Table ‎7.9 summarises the results of the sensitivity analyses implemented depending on the change in key parameters. Sensitivity analyses showed that the optimal solution (or the policies, which are not significantly different with the optimal solution) identified in the base-case was robust to changes in objective, SBP lowering effect, the extension of drug switching period, AE rates and the treatment scenario for CVD and DM, apart from the fourth-line drug. Where the objective function was to maximise the treatment success rate during the drug switching period, the optimal solution started with ACEIs/ARBs, and then moved to Ds+ACEIs/ARBs, Ds+BBs+ACEIs/ARBs and Ds+BBs+CCBs. Where the time-dependent SBP lowering effects calculated based on ALLHAT and Dutch-TIA were used, the optimal solution started with ACEIs/ARBs, and then moved to Ds+ACEIs/ARBs, Ds+BBs+ACEIs/ARBs and Ds+CCBs+ACEIs/ARBs. Where DAE (instead of AE) or the random treatment scenario for CVD and DM (instead of the set of recommended drugs for CVDs and DM) was used, the optimal initial, second and third-line drugs were the same with where the time-dependent SBP lowering effects calculated based on ALLHAT and Dutch-TIA was used, but the optimal fourth-line was BBs+CCBs+ACEIs/ARBs.

Where the drug switching period was extended to six or eight periods, Figure ‎7.19 shows the increase in the percentage of the patients who used all four lines of treatments in a defined sequential treatment policy. Compared with the base model, the percentage of the patients who used all four lines of treatments was increased between 0.021% and 74.85% above the rates estimated for the base-case (average 10.17%). Where the drug switching period was extended to six or eight periods, the total net benefits were also increased by £5,840 to £21,750 (average £9,305) compared with the base-case (see Figure ‎7.20). However, the optimal solutions were the same with the optimal solution identified in enumeration, where the drug switching period was extended to eight, or the seven policies, which were not significantly different with the optimal solution, where the drug switching period was extended to six.

The extension of the drug switching period increased the number of possible disease pathways from 31 to 127, where the drug switching period was six, and 511, where the drug switching period was eight. This also involved the additional modelling codes to allocate a drug based on the assumed decision rules and to allow calculating possible transitions and total net benefits during the extended periods. Due to the increase in the size of the problem and computational complexity, the computational time increased substantially from 12.20 hours in the based model to 73.65 hours, where the drug switching period was six, and to 222.15 hours, where the drug switching period was eight.

Table .. Optimal solutions and total net benefits depending on the change in key parameters

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Policy number | Optimal solution | | | | Optimal value (£) | Computation time (h) |
| 1st | 2nd | 3rd | 4th |
| TNB basis | 3720\* | ACEIs/ARBs | Ds+ACEIs/ARBs | Ds+CCBs+ACEIs/ARBs | Ds+BBs+ACEIs/ARBs | 330,080 | 12.20 |
| TS basis | 3708 | ACEIs/ARBs | Ds+ACEIs/ARBs | Ds+BBs+ACEIs/ARBs | Ds+BBs+CCBs | 0.9984 | 10.18 |
| SBP lowering effect | 3709 | ACEIs/ARBs | Ds+ACEIs/ARBs | Ds+BBs+ACEIs/ARBs | Ds+CCBs+ACEIs/ARBs | 320,100 | 8.65 |
| Extended drug switching period to 6 | 3721\* | ACEIs/ARBs | Ds+ACEIs/ARBs | Ds+CCBs+ACEIs/ARBs | BBs+CCBs+ACEIs/ARBs | 339,020 | 73.36 |
| Extended drug switching period to 8 | 3720\* | ACEIs/ARBs | Ds+ACEIs/ARBs | Ds+CCBs+ACEIs/ARBs | Ds+BBs+ACEIs/ARBs | 343,000 | 222.15 |
| AE | 625\* | Ds | Ds+ACEIs/ARBs | Ds+CCBs+ACEIs/ARBs | BBs+CCBs+ACEIs/ARBs | 330,080 | 13.22 |
| Random treatment scenario for CVD and DM | 625\* | Ds | Ds+ACEIs/ARBs | Ds+CCBs+ACEIs/ARBs | BBs+CCBs+ACEIs/ARBs | 333,320 | 13.48 |

1) The base-case is in grey.

2) The policy numbers with \* are included in the top eight policies identified from the enumeration in Table ‎7.6.

Figure .. Proportion of patients who used four lines of treatments depending on the modelled drug switching period

Figure .. Total net benefit depending on the modelled drug switching period

## Simulated annealing

SA model runs were performed at cooling rates of 0.9, 0.7, and 0.5. The number of iterations at each temperature was 10, 30 and 50. Each test started with a heuristically selected initial solution that had the smallest total net benefit based on the base-case enumeration results. For each iteration, SA randomly selected the next solution from the neighbourhood of the current solution, which was ±50 policy number from the current solution. A random jump was included every 30 iterations to allow better escaping from local optima and exploring other areas of the solution space. Initial temperature was 1, and the stopping temperature was 1e-8. If a policy consistently remained as the best policy until 80% percent of the allowed iterations at each temperature were searched, the algorithm stopped searching at the current temperature and moved to the next temperature.

Each test was repeated 20 times to evaluate the average performance of SA using 1) the probability to find the optima and 2) the average penalty rate. The probability to find the optima shows what percentage of the separate simulation runs of SA finds the global optimum or the policies, which were not significantly different with the global optimum. The average penalty rate, which represents the difference in the value of the objective function between the global optimum and the heuristic solution, was also calculated using the following equation[202]:

Average penalty rate = Equation 7.1.

where is the optimal solution identified in enumeration and is the solution from SA.

Table ‎7.10 shows that SA is capable of finding good solutions in a much shorter computational time than enumeration. The algorithm repeated the evaluation of the objective function (each evaluation includes 100 Monte Carlo simulation replications) from a minimum 280 times to a maximum 2,220 times, compared to 4,128 times using enumeration. Total computational time ranges from a minimum 0.73 hours to a maximum 6.22 hours, compared to 12.20 hours using enumeration. Depending on the selected parameter, 5.04-32.85% of the search space was examined. Nevertheless, most SA experiments implemented by the combinations of cooling rate and maximum number of iterations allowed at the same temperature found the optimal solution or the statistically equivalent solutions.

Better solutions were obtained where the cooling rate yielded slower sequences of temperature decreases (i.e., where the cooling rate was 0.9 and the maximum number of iterations within a temperature was 50) (see Table ‎7.10). Regardless of what the other parameters were used, the quality of solution was consistently good where the cooling rate was 0.9 and the maximum number of iterations within a temperature was 50 (see Figure ‎7.21). The probability to find the global optimum was also higher when using a slower cooling rate than when using a faster cooling rate; and when allowing a larger number of iterations within the same temperature than when the maximum number of iterations within the same temperature was 10 or 30 (see Table ‎7.11). The average penalty rate was reduced where a slower cooling rate and a larger number of iterations within the same temperature were allowed. Figure ‎7.22 also shows the potential risk of premature convergence where a fast cooling rate was employed. Search rates were higher as the cooling rates were increased; however, it was not always increased as the maximum number of iterations with a temperature increased (see Figure ‎7.23).

Figure .. Maximum total net benefit depending on the cooling rate and the number of iterations within a temperature

Table .. Computational results from SA depending on cooling rate and the maximum number of iterations within the same temperature

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Cooling rate | Maximum number of iterations within the same temperature | Maximum number of success within the same temperature | Total iteration number1) | Time (h) | Time per iteration (s) | Solution number2) | Total net benefit of the solution (£) | Search rate (%)3) |
| 1 | 0.5 | 10 | 8 | 280 | 0.73 | 9.41 | 1656 | 328,610 | 5.04 |
| 2 | 0.5 | 30 | 24 | 840 | 2.26 | 9.69 | 3719\* | 330,030 | 17.61 |
| 3 | 0.5 | 50 | 40 | 1400 | 3.69 | 9.50 | 624\* | 330,130 | 19.91 |
| 4 | 0.7 | 10 | 8 | 530 | 1.37 | 9.32 | 2051 | 329,310 | 9.74 |
| 5 | 0.7 | 30 | 24 | 1590 | 4.11 | 9.31 | 624\* | 330,070 | 30.98 |
| 6 | 0.7 | 50 | 40 | 2100 | 5.49 | 9.41 | 3721\* | 330,130 | 19.60 |
| 7 | 0.9 | 10 | 8 | 1250 | 3.72 | 10.71 | 3721\* | 330,060 | 17.34 |
| 8 | 0.9 | 30 | 24 | 2220 | 4.56 | 7.39 | 3720\* | 330,060 | 32.85 |
| 9 | 0.9 | 50 | 40 | 1900 | 6.22 | 11.79 | 3721\* | 330,130 | 22.87 |

1) Iteration number means the evaluation of the objective function including 100 Monte Carlo simulations.2) The solution numbers with \* are included in the top eight policies identified from the enumeration in Table ‎7.6.

3) Search rate = (The number of policies evaluated by SA / Total number of possible policies (= 4,128)) x 100.

4) The base-case is in grey.

Table .. The average performance of SA from 20 repeated runs

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | C0.5xR10 | C0.5xR30 | C0.5xR50 | C0.7xR10 | C0.7xR30 | C0.7xR50 | C0.9xR10 | C0.9xR30 | C0.9xR50 |
| 1 | 0.00 | 0.00 | 0.00 | 0.00 | 3.60 | 0.00 | 0.00 | 0.00 | 0.00 |
| 2 | 14.33 | 0.90 | 0.00 | 8.86 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 3 | 30.69 | 0.00 | 0.00 | 0.00 | 0.00 | 5.96 | 0.00 | 0.00 | 0.00 |
| 4 | 8.08 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 5 | 0.00 | 0.00 | 0.00 | 27.58 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 6 | 0.59 | 0.00 | 0.00 | 18.12 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 7 | 21.33 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 8 | 14.48 | 0.00 | 0.00 | 0.60 | 0.00 | 4.61 | 0.00 | 0.00 | 0.00 |
| 9 | 0.00 | 0.00 | 0.00 | 32.82 | 0.66 | 0.00 | 0.00 | 0.00 | 0.00 |
| 10 | 0.00 | 6.19 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 11 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 12 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 13 | 17.13 | 4.10 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 14 | 8.18 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 15 | 9.90 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 16 | 0.00 | 0.00 | 0.00 | 2.84 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 17 | 12.42 | 0.00 | 0.00 | 4.53 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 18 | 8.30 | 0.81 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 19 | 0.00 | 0.00 | 0.00 | 11.48 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 20 | 0.00 | 1.55 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| Average penalty rate (%) | 13.22 | 2.71 | 0.00 | 13.35 | 2.13 | 5.28 | 0.00 | 0.00 | 0.00 |
| Probability to find the optima (%) | 45.00 | 75.00 | 100.00 | 60.00 | 90.00 | 90.00 | 100.00 | 100.00 | 100.00 |

1) **C** stands for the cooling rate and **R** stands for the maximum number of iterations within the same temperature.

|  |
| --- |
|  |

1) **C** stands for the cooling rate and **R** stands for the maximum number of iterations within the same temperature.

Figure .. Convergence of SA depending on the cooling rate and the maximum number of iterations

|  |  |  |
| --- | --- | --- |
|  |  |  |
|  |  |  |
|  |  |  |

1) X-axis represents the policy numbers; Y-axis represents the number of times that each policy was searched during the optimisation procedure.

2) **C** stands for the cooling rate and **R** stands for the maximum number of iterations within the same temperature.

Figure .. Search rate of SA depending on the cooling rate and the maximum number of iterations

## Genetic algorithm

Initial tests of GA were undertaken to determine the best setup of the number of generations and the population size. The population size in GA means the number of policies evaluated at the same time in each generation. A total of nine sets of experiments with different combinations of generations (25, 50 and 100) and population sizes (10, 30, 50 and 100) were implemented. In each generation, 90% of the fittest parents were assumed to remain in the future generation. The initial population was selected randomly. In the base-case, crossover rate was assumed to be 0.7, and mutation rate was 0.1. Each test was repeated 20 times to evaluate the percentage of the separate GA simulation runs to find the global optimum and the average penalty rate using Equation 7.1.

Table ‎7.12 summarises the computational results of the GA experiments. The evaluation of the objective function (each evaluation includes 100 Monte Carlo simulation replications) was repeated from a minimum 235 times to a maximum 2,730 times, compared to 4,128 times using enumeration. Overall computational time increased as the number of iterations increased. Population size had a greater impact on computational time. Average computation time was approximately 10.97 seconds per run. All GA experiments found the optimal solution or the statistically equivalent solutions. The potential reason that the point estimate of the total net benefits of the same policy numbers were slightly different is due to the noise from the random drug allocation after the use of fourth-line drug and for the patients who have a CVD or DM. Search rates increased as the number of iterations increased; however, the objective function value was not always increased proportionally to the increment in iterations or computational time. The maximum total net benefit was obtained when the number of generations was 100 and the size of population was 10. However, premature convergence may happen when the population size was small (i.e., 10) (see Table ‎7.13 and Figure ‎7.24).

The performance of GA also depends on the crossover and mutation rates. The following eight combinations of crossover rates (0.7 and 0.8) and mutation rates (0.01, 0.05, 0.1 and 0.2) were implemented where the population size was 30 and the number of generation was 100. Table ‎7.14 and Table ‎7.15 shows that the decrease in the crossover and mutation rates has a potential risk of premature convergence due to a lack of population diversity. On the contrary, the trade-off between population diversity and the quality of solution may also exist, depending on the choice of the crossover and mutation rates, although this was not clear in this study.

Table .. Computational results by the number of generations and population size from GA

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Generation number | Population size | Total iteration number1) | Time (h) | Time per iterations (s) | Solution number2) | Total net benefit of the solution (£) | Search rate (%) |
| 1 | 25 | 10 | 235 | 0.68 | 10.42 | 625\* | 330,080 | 3.78 |
| 2 | 25 | 30 | 705 | 2.12 | 10.83 | 623\* | 330,110 | 10.05 |
| 3 | 25 | 50 | 1,175 | 3.56 | 11.18 | 624\* | 330,120 | 15.12 |
| 4 | 25 | 100 | 2,350 | 6.56 | 10.05 | 623\* | 330,120 | 25.53 |
| 5 | 50 | 10 | 460 | 1.44 | 11.28 | 623\* | 330,130 | 6.18 |
| 6 | 50 | 30 | 1,380 | 4.10 | 10.70 | 3721\* | 330,120 | 14.85 |
| 7 | 50 | 50 | 2,300 | 7.41 | 11.60 | 625\* | 330,140 | 18.65 |
| 8 | 100 | 10 | 910 | 2.88 | 11.39 | 623\* | 330,160 | 9.52 |
| 9 | 100 | 30 | 2,730 | 8.58 | 11.31 | 623\* | 330,130 | 21.75 |

1) Iteration number means the evaluation of the objective function including 100 Monte Carlo simulations.

2) The solution numbers with \* are included in the top eight policies identified from the enumeration in Table ‎7.6.

3) Crossover rate was set to 0.7 and mutation rate was set to 0.1.

4) The base-case is in grey.

Table .. The average performance of GA from 20 repeated runs, depending on the generation number and the population size

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | G25xP10 | G25xP30 | G25xP50 | G50xP10 | G50xP30 | G50xP50 | G100xP10 | G100xP30 |
| 1 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 2 | 0.00 | 1.01 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 3 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 4 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 5 | 3.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 6 | 0.00 | 1.02 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 7 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 8 | 1.21 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 9 | 0.79 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 10 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 11 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 12 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 13 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 14 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 15 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 16 | 2.15 | 0.00 | 0.00 | 0.03 | 0.00 | 0.00 | 0.00 | 0.00 |
| 17 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 18 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 19 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 20 | 0.00 | 0.02 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| Average penalty rate (%) | 1.79 | 0.69 | 0.00 | 0.03 | 0.00 | 0.00 | 0.00 | 0.00 |
| Probability to find the optima (%) | 80.00 | 85.00 | 100.00 | 95.00 | 100.00 | 100.00 | 100.00 | 100.00 |

1) **G** represents the generation number and **P** represents the population size.

|  |
| --- |
|  |

1) **G** represents the generation number and **P** represents the population size.

Figure .. Convergence of GA depending on the number of generation and population

Table .. Computational results by crossover and mutation rates from GA

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Crossover rate | Mutation rate | Total iteration number1) | Computation time (h) | Time per iteration (s) | Solution number2) | Total net benefit of the solution (£) | Search rate (%) |
| 1 | 0.7 | 0.01 | 2730 | 8.33 | 10.98 | 3711 | 329,950 | 4.23 |
| 2 | 0.7 | 0.05 | 2730 | 8.26 | 10.89 | 623\* | 330,150 | 9.45 |
| 3 | 0.7 | 0.10 | 2730 | 8.18 | 10.78 | 3721\* | 330,150 | 18.18 |
| 4 | 0.7 | 0.20 | 2730 | 8.54 | 11.26 | 623\* | 330,130 | 21.57 |
| 5 | 0.8 | 0.01 | 2730 | 7.98 | 10.53 | 3711 | 329,940 | 2.65 |
| 6 | 0.8 | 0.05 | 2730 | 7.99 | 10.53 | 623\* | 330,160 | 7.51 |
| 7 | 0.8 | 0.10 | 2730 | 8.04 | 10.60 | 623\* | 330,160 | 18.18 |
| 8 | 0.8 | 0.20 | 2730 | 8.74 | 11.53 | 625\* | 330,130 | 34.09 |

1) Iteration number means the evaluation of the objective function including 100 Monte Carlo simulations.

2) The solution numbers with \* are included in the top eight policies identified from enumeration in Table ‎7.6.

3) The population size was set to 30 and the number of generation was set to 100.

4) The base-case is in grey.

Table .. The average performance of GA from 20 repeated runs, depending on the crossover rate and the mutation rate

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | C0.7xM0.01 | C0.7xM0.05 | C0.7xM0.10 | C0.7xM0.20 | C0.8xM0.01 | C0.8xM0.05 | C0.8xM0.10 | C0.8xM0.20 |
| 1 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 2 | 2.98 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 3 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 4 | 0.00 | 0.00 | 0.00 | 0.00 | 0.04 | 0.00 | 0.00 | 0.00 |
| 5 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 6 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 7 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 8 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 9 | 4.51 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 10 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 11 | 0.42 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 12 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 13 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 14 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 15 | 0.75 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 16 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 17 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 18 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 19 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 20 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| Average penalty rate (%) | 2.17 | 0.00 | 0.00 | 0.00 | 0.04 | 0.00 | 0.00 | 0.00 |
| Probability to find the optima (%) | 80.00 | 100.00 | 100.00 | 100.00 | 95.00 | 100.00 | 100.00 | 100.00 |

1) **C** represents the cooling rate and **M** represents the mutation rate.

|  |  |
| --- | --- |
|  |  |
|  |  |
|  |  |
|  |  |

1) X-axis represents the policy numbers; Y-axis represents the frequency of evaluation; **C** represents the cooling rate; and **M** represents the mutation rate.

Figure .. Search rate of GA depending on the crossover and mutation rates

## Reinforcement learning: Q-learning

RL, which is based on Q-learning, was implemented for the hypertension SDDP model. In the base-case, Q-values were gradually updated using both the immediate reward and the one-step future reward. Q-learning using a two or three-step future reward was also implemented to compare the performance; in this case, the feedback is the immediate rewards and the mean total net benefit from two or three transitions in the future. The total number of cases was also increased from 1,000 to 1,000,000 times to test the impact on the quality of the solution and the computational time. A penalty function forced the Q-value to 0 if the selected drug to be evaluated was against the feasibility restrictions made in the hypertension SDDP model.

Table ‎7.16 summarise the results from Q-learning in the base-case. Compared with the optimal solution (and statistically equivalent solutions) identified by enumeration, the solutions identified by RL were more heavily influenced by the three month SBP lowering effect of the drugs; this was more evident where the feedback was from the one-step future reward (see Table ‎7.16) than where the feedback was from the two-step or three-step future reward (see Table ‎7.17 and Table ‎7.18). Whereas the optimal initial solution found by enumeration was Ds or ACEIs/ARBs, the optimal solutions identified by Q-learning either started with BBs (1000, 100,000, and 1,000,000 cases) or CCBs (10,000 cases). The optimal subsequent treatments after initial drug were also sensitive to the number of cases. In the base-case, the optimal second-line treatment was switching to BBs+ACEIs/ARBs (1,000, and 10,000 cases) or Ds (100,000, and 1,000,000 cases). For the patients who again failed to achieve the treatment goal, the optimal third-line treatment was Ds+CCBs for all scenarios. In the fourth period, the optimal solution for the patients who had never achieved the treatment goal with the previous treatments was Ds (1,000, and 10,000 cases), Ds+BBs (100,000 cases) or Ds+BBs+CCBs (1,000,000 cases).

A better solution was found when more cases were observed. In the base-case, the solution identified from 1,000,000 cases produced a total net benefit of £312,822, whereas from 1,000 cases it was £294,335. Where two-step future expected rewards were used, the total net benefit of the solution identified from 1,000,000 cases was again higher than the total net benefit of the solution identified from 1,000 cases (£313,497 versus £302,699). The same pattern was also observed where three-step future expected rewards were used, although the difference was smaller than other scenarios (£302,363 versus 302,327). This agreed with a general rule that RL converges to the optimal solution where more cases are continuously observed.

The best solution was identified when the future feedback was from two transitions in the future (see Table ‎7.17). Where 100,000 cases were observed, the optimal treatment sequence was using Ds initially and then switching to Ds+ACEIs/ARBs, Ds+BBs+ACEIs/ARBs and Ds+BBs+CCBs in order for the patients who failed to achieve the treatment goal consecutively: the expected total net benefit was £314,297 from this solution. More stable convergence in the Q-value was achieved when the observed cases were more than 100,000; whereas the discrepancy in the Q-value did not fully converge where the observed cases were less than 10,000 (see Figure ‎7.26). The computational time for 1,000,000 cases was much longer than SA and GA, and even longer than enumeration, and the quality of solutions was less than those methods; as such, Q-leaning was not deemed computationally efficient when 1,000,000 cases were generated.

Table .. Results from RL depending on the number of iterations where the feedback is from one-step future reward

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  | The number of cases | | | |
|  | | | | | | 1000 | 10000 | 100000 | 1000000 |
| Optimal solution | t=1 | Failure |  |  |  | CCBs | BBs | CCBs | CCBs |
| t=2 | Failure | Failure |  |  | BBs+ACEIs/ARBs | BBs+ACEIs/ARBs | Ds | Ds |
| Failure | Success |  |  | CCBs | BBs | CCBs | CCBs |
| t=3 | Failure | Failure | Failure |  | Ds+CCBs | Ds+CCBs | Ds+CCBs | Ds+CCBs |
| Failure | Failure | Success |  | BBs+ACEIs/ARBs | BBs+ACEIs/ARBs | Ds | Ds |
| Failure | Success | Failure |  | ACEIs/ARBs | Ds+CCBs | Ds+CCBs | Ds+CCBs |
| Failure | Success | Success |  | CCBs | BBs | CCBs | CCBs |
| t=4 | Failure | Failure | Failure | Failure | Ds | Ds | Ds+BBs | Ds+BBs+CCBs |
| Failure | Failure | Failure | Success | Ds+CCBs | Ds+CCBs | Ds+CCBs | Ds+CCBs |
| Failure | Failure | Success | Failure | Ds | Ds | ACEIs/ARBs | ACEIs/ARBs |
| Failure | Failure | Success | Success | BBs+ACEIs/ARBs | BBs+ACEIs/ARBs | Ds | Ds |
| Failure | Success | Failure | Failure | Ds | Ds | Ds | Ds |
| Failure | Success | Failure | Success | ACEIs/ARBs | Ds+CCBs | Ds+CCBs | Ds+CCBs |
| Failure | Success | Success | Failure | BBs | Ds | Ds+CCBs | Ds+CCBs |
| Failure | Success | Success | Success | CCBs | BBs | CCBs | CCBs |
| Optimal value (£) | | | | | | 294,334.5 | 294,552.7 | 300,576.6 | 312,822.2 |
| Computational time1) | | | | | | 1m | 11m | 1.44h | 19.45h |

1) **s** represents seconds, **m** represents minutes and **h** represents hours.

Table .. Results from RL depending on the number of iterations where the feedback is from two-step future reward

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  | The number of cases | | | |
|  | | | | | | 1000 | 10000 | 100000 | 1000000 |
| Optimal solution | t=1 | Failure |  |  |  | CCBs | BBs | Ds | BBs |
| t=2 | Failure | Failure |  |  | Ds+ACEIs/ARBs | Ds | Ds+ACEIs/ARBs | Ds+ACEIs/ARBs |
| Failure | Success |  |  | CCBs | BBs | Ds | BBs |
| t=3 | Failure | Failure | Failure |  | Ds | CCBs+ACEIs/ARBs | Ds+BBs+ACEIs/ARBs | Ds |
| Failure | Failure | Success |  | Ds+ACEIs/ARBs | Ds | Ds+ACEIs/ARBs | Ds+ACEIs/ARBs |
| Failure | Success | Failure |  | Ds | Ds | Ds+CCBs | Ds |
| Failure | Success | Success |  | CCBs | BBs | Ds | BBs |
| t=4 | Failure | Failure | Failure | Failure | BBs+CCBs | Ds+ACEIs/ARBs | Ds+BBs+CCBs | Ds+BBs+CCBs |
| Failure | Failure | Failure | Success | Ds | CCBs+ACEIs/ARBs | Ds+BBs+ACEIs/ARBs | Ds |
| Failure | Failure | Success | Failure | CCBs+ACEIs/ARBs | Ds+ACEIs/ARBs | CCBs+ACEIs/ARBs | CCBs+ACEIs/ARBs |
| Failure | Failure | Success | Success | Ds+ACEIs/ARBs | Ds | Ds+ACEIs/ARBs | Ds+ACEIs/ARBs |
| Failure | Success | Failure | Failure | Ds+ACEIs/ARBs | Ds+ACEIs/ARBs | Ds+ACEIs/ARBs | Ds+ACEIs/ARBs |
| Failure | Success | Failure | Success | Ds | Ds | Ds+CCBs | Ds |
| Failure | Success | Success | Failure | Ds+BBs+ACEIs/ARBs | Ds+ACEIs/ARBs | BBs+CCBs | Ds+BBs+CCBs |
| Failure | Success | Success | Success | CCBs | BBs | Ds | BBs |
| Optimal value (£) | | | | | | 302,699.0 | 306,131.5 | 314,296.6 | 313,496.8 |
| Computational time1) | | | | | | 1.06m | 10.59m | 1.73h | 17.10h |

1) **s** represents seconds, **m** represents minutes and **h** represents hours.

Table .. Results from RL depending on the number of iterations where the feedback is from three-step future reward

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  | The number of cases | | | |
| TD3 | | | | | | 1000 | 10000 | 100000 | 1000000 |
| Optimal solution | t=1 | Failure |  |  |  | ACEIs/ARBs | Ds | BBs | BBs |
| t=2 | Failure | Failure |  |  | CCBs | CCBs | BBs+ACEIs/ARBs | CCBs |
| Failure | Success |  |  | ACEIs/ARBs | Ds | BBs | BBs |
| t=3 | Failure | Failure | Failure |  | Ds+BBs+ACEIs/ARBs | Ds+ACEIs/ARBs | Ds+ACEIs/ARBs | Ds+BBs+ACEIs/ARBs |
| Failure | Failure | Success |  | CCBs | CCBs | BBs+ACEIs/ARBs | CCBs |
| Failure | Success | Failure |  | Ds+BBs+ACEIs/ARBs | Ds+ACEIs/ARBs | Ds+ACEIs/ARBs | Ds+BBs+ACEIs/ARBs |
| Failure | Success | Success |  | ACEIs/ARBs | Ds | BBs | BBs |
| t=4 | Failure | Failure | Failure | Failure | Ds+BBs | Ds+BBs | Ds+BBs | Ds+BBs |
| Failure | Failure | Failure | Success | Ds+BBs+ACEIs/ARBs | Ds+ACEIs/ARBs | Ds+ACEIs/ARBs | Ds+BBs+ACEIs/ARBs |
| Failure | Failure | Success | Failure | Ds+BBs | Ds+BBs | Ds+BBs | Ds+BBs |
| Failure | Failure | Success | Success | CCBs | CCBs | BBs+ACEIs/ARBs | CCBs |
| Failure | Success | Failure | Failure | Ds+BBs | Ds+BBs | Ds+BBs | Ds+BBs |
| Failure | Success | Failure | Success | Ds+BBs+ACEIs/ARBs | Ds+ACEIs/ARBs | Ds+ACEIs/ARBs | Ds+BBs+ACEIs/ARBs |
| Failure | Success | Success | Failure | Ds+BBs | Ds+BBs | Ds+BBs | Ds+CCBs+ACEIs/ARBs |
| Failure | Success | Success | Success | ACEIs/ARBs | Ds | BBs | BBs |
| Optimal value (£) | | | | | | 302,326.6 | 300,539.0 | 300,625.8 | 302,362.5 |
| Computational time1) | | | | | | 59.13s | 9.67m | 1.61h | 15.73h |

1) **s** represents seconds, **m** represents minutes and **h** represents hours.

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Figure .. Convergence of the discrepancy in the Q-values from RL

## Summary of the case study of primary hypertension

In primary hypertension, the optimal solution identified by enumeration is to start with ACEIs/ARBs, followed by Ds+ACEIs/ARBs, Ds+CCBs+ACEIs/ARBs and Ds+BBs+ACEIs/ARBs as second, third and fourth-line treatments. The total expected net benefit for this optimal sequential treatment policy was £330,080 (95% CI £330,013-£330,147). There were seven policies, which were not significantly different with the optimal solution at a significance level of 5%. These solutions include Ds or ACEIs/ARBs as the initial drug, Ds+ACEIs/ARBs for the second-line drug and Ds+CCBs+ACEIs/ARBs for the third-line drug, whereas the fourth-line drug was various.

Sensitivity analyses by population characteristics, objective function, SBP lowering effect, the extension of drug switching period, the use of AE rates and random treatment scenario for CVD and DM showed that the optimal solution in primary hypertension is likely to be starting with ACEIs/ARBs or Ds and then adding Ds to ACEIs/ARBs, where ACEIs/ARBs is used initially, or adding ACEIs/ARBs to Ds, where Ds is used initially. For the third-line treatment, Ds+CCBs+ACEIs/ARBs were optimal in most scenarios, whereas the optimal fourth-line drug was sensitive to the previously used drug and the assumption used in sensitivity analyses. The optimal second-line drug was sensitive to the change in the patients’ initial SBP.

The optimal solution(s) identified by enumeration was not in agreement with the NICE clinical guidelines, which currently recommend starting treatment with ACEIs/ARBs for people aged less than 55 years old and CCBs for patients over 55 years old, and then using a combination of ACEIs/ARBs and CCBs as the step 2 treatment[63]. This may be related with the data used for SBP lowering effect and the assumption to reduce the SBP lowering effect gradually where a drug is used continuously over time. As the SBP lowering effect in three months is higher in CCBs than Ds or ACEIs/ARBs in the hypertension SDDP model, more patients who use CCBs as the initial drug are likely to stay with the same drug in the next period than Ds or ACEIs/ARBs. As the SBP lowering effect is assumed to be gradually reduced where a drug is continuously used, the subsequent SBP lowering effect is smaller for the patients who continues the same drug than those who switches to the next drug in most cases. Furthermore, the size of subsequent SBP lowering effects in CCB is smaller than other single antihypertensive drugs. These cause a relatively smaller treatment benefit in subsequent states where CCBs are used initially than where Ds or ACEIs/ARBs are used initially. The optimal third-line drug was the same with NICE’s recommendation. As this model did not include four drug combinations, which are recommend as step 4 treatment from the NICE hypertension model, optimal fourth-line treatments were not compared with the NICE hypertension model.

The results from the cluster analyses imply that the cost-effectiveness of antihypertensive drugs can be affected by the subsequent drug use, particularly the use of second-line drug. Where 4,128 sequential treatment policies were divided by initial drug, the cluster analysis showed that there was no significant difference in total net benefit depending on the initial drug. However, a significant difference in total net benefit was found where the cluster analysis was undertaken in 39 groups defined by the combination of the initial and second-line drugs. Regardless of initial drugs, using CCBs+ACEIs/ARBs as the second-line treatment provided the higher total net benefits than other second-line treatment options. The policies using a single drug, BBs+CCBs or BBs+ACEIs/ARBs as a second-line drug provided a significantly lower total net benefit, whereas the policies using Ds+CCBs or Ds+ACEIs/ARBs as a second-line drug were not significantly different with the policy using CCBs+ACEIs/ARBs as the second-line treatment. In the cluster analyses of top 10% policies, most policies had CCBs+ACEIs/ARBs, Ds+ACEIs/ARBs or Ds+CCBs as the second-line drug, while the first and fourth-line drug were distributed evenly.

Table ‎7.19 compares the base-case of enumeration, SA, GA and RL in terms of the size of the decision space, optimal solution, maximum total net benefit, the number of iterations, search rate, computation time, the probability to find the optimum and the average penalty rate. The results of the hypertension SDDP model showed that, in spite of computational complexity of the underlying evaluation model, SA and GA are capable of identifying good solutions in reasonable computational times. While enumeration took 12.20 hours to identify the optimal solution, SA and GA achieved the same or equivalent solutions by only taking 4.1-4.56 hours. The probability to find the optima was 100% in both methods after tuning the models. The reason that the point estimate of the maximum total net benefit in GA is higher than enumeration or SA is due to noise from the random drug allocation after the use of fourth-line drug and for the patients who have a CVD or DM. SA searched 32.85% of the search space with 2,220 repetitions, whereas GA searched 14.85% of the search space with 1,380 repetitions. The efficiency in search can be improved by adjusting the key tuning parameters in the algorithm.

The quality of solution identified by RL was less favourable in spite of more complex coding. The maximum net benefit identified by RL was the lowest, even with 1,000,000 cases, which took longer than enumeration. Although the quality of solution was improved where more cases were observed or two or three-step future rewards were considered, it was still not good enough compared with SA and GA. One of the potential reasons can be found in the structure of the hypertension SDDP model. In the hypertension SDDP model, the impact of the costs and effectiveness from the long-term CVD model is relatively huge after the drug switching period compared with those during the drug switching period. Therefore, the mechanism of updating Q-values based on the immediate reward or the reward from future transitions may not fully consider the potential huge impact after the drug switching period. Despite the convergence of the Q-values where 100,000 or 1,000,000 cases were used, the solutions from RL were sensitive to a slight fluctuation in the Q-values. This may be because the difference in the total net benefits between sequential treatment polices was small. No benefit by allowing a freedom in drug choice, like the simple hypothetical case, was observed.

The direct comparison of the iteration number between RL and SA (or GA) was not possible because the time period evaluated in each iteration was different. For enumeration, SA and GA, each iteration passes the whole underlying evaluation model to calculate the total net benefit for lifetime, whereas each iteration in RL involves calculating the transitions in one or two-steps and related rewards from the decomposed decision tree. Although RL started with a smaller size of the decision space, it was shown that the computational time can be much longer than SA and GA depending on how many cases are required to achieve the convergence in Q-values.

Compared with the simple hypothetical SDDP in section 3.5.4, the size of the decision space was considerably larger in the hypertension SDDP model. This increase was mainly due to the increase in the size of the search space, especially where the search space was not decomposed (i.e., where enumeration, SA and GA were used). Computational time was also substantially increased in the hypertension SDDP model. The increase in the computational time was around three times for enumeration compared with SA, GA and RL. This increase would have been much greater if Iceberg and parallel computing were not supported. The advantage of SA and GA in computational efficiency was clearly evident in the hypertension SDDP, whereas it was unclear in the simple hypothetical SDDP. With a smaller search rate and iteration number, SA and GA found the same optimal solution that was identified in enumeration.

Table .. Comparison of the optimisation results in the case study of primary hypertension

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Enumeration | Simulated annealing1) | Genetic algorithm2) | Reinforcement learning3) |
| The size of the health state transition space *Z(HS)* | Z(HS)=31 | | | Z(HS1)=3^0 |
| Z(HS2)=3^1 |
| Z(HS3)=3^2 |
| Z(HS4)=3^3 |
| The size of the search space *Z(SS)* | Z(SS)=4,128 | | | Z(SS1)=4 |
| Z(SS2)=10 |
| Z(SS3)=14 |
| Z(SS4)=14 |
| The size of the decision space *Z(DS)* | Z(DS)=31\*4,128\*8=1023744 | | | Z(DS1)=1x4=4 |
| Z(DS2)=3^1x10=30 |
| Z(DS3)=3^2x14=126 |
| Z(DS4)=3^3x14=378 |
| Optimal solution number | 3720 | 3720 | 3721 | See Table ‎7.16 - Table ‎7.18. |
| Maximum total net benefit (£) | 330,080 | 330,060 | 330,120 | 320,158 |
| The number of iterations | 4,128 | 2220 | 1380 | 2690000 |
| Search rate (%) | 100 | 32.85 | 14.85 | N/A |
| Computation time (h) | 12.20 | 4.56 | 4.1 | 4.51 |
| Probability to find the optima (%) | N/A | 100 | 100 | N/A |
| Average penalty rate (%) | N/A | 0 | 0 | N/A |

1) The cooling rate of 0.9 and the maximum tree of 30 was applied.

2) The generation number of 50, the population size of 30, the crossover rate of 0.7 and the mutation rate of 0.1 was applied.

3) 5000 iterations per health state and drug in each period was allowed. The feedback is based on the immediate reward and one-step future reward

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1) ***Z(HS)*** represents the size of the health state transition space; ***Z(SS)*** represents the size of the search space; ***Z(DS)*** represents the size of the decision space.

Figure .. Comparison of the size of decision space between the simple hypothetical model and the hypertension SDDP model

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Figure .. Comparison of the computational time, search rate and iteration number between the simple hypothetical model and the hypertension SDDP model

# Discussion

## Chapter overview

This chapter summarises what was achieved in this study. The advantages and disadvantages of the proposed methods, and the potential trade-offs between model validity and computational complexity are discussed based on the model results in the previous chapter. Implications of the hypertension SDDP analysis are also discussed from a methodological and a decision-maker’s perspective. Future directions in research are suggested based on the limitations of this study.

## Summary of research

This thesis was concerned with solving large and complex SDDPs associated with long-term medical conditions, using simulation-based optimisation approaches. The nature of the SDDP was described and defined mathematically. A classification of modelling structures for economic evaluation was proposed to guide the appropriate selection of modelling approaches for SDDPs in the context of economic evaluation in a long-term medical condition. A hypothetical SDDP case-study was undertaken to test the proposed model structures. Lastly, the proposed methods were applied to a comprehensive case study of SDDP in primary hypertension.

This research found that the computational complexity of SDDPs comes from a range of factors: 1) the number of relevant health states, 2) the number of potential drug treatment options, 3) the number of times that a treatment change may occur, particularly where a time-sliced modelling approach is adopted, 4) whether the transition probabilities between health states depend on historic health states and drug uses and 5) relevant clinical-based rules to be incorporated (e.g., contraindication of certain drugs in the event of certain health states). This suggests that for modelling such situations there might be a trade-off between computational complexity and model validity. That is, increasing the number of health states, treatment options and time periods, considering the patient’s medical history and incorporating the treatment decision rules in practice into modelling may improve model validity, but will inevitably increase the computational complexity of the underlying evaluation model. This is also associated with the trade-off between the underlying evaluation model and the optimisation model. Given a limited time to spend on solving the overall SDDP problem, a trade-off option might be a more sophisticated optimisation algorithm applied to a simple evaluation model. However, it is also important to capture those elements of complexity that render the SDDP approach necessary to ensure added value is captured. In this case, a more efficient optimisation algorithm that guarantees a good solution, but saves a computational time, is necessary.

Where classic mathematical programming has a limited capacity for dealing with the complexities required for SDDP, this study suggested the approximate optimisation methods using simulation. Successive decision tree and semi-Markov models can be used as the underlying evaluation model if the programming software selected is fast and capable of handling the partially-relaxed Markovian assumption of the SDDP. However, the conventional modelling software for decision tree and Markov models, such as Microsoft Excel with Visual Basic for Applications (VBA) or TreeAge (2015 TreeAge Software, Inc), would be limited in its ability to build the underlying evaluation model for SDDP and to link the evaluation model with the optimisation model. The hypertension SDDP model was built using Matlab, which enabled a fast and efficient matrix calculation and a flexible model to store previous information and to reuse within the framework of the decision tree and the Markov model. Matlab also facilitates parallel computation, which saved the computational time substantially.

Considering the historical information in guiding treatment choice naturally involves the extension of the standard memoryless decision trees or Markov models and increases the computational complexity. In the hypertension SDDP model, state aggregation was employed to construct a fully observable successive decision tree with reduced computational complexity. State aggregation is an approach to alleviate the curse of dimensionality, where the states aggregated were similar with respect to transition probabilities or rewards. This allowed storing all the information necessary to calculate the transition probability and using them to determine the optimal solution in the next period. Setting a maximum number of drug switches based on clinical ground also greatly contributed to reducing the computational complexity and time where the number of health states was predicted to increase exponentially.

The choice of the search methods in the hypertension SDDP optimisation model depends on whether it is possible to search all possible solutions in a bounded time or not. This study did not try to define the bounded time explicitly because it can be problem-specific and another research area in computer science, which is beyond the scope of this thesis. The total computational time can be approximated by testing a smaller number of policies and calculating the computational time per policy. Taking an example of a decision problem, which has 5,000 possible policies and the computational time per policy (including PSA runs) is 1 hour, the total computational time, which increases linearly with the number of policies, will be approximately 5,000 hours (i.e., 208.33 days). This approach appears to naïve but enables one to make an informed judgement and choice of a feasible first approach to develop. If the estimated computational time of enumeration is not prohibitive, enumeration can guarantee the optimal solution; otherwise, other fast and efficient computational options should be considered. If parallel computation is possible (e.g., using 12 processors like the hypertension SDDP model), the computational time of enumeration can be reduced to 416.67 hours (i.e., 17.36 days). However, this is not the case in most cases: thus, a range of heuristics or meta-heuristics can be used as introduced in this thesis. Although they do not guarantee the optimal solution, the results of the hypertension SDDP model showed that SA and GA are capable of identifying good solutions in reasonable computational times where the given decision problem is large and complex.

As a general rule, the performance of SA depends on the choice of a number of key tuning parameters, such as the initial and stopping temperatures, the neighbourhood structure, the cooling schedule and the maximum number of iterations within a single temperature. Searching within a neighbourhood of the current solution is a useful compromise, but there may be an implicit trade-off between the amount of computational time to search the decision space and the quality of the solution. The hypertension SDDP model indicated that SA gave a better performance where slow cooling schedule was applied. This was agreed with a general finding in other SA literature. Unfortunately, slow cooling schedules may not be feasible in some applications because it increases the computational time; therefore, faster cooling schedules are often adopted in SA applications instead[208].

The strength of GA is maintaining a population of solutions and recombining good solutions to obtain new ones, which improves on average over the generations: therefore, it is important to select the population for the next generation and to mate them in an intelligent manner. Particularly, the hypertension SDDP model shows that selecting the suitable value of crossover and mutation is important to balance preserving the good elements of the population and maintaining the diversity in the population. Population size also affects the performance of the GA. If there are too many policies in the population, the algorithm slows down and leads to a long computational time. If the selected population size is too small, then the algorithm may result in premature convergence without finding an appropriate solution.

The case-study of primary hypertension shows the general rules in the relationship between the key parameter settings and the performance of SA and GA. However, it does not guarantee that the parameter settings used in the hypertension SDDP model will be equally as effective as other SDDPs because they are problem specific. In the absence of an enumeration gold standard, it would be more difficult to judge what the best parameter settings are for the given problem. In this case, a general approach to find the most effective set of parameters is to compare the performance of different scenarios with many different sets of parameters[376-379]. The tuning procedure can start with the values, which have been previously used for similar problems (as the hypertension SDDP model did). The variations in the set of parameter values will show whether the performance of SA or GA are sensitive to the parameter setting, and if so what parameter setting leads to the best performance. For a large and complex problem, the tuning procedure usually starts with a smaller proto-type of problem and then gradually scales up to a bigger problem with a better set of parameters, as the tuning procedure could be inappropriately lengthy.

The applied RL works along with the decomposition method. The strength of RL is that it possesses the strengths of both forward method (i.e., simulation) and backward method (i.e., DP). The backward approach provides the global optimal solution by balancing the immediate reward and the future reward, whereas there is a concern about a logical conflict between backward computation and the nature of real clinical decision-making based on the patient’s medical history. In contrast, the forward approach is able to use historical information to identify the optimal solution in the next period, whereas decision making based on the step-by-step incremental computation is unable to consider the impact of future situations on the optimal solution. Using both forward and backward mechanisms enables RL to progress toward a desirable goal by repeatedly observing the future situations and actions. Another benefit of RL is to reduce the size of the decision space and to allow more freedom in drug choice than constructing a search space with pre-set drug sequences; although this did not lead to a better solution than the other applied heuristic methods in the case of primary hypertension.

Two types of randomness - randomness in evaluating the value of the objective function and randomness in heuristic search - exists in SDDPs. The former comes from the underlying evaluation model that describes the problem using random variables with known probability distributions (e.g., distributions for initial SBP level and SBP lowering effects). In this case, the objective function strongly depends on the probabilistic structure of the model: thus, the final value of the objective function is usually estimated by averaging over a number of replications generated by Monte Carlo simulation. In theory, increasing the sample size reduces the variance of the estimated value of the objective function as the mathematical rule of Monte Carlo sampling; however, multiple replications of simulation runs might be extremely time-consuming where the given problem is large and complex.

The latter randomness is related to stochastic search, which may not be purely random but may be biased depending on the applied heuristic rules. The random search allows for spontaneous movements to explore the unsearched area to find a better solution. Due to the stochastic nature of meta-heuristics, there will always be the possibility that the optimal solution could exist in the unexplored region; thus, the optimal or near optimal solutions obtained from meta-heuristics should be treated as probabilistic.

### Methodological implication of Hypertension SDDP modelling

The hypertension SDDP model is a novel cost-effectiveness model, which involves the real drug switching rules for treatment success/failure, maintenance and contraindication. Whereas most previous CEAs in primary hypertension assumed that a drug of interest was continuously used over the follow-up period, this model attempts to represent clinical practice that includes switching the drug treatment option depending on the patient’s SBP level and other relevant health states over time. This was achieved by the surrogate outcome modelling based on the relationship between SBP lowering effect and CVD prevention effect. Rather than relying on the conventional RR approach to estimate the CVD prevention effect, the hypertension SDDP model used QRISK2, which is a validated CVD risk engine in the UK, to predict the CVD risk based on the SBP level. QRISK2 also includes other key risk factors of CVD such as age, gender, ethnicity, height, weight, Townsend score, TC, HDL, CHD, family history, smoking, treated hypertension, type 2-DM, RA, AF and RD. Utilising the functionality provided by the modelling software Matlab, Monte Carlo sampling was used in the underlying evaluation model to consider the population variation in the baseline SBP and SBP lowering effect. Changes in patients’ SBP levels and relevant risk factors over time were stored and used to calculate the CVD risk in the next period. Parallel computing with 12 cores in a fast and high performance computer facilitated the enumeration of 4,128 sequential treatment policies (including Monte Carlo sampling of SBP and SBP lowering effects within the underlying evaluation model, and 100 replications to obtain mean estimate for each option).

Whereas the studies by Richter et al[257] and Martikainen et al[380] tried to identify the most cost-effective sequential treatment policy in a short-term model, the SDDP hypertension model tried to consider the long-term impact of sequential treatment strategies. In the initial stage of model development, the hypertension SDDP model was divided into two sub-models – the short-term drug switching model and the long-term CVD model, which had different structures and employed different mechanisms to estimate the cost and effectiveness of sequential treatment policy. The drug switching rules were only modelled in the short-term drug switching period, whereas the long-term CVD model followed a standard Markov-based economic evaluation based on the result. Clinically and economically relevant events were selected based on a widely accepted underlying disease process of primary hypertension and the causal linkages between major CVD and antihypertensive treatment. The potential impact of DM and other AEs on the long-term costs and effectiveness was also considered.

The short-term drug switching model resembles a form of successive decision tree that allows drug switching depending on SBP level, CV events and AEs in each period. Each state in the decision tree has a ‘memory’, which includes the information about SBP, CVD and AE after treatment, and then uses them to determine the transition probabilities to the next state. The main concern of the short-term model was how to store and utilise historical information efficiently, which inevitably involved the extension of decision tree branches. To reduce the number of health states in the drug switching period, the short-term drug switching model used the aggregated health states (e.g., the uncontrolled state including the patients with high blood pressure, CVD or AEs) and then applied different CVD risks based on the medical history for the patients who were controlled and uncontrolled. Once the patients in the aggregated uncontrolled state have a CV event or DM, different transition probabilities were applied to them in the long-term CVD model. By doing so, any impact, which could be missed by aggregating health states, was minimised.

From the health economic modeling perspective, the hypertension SDDP model made a contribution by introducing a new type of dynamic and stochastic optimisation approach and applying the approximate optimisation techniques to solve a real decision problem. Several studies have developed a comprehensive policy model that can simultaneously evaluate the cost and benefit associated with the prevention and therapeutic interventions across the entire disease pathway. The hypertension SDDP model moves a step forward from the comprehensive modelling approach by incorporating an additional outer loop, which identifies the optimal or near optimal solutions through optimisation searching methods, which has not been studied before.

### Implications of Hypertension SDDP modelling for decision-makers

Despite extensive economic evaluations that have been performed on antihypertensive drugs, previous economic evaluations have been mostly focused on comparing the cost-effectiveness of initial treatment options Ds, BBs, CCBs, ACEIs and ARBs; however, the principles of evidence-based medicine should be also applied to drug switching because the selection of subsequent treatments is directly associated with treating a patient with hypertension effectively and managing healthcare expenditure efficiently in the long-term. The results of the hypertension SDDP model show that decision-makers may risk potentially accepting a locally optimal solution if subsequent treatments are not explicitly modelled.

The hypertension SDDP model is a comprehensive and flexible model, which could address a wide range of questions that would interest decision makers. The hypertension SDDP model is capable of not just analysing the cost-effectiveness of initial drugs (as can be seen from the validation scenario in Section 7.2), but also evaluating the impact on health outcomes and resource use for subsequent treatment options. The main goal of the hypertension SDDP model was to identify the optimal treatment pathway in primary hypertension. While the conventional economic evaluation involves the development of partial decision models to identify the cost effective treatment options for patients in a certain period of the entire disease pathway, the hypertension SDDP model is a single comprehensive modelling framework that is capable of evaluating the cost-effectiveness of multiple treatment options across the broader pharmacological treatment pathway.

In SDDPs, decision-makers may have different research questions depending on their perspective. Although the decision-makers generally pursue maximising total treatment net benefits in SDDPs, some decision-makers may be interested in developing evidence-based stepped-care guidelines from a population perspective (i.e., what is the optimal initial drug and then what is the optimal second or third-line drug after the previous drug fails to control the disease), and some decision-makers may be interested in dynamic treatment assignment from an individual patient’s perspective to provide a tailored optimal treatment sequence to individual patients’ need for treatment. Both perspectives can be addressed in the hypertension SDDP model. Like the approaches used for enumeration, SA and GA, the former population-perspective decision problem can be addressed by constructing the decision space with complete solutions (i.e., all possible treatment sequences) and then examining probabilistically the aggregated results of all individual patient’s cases in a cohort model. In the latter individual-perspective decision problem, RL would be the natural choice to facilitate the interactive sequential decision-making process, considering inter-patients variability in risk factors and response to treatment.

For movement to the comprehensive but complex modelling approach, Lord et al said that the comprehensive modelling approach could be able to produce consistent cost-effectiveness estimates under a common framework of methods, baseline data and assumptions, but the adaption of such a large and complex model by regulatory and HTA bodies is still uncertain because of the considerable resource requirements and time constraints[39]. The hypertension SDDP model introduced potential methods to reduce the computational complexity and to save computational time for a large and complex problem. Enumeration may be of limited use in many large and complex SDDPs, especially where high speed computers are not available and efficient and flexible programming languages are not supported, because the computational times are likely to be too long to be of use in practice. In this situation, heuristic methods were proposed as a good alternative to find optimal or near optimal solutions in a reasonable amount of time. The proposed approaches are particularly useful in long-term medical conditions that have a lot of potential health states and treatment options.

### Limitations

Although the hypertension SDDP model is based on the best available date, systematic reviews, which were recognised as the gold standard in evidence-based decision making, were not fully conducted to inform the values of parameters used for the underlying evaluation model. Therefore the results can be updated if the newer or systematically pooled date is available.

Internal validity was checked during the process of building the model. However, the comparison of the final results against those of previous models was a challenge because there was no directly comparable existing study. For this reason, the enumeration result was reviewed by two clinical experts (their names and affiliation are provided in section 7.2), who confirmed that the results are plausible and can be explained at an intuitive level. Furthermore, comparing with the current recommendations from major clinical guidelines, the results of the hypertension SDDP model appear reasonable.

The SDDP hypertension model tried to capture the essential part of the dynamic relationship between sequential treatment choices and the underlying disease process in primary hypertension. However, model simplifications in the drug switching period and the transitions between health states were inevitable because of the computational complexity and data availability. Clinically plausible, but rather arbitrary, assumptions were used to combine the short-term drug switching model and the long-term CVD model. For example, after the pre-defined drug switching period, the controlled patients were assumed to continue the currently used treatment, and uncontrolled patients were assumed to switch to a randomly selected drug until a CV event or DM happened. The patients who have used all four lines of treatments but were never controlled during the drug switching period were assumed to have resistant hypertension and were assumed to see a specialist to correct the underlying cause. This study did not specify the impact of resistant hypertension because treatments can be varied depending on the exact causes and may involve drug therapy, surgery or renal dialysis. For the simplification of search space, the hypertension SDDP model did not consider drug switching within the same class: this decision was based on the evidence of equivalent efficacy within the same class[381, 382].

For Ds, BBs and CCBs, which may have different efficacy depending on dosage, the patients were assumed to take the equivalent dosages of the drugs included in the same class[383-385]. Dose-titration was not considered as a separate treatment option, but it was assumed that the patients take the equivalent dose of each drug. If dose titration of a single drug is considered as a separate treatment option and only low dose drugs are combined, there will be eight single treatment options, six two-drug combinations and four-three drug combinations. The size of the search space will be increased from 4,128 to 20,256:

Z(SS) = 8\*(14-1)\*(18-2)\*(18-3)-4704 = 20256 Equation 8.1.

For the same size of health state space, the decision space will be expanded to 5,023,488:

Z(DS) = 31\*20256\*8 = 5023488 Equation 8.2

Assuming the same computational time per policy with the hypertension SDDP model, it will take 59.87 hours to enumerate all the possible treatment sequences:

10.64 seconds \* 20256 = 215523.84 seconds (≈59.87 hours) Equation 8.3

If a fast computer and parallel computation is not possible, the computational time will take more than 12 times as long as the hypertension SDDP model would take for enumeration.

As the structure of the long-term CVD model is based on the NICE hypertension model, the limitations of the NICE hypertension model also apply to this model. For example, the NICE hypertension model excluded some CVDs (such as stable angina, peripheral vascular disease and transient ischemic attacks) and also excluded the health states for patients having more than two health states (e.g., the patient having several CVDs or DM together) because of inconsistently reported data in the trials[63].

Some of the limitations were driven by the lack of data availability. Although an absence of data does not justify the simplification in itself, it commonly happens in CEAs. For example, there was no meta-analysis or systematic review in the treatment effectiveness of combination treatment with antihypertensive drugs. Data from RCTs were not directly comparable with each other because of the heterogeneity in participants, follow-up period and treatment regimen used in different trials. Due to this, the hypertension SDDP model assumed that the SBP lowering effect is additive and the RR of CVD is multiplicative when two or three single drugs were combined. Therefore, clinically positive or negative interactions among different drugs, and safety and tolerability issues may be missed where two or three drugs are combined[369].

There may be an impact of drug switching on health outcome and resource use that is not accounted for in the hypertension SDDP model; for example, baseline risk may be higher in patients who are not controlled with the initial drug[386]. Drug switching could disturb the therapeutic consistency, which could delay blood pressure control and increase the risks of mortality and morbidity associated with hypertension[3, 347, 351, 386, 387]. Drug switching may also cause patients concern or dissatisfaction with the process and might reduce QoL[387]. Some studies highlighted the additional costs of health care incurred by drug switches. The additional costs could incur either in the process of switching such as costs for additional clinic visits and extra laboratory tests; or as a consequence of switching such as hospitalisation due to adverse-events[6, 387, 388]. From the patients’ perspective, change in treatment regimen was one of the main reasons for decreasing medication compliance[346]. Low compliance increases the risk of treatment failure, and leads to further change in treatment regimen. The vicious circle between increased drug switching, low compliance and higher risk of treatment failure can be perceived intuitively, but was difficult to incorporate practically in the hypertension SDDP model. If an IBM is used as an alternative to the cohort-based structure of the hypertension SDDP model, the correlations between drug switching, low compliance and higher risk of treatment failure at an individual level could be incorporated easily within the mathematical structure of such a model.

## Future research

### Individual-based model

The structural limitations of the Markov state-transition model may be solved by IBMs such as DES. While Markov state-transition models conceptualise the problem as a series of states that a cohort of objects can move from one state to another at each fixed cycle, DES does not need to define a fixed cycle length. DES moves forward by the occurrence of an event, which is governed by the parameters describing time-to-event[75, 389]. This may reduce complexity in SDDPs, where a series of actions take place according to the patient’s condition over time. For example, the hypertension SDDP model used the successive decision tree to depict the sequential decision making process. The number of possible health states in a Markov state-transition model was exponentially increased for each additional cycle to embed previous history in each state. Because of the computational complexity increased by the number of possible health states in each period, the hypertension SDDP model had to restrict the number of drug switching period. However, DES may reduce the complexity where there are no events happening, for example, a patient in DES may have nothing happening for several cycles defined in the Markov state-transition model.

Furthermore, DES does not have the memory limitations of the Markov model. Entities in DES can carry their history as attributes, whereas all history information needs to be explicitly embedded in the states for cohort models[66]. By more easily embedding memory and historical information into the entities, DES provides flexibility to address the complex relationship between individual patients’ various current and historical risk factors and the final outcome. These values may be updated while the patients go through the entire simulation. The updated information is stored as entity attributes and can be used to determine the transition to the subsequent disease pathway, as well as to estimate costs and effectiveness.

The disadvantage of DES is that it normally takes more time to obtain results than cohort models because DES usually requires sampling a large number of patients and/or multiple replications to increase the precision of model outputs[75, 389]. With a given total time to spend, increasing computational time in the evaluation model means spending less time to search the decision space. DES also requires a much greater number of calculations and detailed data to apply the various risks, decisions, resource use, and other elements that are variable[66, 75, 389]. Therefore, there will be a trade-off between the flexibility of model and the effort required to build a model.

### Technical improvement of heuristic algorithms

The hypertension SDDP model applied the standard SA, GA and RL. However, there is evidence of the improved performance of heuristic by modifications and/or integration with other heuristics. For SA, the average performance can be improved by extending the neighbourhood[390-392]; or to sample locally optimal configurations in a more efficient way[393, 394]. Dynamic cooling rate, which decreases linearly or geometrically, can be applied to increase the speed of convergence without compromising the solution quality[180, 395]. There is also increasing interest in parallel implementation, which uses a number of parallel processors during the annealing procedure[396-398]. Parallel processing can be used to generate different chains of solutions within the same temperature or to allow all the processors to test several random neighbours for acceptance independent[53]: this allows a single-solution based method to blur the structural difference with population-based meta-heuristics.

To enhance the performance, GA often makes use of a local search method as a form of selection, crossover and mutation. The strength of a local search method is to explore a promising area in the search space in a more structured way, whereas the strength of GA is to identify promising areas in the search space. Through the hybridisation between GA and local search, the applied local search improves the solution until a local optimum is reached, and then the GA operators sample the search space with solutions that are then processed by the local search[399-401]. Independent sub-populations of chromosomes can be also used as parallel processors to explore the search space[402-404]. In this case, the sub-populations constitute the local mating pools in a population and the best individuals in the sub-populations are re-distributed to the next generation.

The performance of SA and GA can be improved by changing the structure of neighbourhood. In the current hypertension SDDP model, the choices of neighbourhoods for SA and the crossover rule for the GA were based on the numbering of drug sequences in their list order. However, it was noted that some movements in the neighbourhood did not consider the actual similarity in drugs used, particularly where the size of the neighbourhood defined was big (i.e., where the size of the neighbourhood was 100 or 200 in SA) or for the policy located near the borderline between the policies starting with a different initial drug (e.g., the policy number 1032 starting with D following by CCB+ACEI/ARB, BB+CCB+ACEI/ARB and D+CCB+ACEI/ARB and the policy number 1033 starting with BB, D, CCB and ACEI/ARB). For SA, an alternative analysis would regard two drug sequences X1-X2-X3-X4 and Y1-Y2-Y3-Y4 as neighbours if exactly three of the equations X1=Y1, X2=Y2, X3=Y3, X4=Y4 are satisfied. A wider neighbourhood would allow two or three of the equations to be satisfied. In GA, a possible offspring of the two sequences given might be X1-Y2-Y3-X4, with 14 different ways of choosing Xs and Ys here so that the offspring is not the same as either parent.

The RL applied in the hypertension SDDP model uses a look-up table, which stores all the Q-values associated with each state and action and finds the action, which brings the best Q-value for each state. For large-scale problems with millions of state-action pairs, however, the look-up table is inefficient not just because of the memory required, but also the time and data needed to fill them accurately[200]. To overcome this problem, function approximation using regression is commonly used. For example, the objective function is fitted with regression using the available data related to the function, and tries to use the predictions to find a better solution.

### Data generation

Although the hypertension SDDP model developed in this study focused on the investigation of computational complexity, SDDP modelling is considerably constrained by availability of relevant clinical date. The quality of solution relies on the reliability and robustness of data, which will impact on the accuracy of parameter estimation. Access to relevant patient-level data is necessary to collect the data required for SDDPs, particularly the direct and indirect time-varying treatment effects and the correlation between treatment options. However, these data are unlikely to be collected by conventional RCTs because subsequent treatments are normally not based on random assignment and most interventions are considered as an aggregation of a set of components rather than providing the effects of individual components[405]. In this respect, the sequential multiple assignment randomised trial (SMART), which involves re-randomisations at each therapeutic stage for identifying optimal sequential treatment strategies in clinical trials, has the potential to provide clinical data regarding sequential decisions[406]. The primary goal of SMART trials is to identify the best sequencing of treatment options that lead to improved clinical outcomes. SMART trials also provide the effect of certain components of the sequential treatment policy as SMART trials apply factorial designs in a sequential setting. They could also inform time-dependent variables, which are important predictors of the response in the next period and the resulting actions. However, SMART trials are not widely implemented in practice because of feasibility and acceptability[407]. Executing a SMART trial takes a long-time and costly more than conventional RCTs. It is also uncertain whether the trial design is tolerated by the participants; and whether the assessment procedures and the results are acceptable by clinicians and policy maker. Therefore only a small number of SMART trials have been implemented in “real-world” clinical settings funded by public institutions[408, 409].

Considering their importance in informing the clinical data and evidence for sequential treatment strategies, potential funding bodies may be interested in whether a SMART trial is feasible and worth pursuing before executing the trial. Modelling an SDDP with existing data may provide preliminary knowledge about the trial design and the likely direction of its effect. The SDDP model could also demonstrate feasibility and the need for SMART trials and thereby assist in their development and implementation. The research questions that can be addressed by a SDDP model may be whether a proposed SMART trial is worth pursuing, and if so what the most feasible design is. Specifically, SDDP modelling could help to address the following questions: how many treatment steps should be allowed, which variables/outcomes should be used to assess treatment response/non-response to inform drug switching, how frequent the patients should be reassessed and how sensitive the outcomes need to be to allow drug switch. The SDDP modelling could also help to decide time and resource implications of the SMART trial, for example, how many participants are required and how long the trial would take.

Four core tasks are proposed for the application of SDDP modelling in preparation for the SMART trial: 1) literature review, 2) modelling of an underlying evaluation model, 3) incorporating an optimisation method into the underlying evaluation model and 4) resulting analysis and discussion.

A comprehensive literature review will be required to understand the key features of the disease and treatment options and to identify the data availability to populate the model. As SDDP modelling covers a broader disease pathway and all possible treatment options, this task could be time-consuming and require the integration of evidence from a range of relevant sources including clinical trials, observational studies, administrative data sets and expert opinion.

The underlying evaluation model is a representation of the real clinical pathway of the disease of interest with drug switching being incorporated. The complexity of the underlying evaluation model depends on the size of the health state space, the assumptions in the transitions between the health states and the complexity of the drug switching rules. IBM such as DES may be more efficient for more effectively describing the complex relationship between the disease pathway and the sequential use of drug(s). However, any decision analytic models such decision-tree and Markov models can be used for the evaluation model if the size and computational complexity of the given problem can be reduced. The evaluation model will estimate the expected total net benefit for different treatment options.

The incorporation of the optimisation method helps to generate the sequential treatment strategies to be evaluated by the evaluation model efficiently. If the SDDP under investigation is relatively simple and manageable, then enumeration can be performed. Otherwise, heuristics (or meta-heuristics) need to be used to identify optimal or ‘near-optimal’ solutions. The applications of these optimisation methods for SDDPs and the general guidance on the trade-offs between key parameters were discussed in this thesis. Their computational efficiency was also demonstrated in the case study of primary hypertension.

Results from the SDDP models can be presented in base-case analysis, scenario analyses and value of information analysis (VOI). The base-case results could be used to rule out sequential drug policies, which are unlikely to be cost-effective, from the proposed SMART trial. Various scenario analyses can help to inform the impact of different trial designs and variable settings on the expected outcome (e.g., time cycle, the follow-up period, sample size, population characteristics and the definition of response/non-response). VOI methods have been proposed as a systematic decision-analytic approach for aiding decision makers in assessing whether there is enough evidence to support new therapies or research for HTA[410-412]. It is expected that VOI could allow quantifying the potential value of further data collection from SAMRT trials directly from the simulated results. If the VOI exceeds the expected costs of executing the SMART trial, then it is potentially valuable to conduct the SMART trial. Practical issues to conduct the SMART trials, such as time, costs, recruiting participants and staff availability, can be discussed the confirmed design and treatment algorithms of the SMART trial.

# Conclusion

In the healthcare sector, selecting drug(s) among competing alternatives has been a key interest of decision-makers not just for clinical decisions, but also for resource allocation policy. Existing economic evaluations are normally concerned with evaluating drug alternatives provided at a specific point in a disease pathway, which could be first, second or third line drugs. However, decision-makers are also interested in which subsequent drug(s) should be used when the current drug needs to be replaced or complemented due to inefficacy, diminishing efficacy or AEs. These questions represent an SDDP that aims to identify a sequence of drugs along the disease pathway of a health condition with the objective of maximising the net benefits of treatment.

Studying the dynamic nature of SDDPs can be challenging because of the computational complexity caused by the potentially large number of drug sequences and disease pathways and the interdependence between the drug sequences and the disease pathways over time. Therefore, this research concerned the nature of SDDPs associated with computational complexity and suggested potential methods to solve SDDPs using a case study of primary hypertension.

In Chapter 2, a classification of model structures for the economic evaluation of SDDPs was proposed based on the taxonomy proposed by Brennan et al. The strengths and weaknesses of three main types of economic evaluation models – cohort-level decision-tree models, cohort-level Markov models and IEH including DES and ABS – were discussed in the context of modelling SDDPs. SDDPs were compared with - traveling salesman problems and job-shop scheduling problems to benchmark the well-known combinatorial optimisation problems for SDDPs. Different ways to define the SDDPs were discussed depending on the set of time defined and the decision-maker’s perspective. The SDDP was defined mathematically assuming that the given SDDP is a discrete-time Markov problem having a finite state/action spaces in a finite set of decision times. This indicated that the computational complexity of SDDPs mainly comes from the following factors: 1) the number of relevant health states, 2) the number of potential drug treatment options, 3) the number of times that a treatment change may occur, particularly where a time-sliced modelling approach is adopted, 4) whether the transition probability between health states depend on historic health states and drug uses and 5) relevant clinical-based rules to be incorporated (e.g., contraindication of certain drugs in the event of certain health states).

In Chapter 3, a systematic review was conducted to identify the potential the potential approximate optimisation methods to solve SDDPs. The studies classified as mathematical programming showed a limitation of that method to cope with large and complex problems and included simulation and/or a function approximation under the theoretical foundations in the traditional mathematical programming. For heuristic methods, three constructive methods, five single solution meta-heuristic methods and eight population-based meta-heuristic methods were identified. Based on the rank, RL, SA and GA were selected as the promising optimisation methods to solve SDDPs. The theoretical background and methodological application of the selected methods was explained. A hypothetical SDDP was used to show the feasibility of incorporating the proposed methods into an economic evaluation model and to identify some issues to be considered for the SDDP modelling in a real case. SA found exactly the same optimal solution with enumeration, although the advantage of SA in computational efficiency was not observed due to the small size of the decision problem. Classic DP identified the optimal solution, which had higher net benefits than enumeration. This can be explained by the stochastic scheme for choosing a next action where a problem is decomposed. This was also partially because of infeasible solutions as classic DP was limited to consider the medical history under the backward induction. Even though the applied one-step Q-learning identified a better solution excluding infeasible solutions, it required a considerable number of cases for convergence to the optimum and higher computational intensity to update the Q-values based on the newly observed data and to bootstrap the partial optimal solutions to construct the complete solution.

Chapter 4 was prepared to understand hypertension and pharmacological treatment of primary hypertension. An extensive literature review in previous economic evaluations of antihypertensive drugs in primary hypertension was included to understand the structures of previous CEA models and their limitations regarding the consideration of drug switching. Most previous models focused on the impact of an initial drug on long-term costs and health outcomes assuming that a patient continues with the drug for a defined time period regardless of the health state transitions. The main reasons that they could not consider drug switching were limited clinical or economic data of each drug and the complexity of modelling the interactive effects between various health states and drug choice over time.

The SDDP in primary hypertension was conceptualised following the mathematical description of the SDDPs in section 2.4. The time cycle was chosen to be three months, as the time to decide whether the drug is well-responded is fairly short in practice. As the NICE clinical guidelines on primary hypertension recommend a 4-step treatment algorithm, the maximum number of drug switching was assumed to be three after the initial drug was prescribed. Clinically and economically relevant health states – uncontrolled state without CVD or DM, controlled state without any CVD or DM, UA, MI, stroke, HF and DM – were selected based on a widely accepted underlying disease process of primary hypertension. Similar states with respect to transition probabilities or rewards were combined into a smaller number of aggregate states to alleviate the curse of dimensionality. Potential treatment options included four major single antihypertensive drugs – Ds, BBs, CCBs and ACEIs/ARBs – and their two or three-combinations. Dose-titration and drug switching within the same drug were not considered as a separate treatment option. Where the decision rule was based on step-wise treatment, the total number of sequential treatment policies was 4,128. For the transition probability, a semi-Markovian assumption was chosen for the short-term drug switching model because of the importance of considering the interactions between the disease pathway and sequentially used drugs in primary hypertension.

A simulation-based optimisation method, which identifies the optimal solution based on the outcome estimated in the underlying evaluation model, was used to build the hypertension SDDP model. The structure of the underlying evaluation model, data and key assumptions used to populate the model were described in Chapter 5 in detail. The underlying evaluation model has a form of successive decision tree that has an add-on Markov model. While the short-term drug switching model worked with a surrogate outcome modelling to allow drug switching based on SBP level, CV events and AEs, the long-term CVD model used the conventional RR approach to calculate the long-term cost and effectiveness of the sequential treatment policy. Chapter 6 described how various optimisation methods including enumeration, GA, SA and RL were implemented alongside the underlying evaluation model. The structure of the hypertension SDDP model built by m-files and pseudo-codes were provided.

Chapter 7 showed the outcomes of the hypertension SDDP model depending on the optimisation method applied, which were enumeration, SA, GA and RL. The optimal solution identified by enumeration was to start with ACEIs/ARBs, followed by Ds+ACEIs/ARBs, Ds+CCBs+ACEIs/ARBs and Ds+BBs+ACEIs/ARBs as second, third and fourth-line treatments. The total expected net benefit for this optimal sequential treatment policy was £330,080 (95% CI £330,013-£330,147). Considering the seven policies that were not significantly different to the optimal solution at 5% significance level, the optimal initial solution in primary hypertension is likely to be Ds or ACEIs/ARBs. The optimal second and third-line drugs were Ds+ACEIs/ARBs and Ds+CCBs+ACEIs/ARBs regardless the previous drug(s). The optimal fourth-line drug was not clearly observed. These results were robust to change in most variables used in sensitivity analyses: treatment objective, SBP lowering effect, the extension of drug switching period, the use of AE rates and random treatment scenario for CVD and DM, but relatively sensitive to the change in the patients’ initial SBP.

The difference between the results of the hypertension SDDP model and the recommendation of the NICE hypertension model demonstrates that considering the problem as a sequential problem makes a difference to the total net benefit compared with decision-making purely based on the cost-effectiveness of the initial drug. In addition, the cluster analyses showed that the cost-effectiveness of antihypertensive treatments can be affected by the subsequent drug use, particularly the use of a second-line drug. While no significant difference in total net benefit was found where 4,128 sequential treatment policies were divided by initial drug, a significantly better net benefit was observed where CCBs+ACEIs/ARBs, Ds+ACEIs/ARBs or Ds+CCBs were used as the second-line drug than where BBs+CCBs or BBs+ACEIs/ARBs were used as the second-line drug. Similar results were also found in the cluster analyses of the top 10% policies.

From the case study of primary hypertension, SA and GA proved their capability to identify the optimal (or statistically equivalent) solutions in a shorter time than enumeration. Their performance depends on the choice of a number of key parameters. The potential risk of premature convergence was observed where fast cooling schedule was employed for SA and where the population size was small or the population diversity was lacking for GA. However, using a slow cooling schedule or increasing the population size and diversity is directly associated with an increase in computational time. Therefore, prior tests are necessary to select key parameters with the aim of tuning the balance between diversification and intensification.

Compared with SA and GA, the quality of solution identified by RL was relatively less favourable. The quality of solution was improved where more cases were generated or where two or three-step future reward was considered than where one-step future reward was used. This may be because the total net benefit of each policy is much more affected by the long-term CVD model after the drug switching period than the short-term drug switching model in the current structure of the hypertension SDDP model. Therefore, the mechanism of updating Q-values based on the immediate reward or the reward from a certain future transitions could not fully consider the potential impact after the drug switching period. RL needs further investigation to improve the performance possibly by using more complicated RL methods or in a different structure of the underlying evaluation model.

The case study of SDDP in primary hypertension shows that various interacting trade-offs can be present in SDDP modelling. Firstly, the trade-off between the computational complexity and model validity was found in the underlying evaluation model. If the model considers more health states, treatment options and drug switching period and applies more complex transition rules considering the patient’s medical history, it potentially improves the model validity, but requires more time and effort to collect data and to build and evaluate the model. In contrast, if the underlying evaluation model is simple, it saves computational time and effort, but may miss something necessary for decision-making in SDDP. In the hypertension SDDP model, for example, drug switching was only considered for a limited period, which was four periods in the base-case. The uncertainty related to the drug switching period was assessed in sensitivity analysis. Although the optimal solution was now much different depending on the drug switching period, the sensitivity analysis indicated that the computational complexity increased considerably where the drug switching period was increased. Thus, it is important to improve the external model validity but also to keep such a large and complex model manageable where a large and complex problem is given like SDDP.

The trade-off between the computational complexity and model validity is also associated with the trade-off between the optimisation model and the underlying evaluation model. Given a limited time, increased computational time in the underlying evaluation model leaves less time to spend on the optimisation model. In particular, where a meta-heuristic is used, there is an implicit trade-off between the amount of search time and the quality of the solution. Where the search time was shorter (i.e., where fast cooling schedule was applied for SA and where the smaller number was selected as the population size for GA), it was more likely to trap at a local optimum. Therefore, the key parameters related to the diversification and intensification of meta-heuristics should be tuned through prior tests.

The hypertension SDDP model is a novel cost-effectiveness model, which involves clinically plausible drug switching rules for treatment success/failure, maintenance and contraindication. It also made a contribution by introducing a new type of dynamic and stochastic optimisation approach that applies approximate optimisation techniques to solve large and complex decision problems in HTA. In particular, methods to reduce the decision space and to efficiently solve large decision problems are promising research areas as more capable but complex modelling methods are introduced in HTA. Future research in developing the underlying evaluation model using individual-based models such as DES, improvements of heuristic algorithms and generating clinical data relevant to SDDPs will help to deal with the limitations of the current study and support better informed decision-making for SDDPs in HTA.

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# Appendix 1. Exploratory literature review on previous studies, which evaluated the cost-effectiveness of sequential treatment policies for long-term medical conditions

A1.1. Search strategies

* Research question:
* Is there an economic evaluation, which tried to address the global optimality of an SDDP?
* How has drug switching been considered and/or modelled in economic evaluation in healthcare?
* Search date: Initial literature search was conducted on 11/11/2011 and updated on 28/08/2014.
* Databases:
* Web of science (SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH)
* Ovid (Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present)
* Search keywords: All literature published between 1990 and 2014 and written in English were included if they have the following search keywords in title, topic or abstract:

1) Drug switching-related keywords

* (drug\* or pharmac\* or treat\* or therap\* or health\* or disease\* or medic\* or hospit\* or clinic\* or care\* or intervention\* or polic\*) near/5
* (multi\* or pathway\* or change\* or add\* or switch\* or sequen\* or substitut\* or subsequent\* or step\* or tailor\* or replac\*)

2) Economic evaluation-related keywords

* cost\* or econom\* or pharmacoeconomic or “cost effectiveness” or CEA\* or “cost utility” or CUA\* or “cost minimization” or CMA\* or (decision and (tree or analys?s)) or Markov or “discrete event simulation” or DES or “computer simulation”

Drug switching-related keywords and economic evaluation-related keywords were combined using the “AND” Boolean operator.

* Inclusion/ exclusion criteria
* A study was regarded as a potentially relevant study if it evaluates ‘a cost-effectiveness of sequential treatment strategies for a long-term medical condition using a CEA modelling technique’. Sequential treatment strategy was defined as a pharmacological treatment regimen, which undergoes a series of changes during the follow-up period.
* A study was excluded if the sequential policy evaluated includes non-pharmacological interventions, such as cancer screening, healthcare policies and lifestyle modifications; if it is a CEA alongside clinical trials without modelling of sequential treatment regimen; or if it only addresses the efficacy, but not the cost-effectiveness.
* Research areas, which are not associated with long-term medical conditions, such as acute or infectious diseases and microbiology, were excluded.
* Biography, data set, editorial, meeting, book, case report, letter, news, reference material, bibliography and unspecified document types were excluded.
* Research areas such as plant sciences, zoology, forestry, engineering, government law, transportation, energy fuels, water resources, history were further excluded in Web of Science.

A1.2. Search results

Table A1.1. Search result of Web of Science

|  |  |  |
| --- | --- | --- |
| Set | Results | Search history |
| # 1 | 7,307,255 | TITLE: ((cost\* or econom\* or pharmacoeconomic\* or "cost effectiveness" or CEA\* or "cost utility" or CUA\* or "cost minimization" or CMA\* or (decision near/2 (tree or analys?s)) or Markov or "discrete event simulation" or DES or "computer simulation")) OR TOPIC: ((cost\* or econom\* or pharmacoeconomic\* or "cost effectiveness" or CEA\* or "cost utility" or CUA\* or "cost minimization" or CMA\* or (decision near/2 (tree or analys?s)) or Markov or "discrete event simulation" or DES or "computer simulation")) Timespan=1990-2014 Search language=English |
| # 2 | 4,026,031 | TITLE: ((drug\* or treat\* or therap\* or disease\* or medic\* or hospit\* or clinic\* or care\*) near/5 (multi\* or pathway\* or change\* or add\* or switch\* or sequen\* or substitut\* or subsequent\* or step\* or tailor\*)) OR TOPIC: ((drug\* or treat\* or therap\* or disease\* or medic\* or hospit\* or clinic\* or care\*) near/5 (multi\* or pathway\* or change\* or add\* or switch\* or sequen\* or substitut\* or subsequent\* or step\* or tailor\*)) Timespan=1990-2014 Search language=English |
| # 3 | 261,002 | #2 AND #1 |
| # 4 | 36,794 | Refined by: document types and research areas. |

Table A1.2. Search result of Ovid MEDLINE

|  |  |  |
| --- | --- | --- |
| Set | Results | Search history |
| #1 | 484,764 | ((drug\*or treat\* or therap\* or disease\* or medic\* or hospit\* or clinic\* or care\*) adj5 (multi\* or pathway\* or change\* or add\* or switch\* or sequen\* or substitut\* or subsequent\* or step\* or tailor\*)).ab,kf,ti. |
| #2 | 662,216 | exp Economics, Medical/ or exp "costs and cost analysis"/ or exp "cost-benefit analysis"/ or (econom\* or pharmacoeconom\* or cost\* or CEA\* or CUA\* or CMA\* or QALY\* or "quality-adjusted life year\*").ab,kf,ti. |
| #3 | 38,070 | 1 and 2 |
| #4 | 27,024 | limit 3 to (english language and humans and yr="1990 - 2014") |



Figure A1.1. Flow-chart of study selection

Table A1.3. The type of studies excluded

|  |  |  |
| --- | --- | --- |
|  | Number of studies excluded | Percentage |
| Not CEA study |  |  |
| - Review or comments | 23153 | 45.00% |
| - Other research areas | 9261 | 18.00% |
| - Natural disease pathway models/Clinical efficacy | 43 | 0.08% |
| CEA study |  |  |
| - Non-pharmacological interventions | 15281 | 29.70% |
| - Acute or infectious diseases | 3150 | 6.12% |
| - CEA alongside clinical trials (no CEA model was included) | 319 | 0.62% |
| - CEA of clinical guideline | 38 | 0.07% |
| - CEA of a limited number of pre-defined drug sequences | 206 | 0.40% |
| Total | 51450 | 100.00% |

A1.3. Summary of the key studies

| No | Authors | Year | Disease | Type of study | Modelling method | Time to switch | Time horizon | Key treatment efficacy used to populate the model | Switching point | Switching policy | The rationale for the selection of the strategies |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 1 | McEwan [33] | 2010 | Type 2 DM | CUA | DES | 1y | Lifetime | Annual incidence and mortality rate. | HbA1c threshold. | • Metformin (MF) -> MF + sulphonylureas (SU) -> MF+SU+D • MF -> MF+D -> MF + D + SU • MF -> MF+DPP-4 -> MF + dipeptidyl peptidase (DPP-4) + SU | Clinical guideline. |
| 2 | Furiak [29] | 2009 | Schizophrenia | CUA | Microsimulation | 3m | 1y | Adherence levels, relapse rates, the risk of AEs, medication discontinuation rates and medication switching patterns. | Relapse, AEs (weight gain, extrapyramidal symptoms, DM and hyperlipidemia). | Any sequences among olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, clozapine. | A set of assumptions regarding the switching patterns that takes into account the reason for the switch. |
| 3 | Bobes [28] | 2004 | Schizophrenia | CEA | Markov | 1m | 12m | The incidence of AEs, the probabilities of non-compliance and rehospitalization due to non-compliance, the action taken by the clinician for AE. | AEs. | Sequences up to four different types of antipsychotics: ziprasidone, olanzapine, risperidone and haloperidol. | EIRE study. |
| 4 | Beard [413] | 2006 | Schizophrenia | CUA | Decision Tree + Markov | 3m | 1y | Clinical response data using Positive and Negative Syndrome Scale (PANSS) score. | Poor clinical response. | Treatment strategies having either first-line olanzapine or risperidone with switching to the alternative drug as second-line treatment such as clozapine, olanzapine, risperidone, quetiapine, ziprasidone, amisulpride and ariprazole. | Not cited. |
| 5 | Maetzel [11] | 2002 | RA | CUA | Markov | 6m | 5y | Treatment termination rates, treatment withdrawal rates, ACR American College of Rheumatology (ACR20) response criteria. | Lack of efficacy and toxicity. | • Methotrxate-based regimes switching to leflunomide, gold, and then cyclosporine  • Methotrxate-based regimes switching to gold, and then cyclosporine | Based on the responses of US and Canadian rheumatologists in a mailed survey. |
| 6 | Barton [414] | 2004 | RA | CUA | DES (BRAM) | 6m | Lifetime | Time to joint replacement, the reduction in HAQ score, toxicity for methotrexate and ciclosporin only. | HAQ increase and quitting the DMARD. | DMARD sequences (any desired sequences of DMARD use can be tested). | Survey of consultant rheumatologists working in the UK. |
| 7 | Welsing [12] | 2004 | RA | CUA | Markov | 3m | 5y | Insufficient response and toxicity. | Non response (based on the DAS). | • Usual care (sulfasalazine and methotrexate)  • Leflunomide to usual care • TNFb to usual care • Leflunomide to TNFb to usual care • TNFb to leflunomide to usual care | Based on the current practice. |
| 8 | Brennan [13] | 2004 | RA | CUA | Patient-level simulation | 6m | Lifetime | HAQ score improvement and the relationship between the HAQ score and radiological progression. | Non-response (based on ACR), loss of efficacy and AEs. | • Etanercept, followed by intramuscular gold and leflunomide • Intramuscular gold, followed by leflunomide and cyclosporin+methotrexate  \* If failure occurs on all DMARDs in the sequence, best care was be provided. | Discussion with clinical experts. |
| 9 | Schadlich [415] | 2005 | RA | CUA  /CEA | The international computerised model | 6m | 3y | ACR criteria. | Loss of effectiveness or adverse drug reaction. | DMARD sequences including leflunomide were compared with those excluding leflunomide. | The conceptual framework of the international computerised model . |
| 10 | Chen [416] | 2006 | RA | CUA | DES | 6m | Lifetime | Time on treatments, HAQ changes on treatment and toxicity. | Toxicity or loss of effectiveness. | Combining inhibit tumour necrosis factor-alpha (TNF-alpha) agents, such as adalimumab, etanercept and infliximab, in a sequence of DMARDs. | NICE guideline. |
| 11 | Brennan [417] | 2007 | RA | CUA | Patient-level simulation | 6m | Lifetime | EULAR response. | AEs or lack of response (assessed using the EULAR). | TNF- antagonist therapies (infliximab, etanercept and adalimumab) as a group versus traditional disease-modifying anti-rheumatic drugs (hydroxychloroquine, methotrexate, intramuscular gold, sulphasalazine and leflunomide). | The British Society for Rheumatology Biologics Registry. |
| 12 | Saraux [17] | 2010 | RA | CEA | Decision Tree | 6m | 2y | Disease  Activity Score (DAS28). | Insufficient response. | • Etanercept -> abatacept -> adalimumab • Etanercept -> rituximab -> adalimumab • Etanercept -> adalimumab -> abatacept • Etanercept -> adalimumab -> infliximab | Based on the current practice. |
| 13 | Merkesdal [18] | 2010 | RA | CUA | Markov | 6m | Lifetime | ACR response. | No response. | • Standard treatment arm: adalimumab + methotrexate, inﬂiximab + methotrexate, gold preparations, cyclosporin A, supportive therapy (including only monotherapy with methotrexate). • Rituximab arm: rituximab+ methotrexate, adalimumab+methotrexate, inﬂiximab+ methotrexate, gold preparations, cyclosporin A, supportive therapy (permitting methotrexate monotherapy only). | Expert opinion. |
| 14 | Hallinen [418] | 2010 | RA | CUA | Markov | 6m | Lifetime | ACR response. | No response. | Initially patients received either best supportive care (BSC) or one of the following treatments, each combined with methotrexate, before BSC: adalimumab, abatacept, etanercept, infliximab, or rituximab. | Based on the current practice. |
| 15 | Wu [20] | 2012 | RA | CUA | Markov | 6m | Lifetime | ACR response. | Poor remission  or AEs. | • DMARDs only • Etanercept followed by DMARD  • Infliximab followed by DMARD  • Adalimumab followed by DMARD  • Etanercept therapy followed by rituximab and DMARD • Infliximab therapy followed by rituximab and DMARD  • Adalimumab therapy followed by rituximab and DMARD | According to the opinion of Chinese rheumatologists. |
| 16 | Puolakka [19] | 2012 | RA | CEA | Decision Tree | 6m | 2y | DAS28. | Insufficient response. | Six sequential biologic strategies composed of three biologic agents and included a first anti-TNF agent, etanercept, adalimumab or infliximab, followed by either abatacept or rituximab as a second therapeutic option in case of an insufficient response, followed by another anti-TNF agent in case of further insufficient response. | Clinical experts opinion. |
| 17 | Diamantopoulos [419] | 2012 | RA | CUA | Individual patient simulation | 6m | Lifetime | ACR response rate. | No response. | • Using adalimumab ahead of etanercept  • Using infliximab ahead of etanercept  • Using tocilizumab + methotrexate, followed by adalimumab and etanercept | The most commonly used treatments used in Italy. |
| 18 | Diamantopoulos [420] | 2014 | RA | CUA | Individual patient simulation | 6m | Lifetime | HAQ score and Visual Analogue Scale (VAS) pain score. | No response. | • The standard of care (SoC) strategy: a sequence of bDMARDs (Certolizumab pegol, Etanercept, Adalimumab, Palliative care).  • Adding tocilizumab to SoC at ﬁrst line and second line. | Based on the current practice. |
| 19 | Bansback [421] | 2006 | Psoriatic arthritis | CUA | Patient-level simulation | 3m/6m | 10y | The Health Assessment Questionnaire Disability Index (HAQ-DI) and data on patients that continued onto open label extension of the clinical trial. | Lack of clinical response, presence of progressive severe and deforming arthritis, withdrawal after initial clinical response due to AEs, or lack of continued efficacy. | • Start with etanercept, followed by ciclosporin/leflunomide and then best standard care if patients do not respond. • Start with ciclosporin/leflunomide, followed by best standard care if patients do not respond. | Current practice guidelines in the study setting. |
| 20 | Havrilesky [422] | 2012 | Ovarian cancer | CUA | Markov | Not stated. | 2y | Progression-free survival and the rates of AEs. | Neurotoxicity and disease progression/recurrence. | Sequential use of docetaxel and carboplatin versus combination docetaxel and carboplatin. | Based on clinical trial. |
| 21 | Marchetti [423] | 2013 | Luminal Crohn's disease | CUA | Markov model | 1m | 5y | The rate of patients requiring additional drug, the relapse-free survival curve and the probability of undergoing surgery. | Symptom exacerbation and relapse. | • Top-down (TD) strategy: starting with combined immunosuppressive therapy, followed by additional inﬂiximab infusions, and then corticosteroids, if necessary.  • The traditional step-up (SU) strategy: starting with corticosteroids, followed by corticosteroids plus azathioprine, and then inﬂiximab, if necessary. | Guideline and literature. |
| 22 | Martikainen [424] | 2010 | High risk patients with elevated LDL | CEA | Decision Tree | 3m | 52w | LDL goal attainment. | The LDL goal achievement. | • Rosuvastatin (R) 10mg • R10mg -> R20mg -> R40mg • Simvastatin (S) 10mg -> S20mg -> S40mg • Atorvastatin (A) 10mg -> A20mg -> A40mg -> A80mg • S20mg -> R10mg -> R20mg -> R40mg • S20mg -> A20mg -> A40mg -> A80mg • S20mg -> S40mg -> R10mg -> R20mg • S20mg -> S40mg -> A20mg -> A40mg | Not stated. |
| 23 | Brennan [72] | 2007 | End-stage renal disease (ESRD) | CUA | Markov | 8w | Lifetime | Serum phosphorus and CaxP product levels. | No response. | • Continued calcium carbonate (CC) • Lanthanum carbonate (LC) to CC if unsuccessful | Discussion with clinicians. |
| 24 | Manca [425] | 2012 | Colorectal cancer | CUA  /CEA | Decision Tree | 3m | 10y | The occurrence of the events being modelled (i.e., start and end treatment dates, death). | Loss of effectiveness or AEs. | • Using ﬂuorouracil (FU), followed by irinotecan • The two weekly de Gramont regimen (dG) or a modiﬁcation of it (MdG), followed by doublet therapy with MdG and irinotecan (IrMdG) • First-line MdG regimen until treatment failure, followed by doublet therapy with MdG and oxaliplatin (OxMdG) • First-line doublet therapy with the IrMdG regimen  • First-line doublet therapy with the OxMdG regimen. | Considered in a recent RCT, the standard care in the UK. |
| 25 | Miyazaki [25] | 2009 | Colorectal cancer | CMA | Markov | 1m | 100m | Median progression-free survival. | No response. | • Folinic acid/5-fluorouracil/irinotecan (FOLFIRI) to folinic acid/5-fluorouracil/oxaliplatin (FOLFOX6) • FOLFOX6 to FOLFIRI | Clinical guideline. |
| 26 | Hertel [426] | 2012 | Chronic obstructive pulmonary disease (COPD) | CUA | Markov | 1y | 30y | The relative rate ratios  (RRRs) of exacerbation. | Continued to exacerbate or remained breathless. | Various combinations of a long-acting muscarinic antagonist (LAMA), a long-acting beta agonist (LABA), an inhaled corticosteroid (ICS), and roflumilast. | Based on clinical guideline. |
| 27 | Thompson [22] | 2007 | Breast Cancer | CUA | Markov | 6m | 35y | Time to events, the HR for exemestane and survival after disease-related events. | Midway through the 5-year tamoxifen regimen. | Switching to exemestane versus continuing tamoxifen therapy. | Not stated. |
| 28 | Risebrough [23] | 2007 | Breast Cancer | CUA | Markov | 6m | 7.5y | Discontinuation due to AEs, cancer recurrence, intercurrent death and death related to breast cancer. | After 2.5 years of tamoxifen. | Switching to exemestane after 2 to 3 years of tamoxifen versus continued tamoxifen. | Based on an expert panel of 4 Canadian oncologists. |
| 29 | Cameron [24] | 2008 | Breast cancer | CUA | Markov | 28d | 10y | Treatment-specific median time to progression (TTP). | Progressed or relapsed on or after previous antioestrogen therapy. | • Non-steroidal aromatase inhibitor (NSAI) -> Exemestane -> docetaxel -> capecitabine -> best supportive care (BSC) • NSAI -> fluvestrant -> exemestane -> docetaxel -> capecitabine -> BSC • NSAI -> exemestane -> fluvestrant -> docetaxel -> capecitabine -> BSC | Based on the interview with seven UK oncologists. |
| 30 | Lux [26] | 2009 | Breast cancer | CUA | Markov | 1m | 10y | TTP. | Progressive event. | • NSAI to fulvestrant to exemestane to docetaxel to capecitabine BSC • NSAI to exemestane to docetaxel to capecitabine to BSC • NSAI to exemestane to fulvestrant to docetaxel to capecitabine to BSC | Based on the interview with seven UK oncologists. |
| 31 | Bachir [427] | 2014 | Bladder Cancer | CEA | Markov | 1y | 5y/10y | Annual rates of disease progression and death. | Disease recurrence. | Bacillus Calmette-Guerin (BCG) and electromotive MMC (EMDA) versus BCG alone. | Data availability. |
| 32 | Tran-Duy [428] | 2011 | Ankylosing spondylitis | CUA | DES | No cycle. | Lifetime | Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI). | BASDAI change and loss of response. | • Five NSAIDs (randomly chosen from 10 possible drugs) available in a random order for each patient, including two cyclo-oxygenase-2 and three cyclo-oxygenase-1 inhibitors. •The same five NSAIDs as in strategy 1 and two anti-TNF agents available also in a random order for each patient. | Expert opinion. |

# Appendix 2. The target papers for the systematic review on approximate optimisation methods

|  | Author | Year | Optimisation problem | Optimisation | Method | Disease | CEA model |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 1 | Rauner [192] | 2010 | To identify mitigation strategies that minimize the total costs. | o | The Pareto ant colony optimisation | Breast cancer | o |
| 2 | Zhao [190] | 2011 | To discover optimal individualized treatment regimens in clinical trial that maximize the overall survival time | o | Adaptive reinforcement learning approach (Q-learning) | Lung Cancer | x |
| 3 | van Gerven [60] | 2007 | To approximate the optimal treatment strategy, which maximizes the global utility defined as a discounted additive combination of the quality of life and the cost. | o | Single policy updating, single rule updating and simulated annealing algorithms | Oncology | o |
| 4 | Vahedi [187] | 2009 | To find a control strategy that minimizes the expected total discounted cost in the long run. | o | Probabilistic Boolean networks (PBNs) | Cancer | x |
| 5 | Tse [188] | 2007 | To optimise the multidrug cancer chemotherapy schedule, which minimizes the tumour size under a set of constraints. | o | Memetic algorithm | Cancer | x |
| 6 | Chi [429] | 2008 | To describe a data mining model for constructing an optimal diagnostic sequence that assists cost-effective sequential decisions. | o | Hill climbing and genetic algorithms | ? |  |
| 7 | Martín-Guerrero [430] | 2009 | To individualize Erythropoietin dosages to optimise Hb levels in the long-term. | o | Reinforcement learning | Hemodialysis | x |
| 8 | Lee [129] | 2008 | To derive approximately optimal strategies (dialysis dose per week and hours) that maximize patient welfare. | o | Reinforcement learning | Dialysis (chronic kidney failure) | o |
| 9 | He [132] | 2010 | To identify the optimal dosage policy, which minimizes the total costs. | o | Dynamic programming | Controlled ovarian hyperstimulation | o |

# Appendix 3. Full search strategies of the systematic review on approximate optimisation methods

A3.1 Web of Science

|  |  |  |
| --- | --- | --- |
| Set | Search history | Results |
| A | ((TI=("NP hard” or “nondeterministic polynomial-time hard” or sequen\* or dynamic or "time-dependent" or Marov\* or multistage\* or multi-stage\*) OR TS=("NP hard” or “nondeterministic polynomial-time hard” or sequen\* or dynamic or "time-dependent" or Marov\* or multistage\* or multi-stage\*))) | 2,040,041 |
| A' | (TI=(("NP hard” or “nondeterministic polynomial-time hard” or sequen\* or dynamic or "time-dependent" or Marov\* or multistage\* or multi-stage\*) near/5 (decision\* or problem\* or pathway\* or polic\* or strateg\*)) OR TS=(("NP hard” or “nondeterministic polynomial-time hard” or sequen\* or dynamic or "time-dependent" or Marov\* or multistage\* or multi-stage\*) near/5 (decision\* or problem\* or pathway\* or polic\* or strateg\*))) | 53,400 |
| A'' | (TI=(("NP hard” or “nondeterministic polynomial-time hard” or sequen\* or dynamic or "time-dependent" or Marov\* or multistage\* or multi-stage\* or multidrug\* or multi-drug\* or individualiz\*) near/5 (decision\* or problem\* or pathway\* or polic\* or strateg\* or treatment\* or regimen\* or therap\*)) OR TS=(("NP hard” or “nondeterministic polynomial-time hard” or sequen\* or dynamic or "time-dependent" or Marov\* or multistage\* or multi-stage\* or multidrug\* or multi-drug\* or individualiz\*) near/5 (decision\* or problem\* or pathway\* or polic\* or strateg\* or treatment\* or regimen\* or therap\*))) | 77,965 |
| B | (TI=(heuristic\* or metaheuristic\* or algorithm\* or (approximat\* near/5 (approach\* or method\* or function\* or search\*))) OR TS=(heuristic\* or metaheuristic\* or algorithm\* or (approximat\* near/5 (approach\* or method\* or function\* or search\*)))) | 585,439 |
| B' | (TI=((heuristic\* or metaheuristic\* or approximat\* or iterative or cyclic or adaptive or backward) near/5 (algorithm\* or approach\* or method\* or function\* or search\*)) OR TS=((heuristic\* or metaheuristic\* or approximat\* or iterative or cyclic or adaptive or backward) near/5 (algorithm\* or approach\* or method\* or function\* or search\*))) | 172,268 |
| C | (TI=(optim\* or minim\* or maxim\*) OR TS=(optim\* or minim\* or maxim\*)) | 2,064,178 |
| A∩B | #1 AND #4 | 125,449 |
| A'∩B' | #2 AND #5 | 6,011 |
| A''∩B' | #3 AND #5 | 6,170 |
| A∩B∩C | #1 AND #4 AND #6 | 51,068 |
| A'∩B'∩C | #2 AND #5 AND #6 | 4,339 |
| **A''∩B'∩C** | #3 AND #5 AND #6 | **4,342** |
| A∩(B∪C) | #1 AND (#4 OR #6) | 378,184 |
| A'∩(B'∪C) | #2 AND (#5 OR #6) | 21,771 |
| A''∩(B'∪C) | #3 AND (#5 OR #6) | 26,339 |

1) The row in grey is the final search result used for the systematic review.

A3.2. Scopus

|  |  |  |
| --- | --- | --- |
| Set | Search history | Results |
| A | TITLE-ABS-KEY("NP hard" OR "nondeterministic polynomial-time hard" OR sequen\* OR dynamic OR "time-dependent" OR marov\* OR multistage\* OR multi-stage\*) | 1,948,450 |
| A' | TITLE-ABS-KEY(("NP hard" OR "nondeterministic polynomial-time hard" OR sequen\* OR dynamic OR "time-dependent" OR marov\* OR multistage\* OR multi-stage\*) W/5 (decision\* OR problem\* OR pathway\* OR polic\* OR strateg\*)) | 50,124 |
| A'' | TITLE-ABS-KEY(("NP hard" OR "nondeterministic polynomial-time hard" OR sequen\* OR dynamic OR "time-dependent" OR marov\* OR multistage\* OR multi-stage\* OR multidrug\* OR multi-drug\* OR individualiz\*) W/5 (decision\* OR problem\* OR pathway\* OR polic\* OR strateg\* OR treatment\* OR regimen\* OR therap\*)) | 80,102 |
| B | TITLE-ABS-KEY(heuristic\* OR metaheuristic\* OR algorithm\* OR (approximat\* W/5 (approach\* OR method\* OR function\* OR search\*))) | 684,764 |
| B' | TITLE-ABS-KEY((heuristic\* OR metaheuristic\* OR approximat\* OR iterative OR cyclic OR adaptive OR backward) W/5 (algorithm\* OR approach\* OR method\* OR function\* OR search\*)) | 233,930 |
| C | TITLE-ABS-KEY(optim\* OR minim\* OR maxim\*) | 2,222,123 |
| A∩B | #1 AND #4 | 119,961 |
| A'∩B' | #2 AND #5 | 7,653 |
| A''∩B' | #3 AND #5 | 7,817 |
| A∩B∩C | #1 AND #4 AND #6 | 47,774 |
| A'∩B'∩C | #2 AND #5 AND #6 | 5,394 |
| **A''∩B'∩C** | **#3 AND #5 AND #6** | **5,834** |
| A∩(B∪C) | #1 AND (#4 OR #6) | 338,674 |
| A'∩(B'∪C) | #2 AND (#5 OR #6) | 23,102 |
| A''∩(B'∪C) | #3 AND (#5 OR #6) | 28,578 |

1) The row in grey is the final search result used for the systematic review.

## 

A3.3. Ovid

|  |  |  |
| --- | --- | --- |
| Set | Search history | Results |
| A | ("NP hard" or "nondeterministic polynomial-time hard" or sequen$ or dynamic or "time-dependent" or Markov$ or multistage$ or multi-stage$).ab,kw,ti. | 858,663 |
| A' | (("NP hard" or "nondeterministic polynomial-time hard" or sequen$ or dynamic or "time-dependent" or Markov$ or multistage$ or multi-stage$) adj5 (decision$ or problem$ or pathway$ or polic$ or strateg$)).ab,kw,ti. | 9,409 |
| A'' | (("NP hard" or "nondeterministic polynomial-time hard" or sequen$ or dynamic or "time-dependent" or Markov$ or multistage$ or multi-stage$ or multidrug$ or multi-drug$ or individualiz$) adj5 (decision$ or problem$ or pathway$ or polic$ or strateg$ or treatment$ or regimen$ or therap$)).ab,kw,ti. | 30,134 |
| B | (heuristic$ or metaheuristic$ or algorithm$ or (approximat$ adj5 (approach$ or method$ or function$ or search$))).ab,kw,ti. | 109,279 |
| B' | ((heuristic$ or metaheuristic$ or approximat$ or iterative or cyclic or adaptive or backward) adj5 (algorithm$ or approach$ or method$ or function$ or search$)).ab,kw,ti. | 25,113 |
| C | (optim$ or minim$ or maxim$).ab,kw,ti. | 961,438 |
| A∩B | #1 AND #4 | 20,703 |
| A'∩B' | #2 AND #5 | 248 |
| A''∩B' | #3 AND #5 | 307 |
| A∩B∩C | #1 AND #4 AND #6 | 6,414 |
| A'∩B'∩C | #2 AND #5 AND #6 | 158 |
| **A''∩B'∩C** | **#3 AND #5 AND #6** | **182** |
| A∩(B∪C) | #1 AND (#4 OR #6) | 111,976 |
| A'∩(B'∪C) | #2 AND (#5 OR #6) | 1,990 |
| A''∩(B'∪C) | #3 AND (#5 OR #6) | 6,141 |

1) The row in grey is the final search result used for the systematic review.

## 

A3.4. Embase

|  |  |  |
| --- | --- | --- |
| Set | Search history | Results |
| A | ("NP hard" or "nondeterministic polynomial-time hard" or sequen$ or dynamic or "time-dependent" or Markov$ or multistage$ or multi-stage$).ab,kw,ti. | 968,771 |
| A' | (("NP hard" or "nondeterministic polynomial-time hard" or sequen$ or dynamic or "time-dependent" or Markov$ or multistage$ or multi-stage$) adj5 (decision$ or problem$ or pathway$ or polic$ or strateg$)).ab,kw,ti. | 10,861 |
| A'' | (("NP hard" or "nondeterministic polynomial-time hard" or sequen$ or dynamic or "time-dependent" or Markov$ or multistage$ or multi-stage$ or multidrug$ or multi-drug$ or individualiz$) adj5 (decision$ or problem$ or pathway$ or polic$ or strateg$ or treatment$ or regimen$ or therap$)).ab,kw,ti. | 38,284 |
| B | (heuristic$ or metaheuristic$ or algorithm$ or (approximat$ adj5 (approach$ or method$ or function$ or search$))).ab,kw,ti. | 118,667 |
| B' | ((heuristic$ or metaheuristic$ or approximat$ or iterative or cyclic or adaptive or backward) adj5 (algorithm$ or approach$ or method$ or function$ or search$)).ab,kw,ti. | 25,061 |
| C | (optim$ or minim$ or maxim$).ab,kw,ti. | 1,157,020 |
| A∩B | #1 AND #4 | 22,356 |
| A'∩B' | #2 AND #5 | 254 |
| A''∩B' | #3 AND #5 | 341 |
| A∩B∩C | #1 AND #4 AND #6 | 6,877 |
| A'∩B'∩C | #2 AND #5 AND #6 | 152 |
| **A''∩B'∩C** | **#3 AND #5 AND #6** | **159** |
| A∩(B∪C) | #1 AND (#4 OR #6) | 128,274 |
| A'∩(B'∪C) | #2 AND (#5 OR #6) | 2,253 |
| A''∩(B'∪C) | #3 AND (#5 OR #6) | 7,885 |

1) The row in grey is the final search result used for the systematic review.

A3.5. Summary of the excluded papers

|  |  |
| --- | --- |
| Reason of exclusion | Count |
| It does not address a stochastic sequential optimisation problem | 6,211 |
| It does not use heuristic or optimisation method | 1,311 |
| It belongs to review, conference, symposium, workshop papers, books, letters, editorials or corrections. | 3 |
| Total excluded papers | 6,396 |

1) Literature not written in English, published before 1990 and conference, symposium or workshop papers, books, letters, editorials or corrections were excluded using the limit function in the databases.

2) Some studies had two reasons together. Therefore, the number of total excluded papers is not equal to the sum of counts of three reasons.

# Appendix 4. The parameters used to populate the hypothetical SDDP model

|  |  |  |
| --- | --- | --- |
|  | Variable description | Deterministic mean |
| Baseline transition probabilities | From Hu to Hu | 0.738 |
| From Hu to He | 0.012 |
| From Hu to Hn | 0.250 |
| From He to Hu | 0.505 |
| From He to He | 0.319 |
| From He to Hn | 0.176 |
| From Hn to Hu | 0.121 |
| From Hn to He | 0.007 |
| From Hn to Hn | 0.872 |
| Relative risks (RR) | To stay in the uncontrolled health state (Hu) |  |
| * Drug A | 0.64 |
| * Drug B | 0.58 |
| * Drug C | 0.51 |
| To develop an AEs (He) |  |
| * Drug A | 1.00 |
| * Drug B | 1.07 |
| * Drug C | 1.43 |
| Increase in the baseline risk of Hu after two successive treatment failures | 1.05 |
| Increase in the baseline risk of Hu after relapse | 1.10 |
| Decrease in the treatment effect after relapse |  |
| * Drug A | 1.20 |
| * Drug B | 1.10 |
| * Drug C | 1.00 |
| Costs | Hu |  |
| * Drug A | 200 |
| * Drug B | 300 |
| * Drug C | 400 |
| He |  |
| * Drug A | 250 |
| * Drug B | 350 |
| * Drug C | 450 |
| Hn |  |
| * Drug A | 100 |
| * Drug B | 200 |
| * Drug C | 300 |
| HRQoLs | Hu | 0.86 |
| He | 0.79 |
| Hn | 1.00 |
| Lamda | | £30,000 |

# Appendix 5. Summary of the included studies in the literature review on previous economic evaluations in primary hypertension

| No | Author | Year | Type of CEA | Baseline Population | Comparators | Follow-up | Cycle | Type of CEA model | Elements of model | Adverse effect | Compliance | Consideration about drug switching |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 1 | Edelson [258] | 1990 | CEA | Hypertensive patients without CHA. | D, BB, ACEI, AB and CCB. | 20y. | 1y. | The Coronary Heart Disease Policy Model. | Alive with/without CHD | Considered in sensitivity analysis as a reduction in quality of life. | Not considered. | Not considered. |
| 2 | Kawachi [249] | 1991 | CUA | Mild-to-moderate hypertension. | D, BB and ACEI. | Lifetime. | 1y. | Based on the assumption of equal efficacy. | Only considered mortality. | Considered as a utility of side effects and the costs of treating side effects of medication. | Not considered. | The annual cost of medication takes account of the quantity, mix and dosage of drugs. |
| 3 | Johannesson [302] | 1994 | CEA | Middle-aged men with mild to moderate uncomplicated hypertension (in MAPHY). | D and BB. | 5y. | 1y. | Computer simulation model using Framingham equations. | Not mentioned. | Not considered. | Not considered. | Not considered. The cost of additional antihypertensive drugs added after randomisation was assumed to be the same in both groups. |
| 4 | Hilleman [250] | 1994 | CMA | Newly diagnosed mild-to-moderate hypertension. | D, BB, AB, A2, ACEI and CCB. | 1y. | No cycle. | Based on the assumption of equal efficacy. | Not included. | Considered as a cost associated with treating side effects. | Not considered. | Not considered. If one antihypertensive agent was substituted for another over the course of treatment, the patient was excluded from the analysis. |
| 5 | Johannesson [303] | 1996 | CEA | Hypertensive patients. | D/BB and ACEI/CCB. | 1y. | No cycle. | Computer simulation model using Framingham equations. | Not mentioned. | Not considered. | Not considered. | Not considered. |
| 6 | Pearce [251] | 1998 | CMA | Uncomplicated Hypertension. | D, BB, ACEI, AB and CCB. | 5y. | No cycle. | Based on the assumption of equal efficacy. | Not included. | Considered as a cost associated with potassium supplementation in sensitivity analysis. | Not considered. | Not considered. |
| 7 | Richter [257] | 2001 | CEA  /CUA | Mild-to-moderate uncomplicated hypertension. | D, CCB, ACEI, BB and ARB. | 15m. | 1m. | Decision tree model. | Decision tree for choosing a particular sequence of drugs. | The model incorporated the instances and severity of each AE, not the number of individuals reporting an AE. Adverse-event costs were calculated based on treatment algorithms. | Not considered. | Every three months, patients may increase the dosage of their drug or switch to another drug because the patient has experienced intolerable adverse events or because the drug has failed to control hypertension.  The model is based on sequential prescribing of monotherapy, because combination therapy was not used consistently in the clinical trials. |
| 8 | Dias [431] da Costa JS | 2002 | CEA | Individuals aged 20-69 years spending expenditure on antihypertensive drugs among sampled. | D, BB, CCB. ACEI, D+BB, D+CCB, D+ACEI, BB+CCB, BB+ACEI and other combinations. | 1y. | No cycle. | Cross-sectional population-based survey. | Not considered. | Not considered. | Not considered. | Not considered |
| 9 | Nordmann [42] | 2003 | CUA | Men aged 40 years without CVD and diabetes requiring antihypertensive drug therapy. | D/BB, ACEI and ACEI based on the presence or absence of LVH on ECG or echocardiography. | Lifetime. | 1y. | Markov model. | Patients with and without LVH, asymptomatic, CAD, stroke, congestive HF or any combination of these complications. | Patients who have intolerable adverse effects were assumed to switching the drug. | Assumed no difference in adherence to therapy between the two treatment options, but higher adherence rate with ACE inhibitors up to 30% was assumed in the sensitivity analysis. | Only one opportunity to switch from conventional to ACE inhibitor therapy or vice versa, in response to intolerable adverse effects, lack of efficacy or congestive heart failure. |
| 10 | Fretheim [252] | 2003 | CMA | Population currently on medication for hypertension and not complicated by cardiovascular diseases. | D and non-diuretic group (including AB, BB, CCB, ACEI and ARB). | 1y. | No cycle. | Based on the assumption of equal efficacy. | Not considered. | Not considered. | Considered in the people using thiazides. | Not considered. |
| 11 | Chen [253] | 2005 | CMA | Isolated systolic hypertension included in the SHEP trial. | D, BB, ACEI, AB and CCB. | 5y. | No cycle. | Based on the assumption of equal efficacy. | Not considered. | CVD was defined as adverse effect. | Not considered. | Diuretic-based stepped care in SHEP. |
| 12 | Stafilas [254] | 2005 | CEA | Mild-to-moderate hypertension. | D, BB, CCB, ACEI and ARB. | 5y. | 1m  /4m. | Decision tree model. | Not mentioned. | Assumed the need of extra laboratory monitoring for chlorthalidone and propranolol. | Applied different compliance with chlorthalidone, propranolol, amlodipine, enalapril and losartan. | One opportunity to switch from one therapeutic class to another, in response to intolerable adverse events or lack of efficacy. |
| 13 | Linjer [255] | 2005 | CA | Elderly (70-84 years) patients participated in STOP-2 trial. | D/ BB, CCB and ACEI. | 5y. | No cycle. | Based on the assumption of equal efficacy. | Not considered. | Not considered. | Not considered. | Based on STOP-2 protocol. |
| 14 | NICE [223] | 2006 | CUA | Essential hypertension without pre-existing CVD, HP or diabetes. | No intervention, D, CCB, BB and ACEI/ARB. | Lifetime. | 6m. | Markov model. | Well (Event free), UA, MI, Stroke, HF, DM and death. | The only side effects modelled were onset of HF and diabetes. Other side effects were was examined in sensitivity analysis by the loss of quality of life due to the side effects. | Not considered. | Not considered. |
| 15 | Tran [246] | 2007 | CUA | Newly diagnosed hypertensive patient, with no significant risk factors. | No treatment, Diuretics, CCB, BB, and ACEI or ARB. | 10y. | 1y. | Markov model. | Well, UA, MI, Stroke and CVD death. | Not considered. | Not considered. | Not considered. |
| 16 | Heidenreich [256] | 2008 | CMA | Hypertensive patients (in ALLHAT). | ACEI, CCB and Diuretics. | Lifetime. | No cycle. | The assumption of non- significant differences in survival observed in ALLHAT. | Not considered. | Not considered. | Not considered. | Based on ALLHAT protocol. |

# Appendix 6. Pooled standard deviation of SBP lowering effect

A6.1. The studies included in Wald et al’s systematic review

Table A6.1. Diuretics in three months

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Placebo | | | Diuretics | | | Total N | Difference | |
| N | SBP | SD | N | SBP | SD | Mean | SD |
| Bateman et al (1979) | 15 | 155.4 | 13.9 | 15 | 139.5 | 17.0 | 30 | 15.9 | 22.0 |
| Chalmers et al (1976a) | 16 | 127.0 | 14.3 | 16 | 117.0 | 14.3 | 32 | 10.0 | 20.3 |
| Chalmers et al (1976b) | 30 | 158.6 | 20.7 | 20 | 144.8 | 16.9 | 50 | 13.8 | 26.7 |
| Chalmers et al (1982) | 16 | 164.0 | 9.2 | 16 | 152.0 | 9.2 | 32 | 12.0 | 13.0 |
| Chrysant et al (1992) | 43 | 153.0 | 13.1 | 41 | 152.0 | 12.8 | 84 | 1.0 | 18.3 |
| Durel et al (1992) | 5 | 146.7 | 23.2 | 5 | 131.3 | 15.0 | 10 | 15.4 | 27.6 |
| Erwteman et al (1984) | 50 | 142.9 | 16.4 | 50 | 137.0 | 13.6 | 100 | 5.9 | 21.3 |
| Frishman et al (1995) | 75 | -3.9 | 6.9 | 133 | -8.5 | 5.8 | 208 | 4.6 | 9.0 |
| Brown et al (1990) | 9 | -3.8 | 11.7 | 10 | -11.3 | 8.9 | 19 | 7.5 | 14.7 |
| Chalmers et al (1986) | 21 | 119.0 | 13.7 | 21 | 113.0 | 13.7 | 42 | 6.0 | 19.4 |
| Fernández et al (1994) | 17 | -2.7 | 13.6 | 17 | -8.5 | 12.8 | 34 | 5.8 | 18.7 |
| **Weighted sum** | | | | | | | | | **15.8** |

Table A6.2. Beta-blockers in three months

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Placebo | | | BBs | | | Total N | Difference | |
| N | SBP | SD | N | SBP | SD | Mean | SD |
| Bateman et al (1979) | 15 | 155.4 | 13.9 | 15 | 134.6 | 13.6 | 30 | 20.8 | 19.4 |
| Chalmers et al (1976a) | 16 | 127.0 | 14.3 | 16 | 116.0 | 14.3 | 32 | 11.0 | 20.3 |
| Chalmers et al (1976b) | 30 | 158.6 | 20.7 | 20 | 142.4 | 16.9 | 50 | 16.2 | 26.7 |
| Chalmers et al (1982) | 16 | 164.0 | 9.2 | 16 | 147.0 | 9.2 | 32 | 17.0 | 13.0 |
| Chrysant et al (1992) | 43 | 153.0 | 13.1 | 86 | 152.5 | 18.5 | 129 | 0.5 | 22.7 |
| Durel et al (1992) | 5 | 146.7 | 23.2 | 5 | 136.6 | 28.3 | 10 | 10.2 | 36.6 |
| Erwteman et al (1984) | 50 | 142.9 | 16.4 | 50 | 134.6 | 15.9 | 100 | 8.3 | 22.8 |
| Frishman et al (1995) | 75 | -3.9 | 6.9 | 151 | -10.5 | 6.1 | 226 | 6.6 | 9.3 |
| Wing et al (1988) | 16 | 171.0 | 8.0 | 16 | 154.0 | 8.0 | 32 | 17.0 | 11.3 |
| Lyons et al (1994) | 12 | 149.0 | 9.4 | 12 | 146.0 | 19.7 | 24 | 3.0 | 21.8 |
| **Weighted sum** | | | | | | | | | **16.7** |

Table A6.3. Calcium channel blockers in three months

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Placebo | | | CCBs | | | Total N | Difference | |
| N | SBP | SD | N | SBP | SD | Mean | SD |
| Lyons et al (1994) | 12 | 149.0 | 9.4 | 12 | 140.0 | 18.0 | 12 | 9.0 | 20.3 |
| Maclean et al (1990) | 32 | 163.0 | 30.9 | 32 | 163.0 | 30.9 | 136 | 0.0 | 43.8 |
| Chan et al (1997) | 27 | -1.1 | 2.2 | 51 | -13.1 | 2.9 | 156 | 12.0 | 3.6 |
| Messerli et al (1998) | 152 | 0.0 | . | 157 | -8.0 | 1.9 | 631 | 8.0 | 23.8 |
| Scholze et al (1998) | 30 | -8.1 | 12.4 | 59 | -11.5 | 17.4 | 424 | 3.4 | 21.4 |
| Veratran Study Group (1997) | 51 | 148.5 | 16.1 | 56 | 145.5 | 20.4 | 272 | 3.0 | 26.0 |
| **Weighted sum** | | | | | | | | | **22.6** |

Table A6.4. Angiotensin-converting-enzyme inhibitors in three months

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Placebo | | | ACEIs | | | Total N | Difference | |
| N | SBP | SD | N | SBP | SD | Mean | SD |
| Brown et al (1990) | 9 | -3.8 | 11.7 | 10 | -11 | 15.2 | 40 | 7.2 | 19.2 |
| Chalmers et al (1986) | 21 | 119.0 | 13.7 | 21 | 108.0 | 13.7 | 21 | 11.0 | 19.4 |
| Fernández et al (1994) | 17 | -2.7 | 13.6 | 18 | -12.9 | 14.0 | 67 | 10.2 | 19.5 |
| Wing et al (1988) | 16 | 171.0 | 8.0 | 16 | 147.0 | 8.0 | 16 | 24.0 | 11.3 |
| Chan et al (1997) | 27 | -1.08 | 2.2 | 26 | -13.30 | 4.0 | 156 | 12.2 | 4.6 |
| Messerli et al (1998) | 152 | 0.0 | . | 159 | -9 | 2.0 | 631 | 9.0 | 25.2 |
| Scholze et al (1998) | 30 | -8.1 | 12.4 | 85 | -14.1 | 21.4 | 424 | 6.0 | 24.8 |
| Veratran Study Group (1997) | 51 | 148.5 | 16.1 | 50 | 138.1 | 12.3 | 272 | 10.4 | 20.3 |
| **Weighted sum** | | | | | | | | | **21.8** |

A6.2. The studies included in Wright et al’s systematic review

Table A6.5. Diuretics in one year

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Placebo | | | Active | | | Total N | Difference | |
| N | Mean | SD | N | SBP | SD | Mean | SD |
| EWPHBPE (1985) | 287 | -10 | 23.0 | 300 | -26 | 17.0 | 587 | -16.0 | 28.6 |
| HYVET (2008) | 1468 | -13.9 | 18.9 | 1540 | -25.7 | 16.5 | 3008 | -11.8 | 25.1 |
| HYVET pilot (2003) | 394 | -7 | 11.0 | 386 | -29.5 | 13.0 | 780 | -22.5 | 17.0 |
| Kuramoto et al (1981) | 32 | 1.0 | 17.9 | 32 | -9 | 16.1 | 64 | -10.0 | 24.1 |
| MRC-O (1992) | 2213 | 167.0 | 17.9 | 1081 | 151.0 | 16.1 | 3294 | -16.0 | 24.1 |
| PATS (1995) | 2824 | 149.6 | 19.2 | 2841 | 144.5 | 18.0 | 5665 | -5.1 | 26.3 |
| SHEP (1991) | 2371 | -13.6 | 17.3 | 2365 | -28 | 15.7 | 4736 | -14.4 | 23.4 |
| SHEP-P (1989) | 108 | -16 | 17.9 | 443 | -32 | 16.1 | 551 | -16.0 | 24.1 |
| HSCSG (1974) | 171 | 0.0 | 17.9 | 179 | -27 | 16.1 | 350 | -27.0 | 24.1 |
| MRC-TMH (1985) | 8654 | -13 | 17.9 | 4297 | -25.2 | 16.1 | 12951 | -12.2 | 24.1 |
| OSLO (1986) | 379 | 147.0 | 17.9 | 406 | 130.0 | 16.1 | 785 | -17.0 | 24.1 |
| USPHSHCSG (1977) | 178 | 1.5 | 16.7 | 175 | -16.5 | 19.4 | 353 | -18.0 | 25.6 |
| VA-II (1970) | 194 | 4.2 | 17.9 | 186 | -27.2 | 16.1 | 380 | -31.4 | 24.1 |
| Wolff et al (1966) | 42 | 15.0 | 17.9 | 45 | -21.2 | 16.1 | 87 | -36.2 | 24.1 |
| **Weighted sum** | | | | | | | | | **24.4** |

Table A6.6. Beta-blocker in one year

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Placebo | | | Active | | | Total N | Difference | |
| N | Mean | SD | N | Mean | SD | Mean | SD |
| Dutch TIA (1993) | 741 | -2.2 | 16.0 | 732 | -8 | 16.0 | 1473 | -5.8 | 22.6 |
| MRC-O (1992) | 2213 | 167.0 | 17.9 | 1102 | 156.0 | 16.1 | 3315 | -11.0 | 24.1 |
| MRC-TMH (1985) | 8654 | -13 | 17.9 | 4403 | -23 | 16.1 | 13057 | -10.0 | 24.1 |
| TEST (1995) | 348 | 0.0 | 16.0 | 372 | -4 | 16.0 | 720 | -4.0 | 22.6 |
| UKPDS39 (1998) | 156 | -6 | 16.0 | 112 | -16 | 14.0 | 268 | -10.0 | 21.3 |
| **Weighted sum** | | | | | | | | | **23.8** |

Table A6.7. Calcium channel blockers in one year

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Placebo | | | Active | | | Total N | Difference | |
| N | Mean | SD | N | Mean | SD | Mean | SD |
| SYST-EUR (1997) | 2297 | -11.9 | 16.0 | 2398 | -20.8 | 17.0 | 4695 | -8.9 | **23.3** |

Table A6.8. Angiotensin-converting-enzyme inhibitors in three months

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Placebo | | | Active | | | Total N | Difference | |
| N | Mean | SD | N | Mean | SD | Mean | SD |
| HYVET (2008) | 394 | -7 | 11.0 | 397 | -30.9 | 13.0 | 791 | -23.9 | 17.0 |
| UKPDS39 (1998) | 156 | -6 | 16.0 | 124 | -15 | 14.0 | 280 | -9.0 | 21.3 |
| **Weighted sum** | | | | | | | | | **18.0** |

A6.3. References

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# Appendix 7. The list of 4,128 treatment sequences tested in the hypertension SDDP model

| No. | 1st drug | 2nd drug | 3rd drug | 4th drug |
| --- | --- | --- | --- | --- |
| 1 | D | BB | CCB | ACEI/ARB |
| 2 | D | BB | CCB | D+BB |
| 3 | D | BB | CCB | D+CCB |
| 4 | D | BB | CCB | D+ACEI/ARB |
| 5 | D | BB | CCB | BB+CCB |
| 6 | D | BB | CCB | BB+ACEI/ARB |
| 7 | D | BB | CCB | CCB+ACEI/ARB |
| 8 | D | BB | ACEI/ARB | CCB |
| 9 | D | BB | ACEI/ARB | D+BB |
| 10 | D | BB | ACEI/ARB | D+CCB |
| 11 | D | BB | ACEI/ARB | D+ACEI/ARB |
| 12 | D | BB | ACEI/ARB | BB+CCB |
| 13 | D | BB | ACEI/ARB | BB+ACEI/ARB |
| 14 | D | BB | ACEI/ARB | CCB+ACEI/ARB |
| 15 | D | BB | D+BB | CCB |
| 16 | D | BB | D+BB | ACEI/ARB |
| 17 | D | BB | D+BB | D+CCB |
| 18 | D | BB | D+BB | D+ACEI/ARB |
| 19 | D | BB | D+BB | BB+CCB |
| 20 | D | BB | D+BB | BB+ACEI/ARB |
| 21 | D | BB | D+BB | CCB+ACEI/ARB |
| 22 | D | BB | D+BB | D+BB+CCB |
| 23 | D | BB | D+BB | D+BB+ACEI/ARB |
| 24 | D | BB | D+BB | D+CCB+ACEI/ARB |
| 25 | D | BB | D+BB | BB+CCB+ACEI/ARB |
| 26 | D | BB | D+CCB | CCB |
| 27 | D | BB | D+CCB | ACEI/ARB |
| 28 | D | BB | D+CCB | D+BB |
| 29 | D | BB | D+CCB | D+ACEI/ARB |
| 30 | D | BB | D+CCB | BB+CCB |
| 31 | D | BB | D+CCB | BB+ACEI/ARB |
| 32 | D | BB | D+CCB | CCB+ACEI/ARB |
| 33 | D | BB | D+CCB | D+BB+CCB |
| 34 | D | BB | D+CCB | D+BB+ACEI/ARB |
| 35 | D | BB | D+CCB | D+CCB+ACEI/ARB |
| 36 | D | BB | D+CCB | BB+CCB+ACEI/ARB |
| 37 | D | BB | D+ACEIs/ARB | CCB |
| 38 | D | BB | D+ACEIs/ARB | ACEI/ARB |
| 39 | D | BB | D+ACEIs/ARB | D+BB |
| 40 | D | BB | D+ACEIs/ARB | D+CCB |
| 41 | D | BB | D+ACEIs/ARB | BB+CCB |
| 42 | D | BB | D+ACEIs/ARB | BB+ACEI/ARB |
| 43 | D | BB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 44 | D | BB | D+ACEIs/ARB | D+BB+CCB |
| 45 | D | BB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 46 | D | BB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 47 | D | BB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 48 | D | BB | BB+CCB | CCB |
| 49 | D | BB | BB+CCB | ACEI/ARB |
| 50 | D | BB | BB+CCB | D+BB |
| 51 | D | BB | BB+CCB | D+CCB |
| 52 | D | BB | BB+CCB | D+ACEI/ARB |
| 53 | D | BB | BB+CCB | BB+ACEI/ARB |
| 54 | D | BB | BB+CCB | CCB+ACEI/ARB |
| 55 | D | BB | BB+CCB | D+BB+CCB |
| 56 | D | BB | BB+CCB | D+BB+ACEI/ARB |
| 57 | D | BB | BB+CCB | D+CCB+ACEI/ARB |
| 58 | D | BB | BB+CCB | BB+CCB+ACEI/ARB |
| 59 | D | BB | BB+ACEI/ARB | CCB |
| 60 | D | BB | BB+ACEI/ARB | ACEI/ARB |
| 61 | D | BB | BB+ACEI/ARB | D+BB |
| 62 | D | BB | BB+ACEI/ARB | D+CCB |
| 63 | D | BB | BB+ACEI/ARB | D+ACEI/ARB |
| 64 | D | BB | BB+ACEI/ARB | BB+CCB |
| 65 | D | BB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 66 | D | BB | BB+ACEI/ARB | D+BB+CCB |
| 67 | D | BB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 68 | D | BB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 69 | D | BB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 70 | D | BB | CCB+ACEI/ARB | CCB |
| 71 | D | BB | CCB+ACEI/ARB | ACEI/ARB |
| 72 | D | BB | CCB+ACEI/ARB | D+BB |
| 73 | D | BB | CCB+ACEI/ARB | D+CCB |
| 74 | D | BB | CCB+ACEI/ARB | D+ACEI/ARB |
| 75 | D | BB | CCB+ACEI/ARB | BB+CCB |
| 76 | D | BB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 77 | D | BB | CCB+ACEI/ARB | D+BB+CCB |
| 78 | D | BB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 79 | D | BB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 80 | D | BB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 81 | D | CCB | BB | ACEI/ARB |
| 82 | D | CCB | BB | D+BB |
| 83 | D | CCB | BB | D+CCB |
| 84 | D | CCB | BB | D+ACEI/ARB |
| 85 | D | CCB | BB | BB+CCB |
| 86 | D | CCB | BB | BB+ACEI/ARB |
| 87 | D | CCB | BB | CCB+ACEI/ARB |
| 88 | D | CCB | ACEI/ARB | BB |
| 89 | D | CCB | ACEI/ARB | D+BB |
| 90 | D | CCB | ACEI/ARB | D+CCB |
| 91 | D | CCB | ACEI/ARB | D+ACEI/ARB |
| 92 | D | CCB | ACEI/ARB | BB+CCB |
| 93 | D | CCB | ACEI/ARB | BB+ACEI/ARB |
| 94 | D | CCB | ACEI/ARB | CCB+ACEI/ARB |
| 95 | D | CCB | D+BB | BB |
| 96 | D | CCB | D+BB | ACEI/ARB |
| 97 | D | CCB | D+BB | D+CCB |
| 98 | D | CCB | D+BB | D+ACEI/ARB |
| 99 | D | CCB | D+BB | BB+CCB |
| 100 | D | CCB | D+BB | BB+ACEI/ARB |
| 101 | D | CCB | D+BB | CCB+ACEI/ARB |
| 102 | D | CCB | D+BB | D+BB+CCB |
| 103 | D | CCB | D+BB | D+BB+ACEI/ARB |
| 104 | D | CCB | D+BB | D+CCB+ACEI/ARB |
| 105 | D | CCB | D+BB | BB+CCB+ACEI/ARB |
| 106 | D | CCB | D+CCB | BB |
| 107 | D | CCB | D+CCB | ACEI/ARB |
| 108 | D | CCB | D+CCB | D+BB |
| 109 | D | CCB | D+CCB | D+ACEI/ARB |
| 110 | D | CCB | D+CCB | BB+CCB |
| 111 | D | CCB | D+CCB | BB+ACEI/ARB |
| 112 | D | CCB | D+CCB | CCB+ACEI/ARB |
| 113 | D | CCB | D+CCB | D+BB+CCB |
| 114 | D | CCB | D+CCB | D+BB+ACEI/ARB |
| 115 | D | CCB | D+CCB | D+CCB+ACEI/ARB |
| 116 | D | CCB | D+CCB | BB+CCB+ACEI/ARB |
| 117 | D | CCB | D+ACEIs/ARB | BB |
| 118 | D | CCB | D+ACEIs/ARB | ACEI/ARB |
| 119 | D | CCB | D+ACEIs/ARB | D+BB |
| 120 | D | CCB | D+ACEIs/ARB | D+CCB |
| 121 | D | CCB | D+ACEIs/ARB | BB+CCB |
| 122 | D | CCB | D+ACEIs/ARB | BB+ACEI/ARB |
| 123 | D | CCB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 124 | D | CCB | D+ACEIs/ARB | D+BB+CCB |
| 125 | D | CCB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 126 | D | CCB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 127 | D | CCB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 128 | D | CCB | BB+CCB | BB |
| 129 | D | CCB | BB+CCB | ACEI/ARB |
| 130 | D | CCB | BB+CCB | D+BB |
| 131 | D | CCB | BB+CCB | D+CCB |
| 132 | D | CCB | BB+CCB | D+ACEI/ARB |
| 133 | D | CCB | BB+CCB | BB+ACEI/ARB |
| 134 | D | CCB | BB+CCB | CCB+ACEI/ARB |
| 135 | D | CCB | BB+CCB | D+BB+CCB |
| 136 | D | CCB | BB+CCB | D+BB+ACEI/ARB |
| 137 | D | CCB | BB+CCB | D+CCB+ACEI/ARB |
| 138 | D | CCB | BB+CCB | BB+CCB+ACEI/ARB |
| 139 | D | CCB | BB+ACEI/ARB | BB |
| 140 | D | CCB | BB+ACEI/ARB | ACEI/ARB |
| 141 | D | CCB | BB+ACEI/ARB | D+BB |
| 142 | D | CCB | BB+ACEI/ARB | D+CCB |
| 143 | D | CCB | BB+ACEI/ARB | D+ACEI/ARB |
| 144 | D | CCB | BB+ACEI/ARB | BB+CCB |
| 145 | D | CCB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 146 | D | CCB | BB+ACEI/ARB | D+BB+CCB |
| 147 | D | CCB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 148 | D | CCB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 149 | D | CCB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 150 | D | CCB | CCB+ACEI/ARB | BB |
| 151 | D | CCB | CCB+ACEI/ARB | ACEI/ARB |
| 152 | D | CCB | CCB+ACEI/ARB | D+BB |
| 153 | D | CCB | CCB+ACEI/ARB | D+CCB |
| 154 | D | CCB | CCB+ACEI/ARB | D+ACEI/ARB |
| 155 | D | CCB | CCB+ACEI/ARB | BB+CCB |
| 156 | D | CCB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 157 | D | CCB | CCB+ACEI/ARB | D+BB+CCB |
| 158 | D | CCB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 159 | D | CCB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 160 | D | CCB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 161 | D | ACEI/ARB | BB | CCB |
| 162 | D | ACEI/ARB | BB | D+BB |
| 163 | D | ACEI/ARB | BB | D+CCB |
| 164 | D | ACEI/ARB | BB | D+ACEI/ARB |
| 165 | D | ACEI/ARB | BB | BB+CCB |
| 166 | D | ACEI/ARB | BB | BB+ACEI/ARB |
| 167 | D | ACEI/ARB | BB | CCB+ACEI/ARB |
| 168 | D | ACEI/ARB | CCB | BB |
| 169 | D | ACEI/ARB | CCB | D+BB |
| 170 | D | ACEI/ARB | CCB | D+CCB |
| 171 | D | ACEI/ARB | CCB | D+ACEI/ARB |
| 172 | D | ACEI/ARB | CCB | BB+CCB |
| 173 | D | ACEI/ARB | CCB | BB+ACEI/ARB |
| 174 | D | ACEI/ARB | CCB | CCB+ACEI/ARB |
| 175 | D | ACEI/ARB | D+BB | BB |
| 176 | D | ACEI/ARB | D+BB | CCB |
| 177 | D | ACEI/ARB | D+BB | D+CCB |
| 178 | D | ACEI/ARB | D+BB | D+ACEI/ARB |
| 179 | D | ACEI/ARB | D+BB | BB+CCB |
| 180 | D | ACEI/ARB | D+BB | BB+ACEI/ARB |
| 181 | D | ACEI/ARB | D+BB | CCB+ACEI/ARB |
| 182 | D | ACEI/ARB | D+BB | D+BB+CCB |
| 183 | D | ACEI/ARB | D+BB | D+BB+ACEI/ARB |
| 184 | D | ACEI/ARB | D+BB | D+CCB+ACEI/ARB |
| 185 | D | ACEI/ARB | D+BB | BB+CCB+ACEI/ARB |
| 186 | D | ACEI/ARB | D+CCB | BB |
| 187 | D | ACEI/ARB | D+CCB | CCB |
| 188 | D | ACEI/ARB | D+CCB | D+BB |
| 189 | D | ACEI/ARB | D+CCB | D+ACEI/ARB |
| 190 | D | ACEI/ARB | D+CCB | BB+CCB |
| 191 | D | ACEI/ARB | D+CCB | BB+ACEI/ARB |
| 192 | D | ACEI/ARB | D+CCB | CCB+ACEI/ARB |
| 193 | D | ACEI/ARB | D+CCB | D+BB+CCB |
| 194 | D | ACEI/ARB | D+CCB | D+BB+ACEI/ARB |
| 195 | D | ACEI/ARB | D+CCB | D+CCB+ACEI/ARB |
| 196 | D | ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB |
| 197 | D | ACEI/ARB | D+ACEIs/ARB | BB |
| 198 | D | ACEI/ARB | D+ACEIs/ARB | CCB |
| 199 | D | ACEI/ARB | D+ACEIs/ARB | D+BB |
| 200 | D | ACEI/ARB | D+ACEIs/ARB | D+CCB |
| 201 | D | ACEI/ARB | D+ACEIs/ARB | BB+CCB |
| 202 | D | ACEI/ARB | D+ACEIs/ARB | BB+ACEI/ARB |
| 203 | D | ACEI/ARB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 204 | D | ACEI/ARB | D+ACEIs/ARB | D+BB+CCB |
| 205 | D | ACEI/ARB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 206 | D | ACEI/ARB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 207 | D | ACEI/ARB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 208 | D | ACEI/ARB | BB+CCB | BB |
| 209 | D | ACEI/ARB | BB+CCB | CCB |
| 210 | D | ACEI/ARB | BB+CCB | D+BB |
| 211 | D | ACEI/ARB | BB+CCB | D+CCB |
| 212 | D | ACEI/ARB | BB+CCB | D+ACEI/ARB |
| 213 | D | ACEI/ARB | BB+CCB | BB+ACEI/ARB |
| 214 | D | ACEI/ARB | BB+CCB | CCB+ACEI/ARB |
| 215 | D | ACEI/ARB | BB+CCB | D+BB+CCB |
| 216 | D | ACEI/ARB | BB+CCB | D+BB+ACEI/ARB |
| 217 | D | ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB |
| 218 | D | ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB |
| 219 | D | ACEI/ARB | BB+ACEI/ARB | BB |
| 220 | D | ACEI/ARB | BB+ACEI/ARB | CCB |
| 221 | D | ACEI/ARB | BB+ACEI/ARB | D+BB |
| 222 | D | ACEI/ARB | BB+ACEI/ARB | D+CCB |
| 223 | D | ACEI/ARB | BB+ACEI/ARB | D+ACEI/ARB |
| 224 | D | ACEI/ARB | BB+ACEI/ARB | BB+CCB |
| 225 | D | ACEI/ARB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 226 | D | ACEI/ARB | BB+ACEI/ARB | D+BB+CCB |
| 227 | D | ACEI/ARB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 228 | D | ACEI/ARB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 229 | D | ACEI/ARB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 230 | D | ACEI/ARB | CCB+ACEI/ARB | BB |
| 231 | D | ACEI/ARB | CCB+ACEI/ARB | CCB |
| 232 | D | ACEI/ARB | CCB+ACEI/ARB | D+BB |
| 233 | D | ACEI/ARB | CCB+ACEI/ARB | D+CCB |
| 234 | D | ACEI/ARB | CCB+ACEI/ARB | D+ACEI/ARB |
| 235 | D | ACEI/ARB | CCB+ACEI/ARB | BB+CCB |
| 236 | D | ACEI/ARB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 237 | D | ACEI/ARB | CCB+ACEI/ARB | D+BB+CCB |
| 238 | D | ACEI/ARB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 239 | D | ACEI/ARB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 240 | D | ACEI/ARB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 241 | D | D+BB | BB | CCB |
| 242 | D | D+BB | BB | ACEI/ARB |
| 243 | D | D+BB | BB | D+CCB |
| 244 | D | D+BB | BB | D+ACEI/ARB |
| 245 | D | D+BB | BB | BB+CCB |
| 246 | D | D+BB | BB | BB+ACEI/ARB |
| 247 | D | D+BB | BB | CCB+ACEI/ARB |
| 248 | D | D+BB | BB | D+BB+CCB |
| 249 | D | D+BB | BB | D+BB+ACEI/ARB |
| 250 | D | D+BB | BB | D+CCB+ACEI/ARB |
| 251 | D | D+BB | BB | BB+CCB+ACEI/ARB |
| 252 | D | D+BB | CCB | BB |
| 253 | D | D+BB | CCB | ACEI/ARB |
| 254 | D | D+BB | CCB | D+CCB |
| 255 | D | D+BB | CCB | D+ACEI/ARB |
| 256 | D | D+BB | CCB | BB+CCB |
| 257 | D | D+BB | CCB | BB+ACEI/ARB |
| 258 | D | D+BB | CCB | CCB+ACEI/ARB |
| 259 | D | D+BB | CCB | D+BB+CCB |
| 260 | D | D+BB | CCB | D+BB+ACEI/ARB |
| 261 | D | D+BB | CCB | D+CCB+ACEI/ARB |
| 262 | D | D+BB | CCB | BB+CCB+ACEI/ARB |
| 263 | D | D+BB | ACEI/ARB | BB |
| 264 | D | D+BB | ACEI/ARB | CCB |
| 265 | D | D+BB | ACEI/ARB | D+CCB |
| 266 | D | D+BB | ACEI/ARB | D+ACEI/ARB |
| 267 | D | D+BB | ACEI/ARB | BB+CCB |
| 268 | D | D+BB | ACEI/ARB | BB+ACEI/ARB |
| 269 | D | D+BB | ACEI/ARB | CCB+ACEI/ARB |
| 270 | D | D+BB | ACEI/ARB | D+BB+CCB |
| 271 | D | D+BB | ACEI/ARB | D+BB+ACEI/ARB |
| 272 | D | D+BB | ACEI/ARB | D+CCB+ACEI/ARB |
| 273 | D | D+BB | ACEI/ARB | BB+CCB+ACEI/ARB |
| 274 | D | D+BB | D+CCB | BB |
| 275 | D | D+BB | D+CCB | CCB |
| 276 | D | D+BB | D+CCB | ACEI/ARB |
| 277 | D | D+BB | D+CCB | D+ACEI/ARB |
| 278 | D | D+BB | D+CCB | BB+CCB |
| 279 | D | D+BB | D+CCB | BB+ACEI/ARB |
| 280 | D | D+BB | D+CCB | CCB+ACEI/ARB |
| 281 | D | D+BB | D+CCB | D+BB+CCB |
| 282 | D | D+BB | D+CCB | D+BB+ACEI/ARB |
| 283 | D | D+BB | D+CCB | D+CCB+ACEI/ARB |
| 284 | D | D+BB | D+CCB | BB+CCB+ACEI/ARB |
| 285 | D | D+BB | D+ACEIs/ARB | BB |
| 286 | D | D+BB | D+ACEIs/ARB | CCB |
| 287 | D | D+BB | D+ACEIs/ARB | ACEI/ARB |
| 288 | D | D+BB | D+ACEIs/ARB | D+CCB |
| 289 | D | D+BB | D+ACEIs/ARB | BB+CCB |
| 290 | D | D+BB | D+ACEIs/ARB | BB+ACEI/ARB |
| 291 | D | D+BB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 292 | D | D+BB | D+ACEIs/ARB | D+BB+CCB |
| 293 | D | D+BB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 294 | D | D+BB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 295 | D | D+BB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 296 | D | D+BB | BB+CCB | BB |
| 297 | D | D+BB | BB+CCB | CCB |
| 298 | D | D+BB | BB+CCB | ACEI/ARB |
| 299 | D | D+BB | BB+CCB | D+CCB |
| 300 | D | D+BB | BB+CCB | D+ACEI/ARB |
| 301 | D | D+BB | BB+CCB | BB+ACEI/ARB |
| 302 | D | D+BB | BB+CCB | CCB+ACEI/ARB |
| 303 | D | D+BB | BB+CCB | D+BB+CCB |
| 304 | D | D+BB | BB+CCB | D+BB+ACEI/ARB |
| 305 | D | D+BB | BB+CCB | D+CCB+ACEI/ARB |
| 306 | D | D+BB | BB+CCB | BB+CCB+ACEI/ARB |
| 307 | D | D+BB | BB+ACEI/ARB | BB |
| 308 | D | D+BB | BB+ACEI/ARB | CCB |
| 309 | D | D+BB | BB+ACEI/ARB | ACEI/ARB |
| 310 | D | D+BB | BB+ACEI/ARB | D+CCB |
| 311 | D | D+BB | BB+ACEI/ARB | D+ACEI/ARB |
| 312 | D | D+BB | BB+ACEI/ARB | BB+CCB |
| 313 | D | D+BB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 314 | D | D+BB | BB+ACEI/ARB | D+BB+CCB |
| 315 | D | D+BB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 316 | D | D+BB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 317 | D | D+BB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 318 | D | D+BB | CCB+ACEI/ARB | BB |
| 319 | D | D+BB | CCB+ACEI/ARB | CCB |
| 320 | D | D+BB | CCB+ACEI/ARB | ACEI/ARB |
| 321 | D | D+BB | CCB+ACEI/ARB | D+CCB |
| 322 | D | D+BB | CCB+ACEI/ARB | D+ACEI/ARB |
| 323 | D | D+BB | CCB+ACEI/ARB | BB+CCB |
| 324 | D | D+BB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 325 | D | D+BB | CCB+ACEI/ARB | D+BB+CCB |
| 326 | D | D+BB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 327 | D | D+BB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 328 | D | D+BB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 329 | D | D+BB | D+BB+CCB | BB |
| 330 | D | D+BB | D+BB+CCB | CCB |
| 331 | D | D+BB | D+BB+CCB | ACEI/ARB |
| 332 | D | D+BB | D+BB+CCB | D+CCB |
| 333 | D | D+BB | D+BB+CCB | D+ACEI/ARB |
| 334 | D | D+BB | D+BB+CCB | BB+CCB |
| 335 | D | D+BB | D+BB+CCB | BB+ACEI/ARB |
| 336 | D | D+BB | D+BB+CCB | CCB+ACEI/ARB |
| 337 | D | D+BB | D+BB+CCB | D+BB+ACEI/ARB |
| 338 | D | D+BB | D+BB+CCB | D+CCB+ACEI/ARB |
| 339 | D | D+BB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 340 | D | D+BB | D+BB+ACEI/ARB | BB |
| 341 | D | D+BB | D+BB+ACEI/ARB | CCB |
| 342 | D | D+BB | D+BB+ACEI/ARB | ACEI/ARB |
| 343 | D | D+BB | D+BB+ACEI/ARB | D+CCB |
| 344 | D | D+BB | D+BB+ACEI/ARB | D+ACEI/ARB |
| 345 | D | D+BB | D+BB+ACEI/ARB | BB+CCB |
| 346 | D | D+BB | D+BB+ACEI/ARB | BB+ACEI/ARB |
| 347 | D | D+BB | D+BB+ACEI/ARB | CCB+ACEI/ARB |
| 348 | D | D+BB | D+BB+ACEI/ARB | D+BB+CCB |
| 349 | D | D+BB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 350 | D | D+BB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 351 | D | D+BB | D+CCB+ACEI/ARB | BB |
| 352 | D | D+BB | D+CCB+ACEI/ARB | CCB |
| 353 | D | D+BB | D+CCB+ACEI/ARB | ACEI/ARB |
| 354 | D | D+BB | D+CCB+ACEI/ARB | D+CCB |
| 355 | D | D+BB | D+CCB+ACEI/ARB | D+ACEI/ARB |
| 356 | D | D+BB | D+CCB+ACEI/ARB | BB+CCB |
| 357 | D | D+BB | D+CCB+ACEI/ARB | BB+ACEI/ARB |
| 358 | D | D+BB | D+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 359 | D | D+BB | D+CCB+ACEI/ARB | D+BB+CCB |
| 360 | D | D+BB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 361 | D | D+BB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 362 | D | D+BB | BB+CCB+ACEI/ARB | BB |
| 363 | D | D+BB | BB+CCB+ACEI/ARB | CCB |
| 364 | D | D+BB | BB+CCB+ACEI/ARB | ACEI/ARB |
| 365 | D | D+BB | BB+CCB+ACEI/ARB | D+CCB |
| 366 | D | D+BB | BB+CCB+ACEI/ARB | D+ACEI/ARB |
| 367 | D | D+BB | BB+CCB+ACEI/ARB | BB+CCB |
| 368 | D | D+BB | BB+CCB+ACEI/ARB | BB+ACEI/ARB |
| 369 | D | D+BB | BB+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 370 | D | D+BB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 371 | D | D+BB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 372 | D | D+BB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 373 | D | D+CCB | BB | CCB |
| 374 | D | D+CCB | BB | ACEI/ARB |
| 375 | D | D+CCB | BB | D+BB |
| 376 | D | D+CCB | BB | D+ACEI/ARB |
| 377 | D | D+CCB | BB | BB+CCB |
| 378 | D | D+CCB | BB | BB+ACEI/ARB |
| 379 | D | D+CCB | BB | CCB+ACEI/ARB |
| 380 | D | D+CCB | BB | D+BB+CCB |
| 381 | D | D+CCB | BB | D+BB+ACEI/ARB |
| 382 | D | D+CCB | BB | D+CCB+ACEI/ARB |
| 383 | D | D+CCB | BB | BB+CCB+ACEI/ARB |
| 384 | D | D+CCB | CCB | BB |
| 385 | D | D+CCB | CCB | ACEI/ARB |
| 386 | D | D+CCB | CCB | D+BB |
| 387 | D | D+CCB | CCB | D+ACEI/ARB |
| 388 | D | D+CCB | CCB | BB+CCB |
| 389 | D | D+CCB | CCB | BB+ACEI/ARB |
| 390 | D | D+CCB | CCB | CCB+ACEI/ARB |
| 391 | D | D+CCB | CCB | D+BB+CCB |
| 392 | D | D+CCB | CCB | D+BB+ACEI/ARB |
| 393 | D | D+CCB | CCB | D+CCB+ACEI/ARB |
| 394 | D | D+CCB | CCB | BB+CCB+ACEI/ARB |
| 395 | D | D+CCB | ACEI/ARB | BB |
| 396 | D | D+CCB | ACEI/ARB | CCB |
| 397 | D | D+CCB | ACEI/ARB | D+BB |
| 398 | D | D+CCB | ACEI/ARB | D+ACEI/ARB |
| 399 | D | D+CCB | ACEI/ARB | BB+CCB |
| 400 | D | D+CCB | ACEI/ARB | BB+ACEI/ARB |
| 401 | D | D+CCB | ACEI/ARB | CCB+ACEI/ARB |
| 402 | D | D+CCB | ACEI/ARB | D+BB+CCB |
| 403 | D | D+CCB | ACEI/ARB | D+BB+ACEI/ARB |
| 404 | D | D+CCB | ACEI/ARB | D+CCB+ACEI/ARB |
| 405 | D | D+CCB | ACEI/ARB | BB+CCB+ACEI/ARB |
| 406 | D | D+CCB | D+BB | BB |
| 407 | D | D+CCB | D+BB | CCB |
| 408 | D | D+CCB | D+BB | ACEI/ARB |
| 409 | D | D+CCB | D+BB | D+ACEI/ARB |
| 410 | D | D+CCB | D+BB | BB+CCB |
| 411 | D | D+CCB | D+BB | BB+ACEI/ARB |
| 412 | D | D+CCB | D+BB | CCB+ACEI/ARB |
| 413 | D | D+CCB | D+BB | D+BB+CCB |
| 414 | D | D+CCB | D+BB | D+BB+ACEI/ARB |
| 415 | D | D+CCB | D+BB | D+CCB+ACEI/ARB |
| 416 | D | D+CCB | D+BB | BB+CCB+ACEI/ARB |
| 417 | D | D+CCB | D+ACEIs/ARB | BB |
| 418 | D | D+CCB | D+ACEIs/ARB | CCB |
| 419 | D | D+CCB | D+ACEIs/ARB | ACEI/ARB |
| 420 | D | D+CCB | D+ACEIs/ARB | D+BB |
| 421 | D | D+CCB | D+ACEIs/ARB | BB+CCB |
| 422 | D | D+CCB | D+ACEIs/ARB | BB+ACEI/ARB |
| 423 | D | D+CCB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 424 | D | D+CCB | D+ACEIs/ARB | D+BB+CCB |
| 425 | D | D+CCB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 426 | D | D+CCB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 427 | D | D+CCB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 428 | D | D+CCB | BB+CCB | BB |
| 429 | D | D+CCB | BB+CCB | CCB |
| 430 | D | D+CCB | BB+CCB | ACEI/ARB |
| 431 | D | D+CCB | BB+CCB | D+BB |
| 432 | D | D+CCB | BB+CCB | D+ACEI/ARB |
| 433 | D | D+CCB | BB+CCB | BB+ACEI/ARB |
| 434 | D | D+CCB | BB+CCB | CCB+ACEI/ARB |
| 435 | D | D+CCB | BB+CCB | D+BB+CCB |
| 436 | D | D+CCB | BB+CCB | D+BB+ACEI/ARB |
| 437 | D | D+CCB | BB+CCB | D+CCB+ACEI/ARB |
| 438 | D | D+CCB | BB+CCB | BB+CCB+ACEI/ARB |
| 439 | D | D+CCB | BB+ACEI/ARB | BB |
| 440 | D | D+CCB | BB+ACEI/ARB | CCB |
| 441 | D | D+CCB | BB+ACEI/ARB | ACEI/ARB |
| 442 | D | D+CCB | BB+ACEI/ARB | D+BB |
| 443 | D | D+CCB | BB+ACEI/ARB | D+ACEI/ARB |
| 444 | D | D+CCB | BB+ACEI/ARB | BB+CCB |
| 445 | D | D+CCB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 446 | D | D+CCB | BB+ACEI/ARB | D+BB+CCB |
| 447 | D | D+CCB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 448 | D | D+CCB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 449 | D | D+CCB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 450 | D | D+CCB | CCB+ACEI/ARB | BB |
| 451 | D | D+CCB | CCB+ACEI/ARB | CCB |
| 452 | D | D+CCB | CCB+ACEI/ARB | ACEI/ARB |
| 453 | D | D+CCB | CCB+ACEI/ARB | D+BB |
| 454 | D | D+CCB | CCB+ACEI/ARB | D+ACEI/ARB |
| 455 | D | D+CCB | CCB+ACEI/ARB | BB+CCB |
| 456 | D | D+CCB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 457 | D | D+CCB | CCB+ACEI/ARB | D+BB+CCB |
| 458 | D | D+CCB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 459 | D | D+CCB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 460 | D | D+CCB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 461 | D | D+CCB | D+BB+CCB | BB |
| 462 | D | D+CCB | D+BB+CCB | CCB |
| 463 | D | D+CCB | D+BB+CCB | ACEI/ARB |
| 464 | D | D+CCB | D+BB+CCB | D+BB |
| 465 | D | D+CCB | D+BB+CCB | D+ACEI/ARB |
| 466 | D | D+CCB | D+BB+CCB | BB+CCB |
| 467 | D | D+CCB | D+BB+CCB | BB+ACEI/ARB |
| 468 | D | D+CCB | D+BB+CCB | CCB+ACEI/ARB |
| 469 | D | D+CCB | D+BB+CCB | D+BB+ACEI/ARB |
| 470 | D | D+CCB | D+BB+CCB | D+CCB+ACEI/ARB |
| 471 | D | D+CCB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 472 | D | D+CCB | D+BB+ACEI/ARB | BB |
| 473 | D | D+CCB | D+BB+ACEI/ARB | CCB |
| 474 | D | D+CCB | D+BB+ACEI/ARB | ACEI/ARB |
| 475 | D | D+CCB | D+BB+ACEI/ARB | D+BB |
| 476 | D | D+CCB | D+BB+ACEI/ARB | D+ACEI/ARB |
| 477 | D | D+CCB | D+BB+ACEI/ARB | BB+CCB |
| 478 | D | D+CCB | D+BB+ACEI/ARB | BB+ACEI/ARB |
| 479 | D | D+CCB | D+BB+ACEI/ARB | CCB+ACEI/ARB |
| 480 | D | D+CCB | D+BB+ACEI/ARB | D+BB+CCB |
| 481 | D | D+CCB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 482 | D | D+CCB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 483 | D | D+CCB | D+CCB+ACEI/ARB | BB |
| 484 | D | D+CCB | D+CCB+ACEI/ARB | CCB |
| 485 | D | D+CCB | D+CCB+ACEI/ARB | ACEI/ARB |
| 486 | D | D+CCB | D+CCB+ACEI/ARB | D+BB |
| 487 | D | D+CCB | D+CCB+ACEI/ARB | D+ACEI/ARB |
| 488 | D | D+CCB | D+CCB+ACEI/ARB | BB+CCB |
| 489 | D | D+CCB | D+CCB+ACEI/ARB | BB+ACEI/ARB |
| 490 | D | D+CCB | D+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 491 | D | D+CCB | D+CCB+ACEI/ARB | D+BB+CCB |
| 492 | D | D+CCB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 493 | D | D+CCB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 494 | D | D+CCB | BB+CCB+ACEI/ARB | BB |
| 495 | D | D+CCB | BB+CCB+ACEI/ARB | CCB |
| 496 | D | D+CCB | BB+CCB+ACEI/ARB | ACEI/ARB |
| 497 | D | D+CCB | BB+CCB+ACEI/ARB | D+BB |
| 498 | D | D+CCB | BB+CCB+ACEI/ARB | D+ACEI/ARB |
| 499 | D | D+CCB | BB+CCB+ACEI/ARB | BB+CCB |
| 500 | D | D+CCB | BB+CCB+ACEI/ARB | BB+ACEI/ARB |
| 501 | D | D+CCB | BB+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 502 | D | D+CCB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 503 | D | D+CCB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 504 | D | D+CCB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 505 | D | D+ACEI/ARB | BB | CCB |
| 506 | D | D+ACEI/ARB | BB | ACEI/ARB |
| 507 | D | D+ACEI/ARB | BB | D+BB |
| 508 | D | D+ACEI/ARB | BB | D+CCB |
| 509 | D | D+ACEI/ARB | BB | BB+CCB |
| 510 | D | D+ACEI/ARB | BB | BB+ACEI/ARB |
| 511 | D | D+ACEI/ARB | BB | CCB+ACEI/ARB |
| 512 | D | D+ACEI/ARB | BB | D+BB+CCB |
| 513 | D | D+ACEI/ARB | BB | D+BB+ACEI/ARB |
| 514 | D | D+ACEI/ARB | BB | D+CCB+ACEI/ARB |
| 515 | D | D+ACEI/ARB | BB | BB+CCB+ACEI/ARB |
| 516 | D | D+ACEI/ARB | CCB | BB |
| 517 | D | D+ACEI/ARB | CCB | ACEI/ARB |
| 518 | D | D+ACEI/ARB | CCB | D+BB |
| 519 | D | D+ACEI/ARB | CCB | D+CCB |
| 520 | D | D+ACEI/ARB | CCB | BB+CCB |
| 521 | D | D+ACEI/ARB | CCB | BB+ACEI/ARB |
| 522 | D | D+ACEI/ARB | CCB | CCB+ACEI/ARB |
| 523 | D | D+ACEI/ARB | CCB | D+BB+CCB |
| 524 | D | D+ACEI/ARB | CCB | D+BB+ACEI/ARB |
| 525 | D | D+ACEI/ARB | CCB | D+CCB+ACEI/ARB |
| 526 | D | D+ACEI/ARB | CCB | BB+CCB+ACEI/ARB |
| 527 | D | D+ACEI/ARB | ACEI/ARB | BB |
| 528 | D | D+ACEI/ARB | ACEI/ARB | CCB |
| 529 | D | D+ACEI/ARB | ACEI/ARB | D+BB |
| 530 | D | D+ACEI/ARB | ACEI/ARB | D+CCB |
| 531 | D | D+ACEI/ARB | ACEI/ARB | BB+CCB |
| 532 | D | D+ACEI/ARB | ACEI/ARB | BB+ACEI/ARB |
| 533 | D | D+ACEI/ARB | ACEI/ARB | CCB+ACEI/ARB |
| 534 | D | D+ACEI/ARB | ACEI/ARB | D+BB+CCB |
| 535 | D | D+ACEI/ARB | ACEI/ARB | D+BB+ACEI/ARB |
| 536 | D | D+ACEI/ARB | ACEI/ARB | D+CCB+ACEI/ARB |
| 537 | D | D+ACEI/ARB | ACEI/ARB | BB+CCB+ACEI/ARB |
| 538 | D | D+ACEI/ARB | D+BB | BB |
| 539 | D | D+ACEI/ARB | D+BB | CCB |
| 540 | D | D+ACEI/ARB | D+BB | ACEI/ARB |
| 541 | D | D+ACEI/ARB | D+BB | D+CCB |
| 542 | D | D+ACEI/ARB | D+BB | BB+CCB |
| 543 | D | D+ACEI/ARB | D+BB | BB+ACEI/ARB |
| 544 | D | D+ACEI/ARB | D+BB | CCB+ACEI/ARB |
| 545 | D | D+ACEI/ARB | D+BB | D+BB+CCB |
| 546 | D | D+ACEI/ARB | D+BB | D+BB+ACEI/ARB |
| 547 | D | D+ACEI/ARB | D+BB | D+CCB+ACEI/ARB |
| 548 | D | D+ACEI/ARB | D+BB | BB+CCB+ACEI/ARB |
| 549 | D | D+ACEI/ARB | D+CCB | BB |
| 550 | D | D+ACEI/ARB | D+CCB | CCB |
| 551 | D | D+ACEI/ARB | D+CCB | ACEI/ARB |
| 552 | D | D+ACEI/ARB | D+CCB | D+BB |
| 553 | D | D+ACEI/ARB | D+CCB | BB+CCB |
| 554 | D | D+ACEI/ARB | D+CCB | BB+ACEI/ARB |
| 555 | D | D+ACEI/ARB | D+CCB | CCB+ACEI/ARB |
| 556 | D | D+ACEI/ARB | D+CCB | D+BB+CCB |
| 557 | D | D+ACEI/ARB | D+CCB | D+BB+ACEI/ARB |
| 558 | D | D+ACEI/ARB | D+CCB | D+CCB+ACEI/ARB |
| 559 | D | D+ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB |
| 560 | D | D+ACEI/ARB | BB+CCB | BB |
| 561 | D | D+ACEI/ARB | BB+CCB | CCB |
| 562 | D | D+ACEI/ARB | BB+CCB | ACEI/ARB |
| 563 | D | D+ACEI/ARB | BB+CCB | D+BB |
| 564 | D | D+ACEI/ARB | BB+CCB | D+CCB |
| 565 | D | D+ACEI/ARB | BB+CCB | BB+ACEI/ARB |
| 566 | D | D+ACEI/ARB | BB+CCB | CCB+ACEI/ARB |
| 567 | D | D+ACEI/ARB | BB+CCB | D+BB+CCB |
| 568 | D | D+ACEI/ARB | BB+CCB | D+BB+ACEI/ARB |
| 569 | D | D+ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB |
| 570 | D | D+ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB |
| 571 | D | D+ACEI/ARB | BB+ACEI/ARB | BB |
| 572 | D | D+ACEI/ARB | BB+ACEI/ARB | CCB |
| 573 | D | D+ACEI/ARB | BB+ACEI/ARB | ACEI/ARB |
| 574 | D | D+ACEI/ARB | BB+ACEI/ARB | D+BB |
| 575 | D | D+ACEI/ARB | BB+ACEI/ARB | D+CCB |
| 576 | D | D+ACEI/ARB | BB+ACEI/ARB | BB+CCB |
| 577 | D | D+ACEI/ARB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 578 | D | D+ACEI/ARB | BB+ACEI/ARB | D+BB+CCB |
| 579 | D | D+ACEI/ARB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 580 | D | D+ACEI/ARB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 581 | D | D+ACEI/ARB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 582 | D | D+ACEI/ARB | CCB+ACEI/ARB | BB |
| 583 | D | D+ACEI/ARB | CCB+ACEI/ARB | CCB |
| 584 | D | D+ACEI/ARB | CCB+ACEI/ARB | ACEI/ARB |
| 585 | D | D+ACEI/ARB | CCB+ACEI/ARB | D+BB |
| 586 | D | D+ACEI/ARB | CCB+ACEI/ARB | D+CCB |
| 587 | D | D+ACEI/ARB | CCB+ACEI/ARB | BB+CCB |
| 588 | D | D+ACEI/ARB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 589 | D | D+ACEI/ARB | CCB+ACEI/ARB | D+BB+CCB |
| 590 | D | D+ACEI/ARB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 591 | D | D+ACEI/ARB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 592 | D | D+ACEI/ARB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 593 | D | D+ACEI/ARB | D+BB+CCB | BB |
| 594 | D | D+ACEI/ARB | D+BB+CCB | CCB |
| 595 | D | D+ACEI/ARB | D+BB+CCB | ACEI/ARB |
| 596 | D | D+ACEI/ARB | D+BB+CCB | D+BB |
| 597 | D | D+ACEI/ARB | D+BB+CCB | D+CCB |
| 598 | D | D+ACEI/ARB | D+BB+CCB | BB+CCB |
| 599 | D | D+ACEI/ARB | D+BB+CCB | BB+ACEI/ARB |
| 600 | D | D+ACEI/ARB | D+BB+CCB | CCB+ACEI/ARB |
| 601 | D | D+ACEI/ARB | D+BB+CCB | D+BB+ACEI/ARB |
| 602 | D | D+ACEI/ARB | D+BB+CCB | D+CCB+ACEI/ARB |
| 603 | D | D+ACEI/ARB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 604 | D | D+ACEI/ARB | D+BB+ACEI/ARB | BB |
| 605 | D | D+ACEI/ARB | D+BB+ACEI/ARB | CCB |
| 606 | D | D+ACEI/ARB | D+BB+ACEI/ARB | ACEI/ARB |
| 607 | D | D+ACEI/ARB | D+BB+ACEI/ARB | D+BB |
| 608 | D | D+ACEI/ARB | D+BB+ACEI/ARB | D+CCB |
| 609 | D | D+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB |
| 610 | D | D+ACEI/ARB | D+BB+ACEI/ARB | BB+ACEI/ARB |
| 611 | D | D+ACEI/ARB | D+BB+ACEI/ARB | CCB+ACEI/ARB |
| 612 | D | D+ACEI/ARB | D+BB+ACEI/ARB | D+BB+CCB |
| 613 | D | D+ACEI/ARB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 614 | D | D+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 615 | D | D+ACEI/ARB | D+CCB+ACEI/ARB | BB |
| 616 | D | D+ACEI/ARB | D+CCB+ACEI/ARB | CCB |
| 617 | D | D+ACEI/ARB | D+CCB+ACEI/ARB | ACEI/ARB |
| 618 | D | D+ACEI/ARB | D+CCB+ACEI/ARB | D+BB |
| 619 | D | D+ACEI/ARB | D+CCB+ACEI/ARB | D+CCB |
| 620 | D | D+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB |
| 621 | D | D+ACEI/ARB | D+CCB+ACEI/ARB | BB+ACEI/ARB |
| 622 | D | D+ACEI/ARB | D+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 623 | D | D+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+CCB |
| 624 | D | D+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 625 | D | D+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 626 | D | D+ACEI/ARB | BB+CCB+ACEI/ARB | BB |
| 627 | D | D+ACEI/ARB | BB+CCB+ACEI/ARB | CCB |
| 628 | D | D+ACEI/ARB | BB+CCB+ACEI/ARB | ACEI/ARB |
| 629 | D | D+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB |
| 630 | D | D+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB |
| 631 | D | D+ACEI/ARB | BB+CCB+ACEI/ARB | BB+CCB |
| 632 | D | D+ACEI/ARB | BB+CCB+ACEI/ARB | BB+ACEI/ARB |
| 633 | D | D+ACEI/ARB | BB+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 634 | D | D+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 635 | D | D+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 636 | D | D+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 637 | D | BB+CCB | BB | CCB |
| 638 | D | BB+CCB | BB | ACEI/ARB |
| 639 | D | BB+CCB | BB | D+BB |
| 640 | D | BB+CCB | BB | D+CCB |
| 641 | D | BB+CCB | BB | D+ACEI/ARB |
| 642 | D | BB+CCB | BB | BB+ACEI/ARB |
| 643 | D | BB+CCB | BB | CCB+ACEI/ARB |
| 644 | D | BB+CCB | BB | D+BB+CCB |
| 645 | D | BB+CCB | BB | D+BB+ACEI/ARB |
| 646 | D | BB+CCB | BB | D+CCB+ACEI/ARB |
| 647 | D | BB+CCB | BB | BB+CCB+ACEI/ARB |
| 648 | D | BB+CCB | CCB | BB |
| 649 | D | BB+CCB | CCB | ACEI/ARB |
| 650 | D | BB+CCB | CCB | D+BB |
| 651 | D | BB+CCB | CCB | D+CCB |
| 652 | D | BB+CCB | CCB | D+ACEI/ARB |
| 653 | D | BB+CCB | CCB | BB+ACEI/ARB |
| 654 | D | BB+CCB | CCB | CCB+ACEI/ARB |
| 655 | D | BB+CCB | CCB | D+BB+CCB |
| 656 | D | BB+CCB | CCB | D+BB+ACEI/ARB |
| 657 | D | BB+CCB | CCB | D+CCB+ACEI/ARB |
| 658 | D | BB+CCB | CCB | BB+CCB+ACEI/ARB |
| 659 | D | BB+CCB | ACEI/ARB | BB |
| 660 | D | BB+CCB | ACEI/ARB | CCB |
| 661 | D | BB+CCB | ACEI/ARB | D+BB |
| 662 | D | BB+CCB | ACEI/ARB | D+CCB |
| 663 | D | BB+CCB | ACEI/ARB | D+ACEI/ARB |
| 664 | D | BB+CCB | ACEI/ARB | BB+ACEI/ARB |
| 665 | D | BB+CCB | ACEI/ARB | CCB+ACEI/ARB |
| 666 | D | BB+CCB | ACEI/ARB | D+BB+CCB |
| 667 | D | BB+CCB | ACEI/ARB | D+BB+ACEI/ARB |
| 668 | D | BB+CCB | ACEI/ARB | D+CCB+ACEI/ARB |
| 669 | D | BB+CCB | ACEI/ARB | BB+CCB+ACEI/ARB |
| 670 | D | BB+CCB | D+BB | BB |
| 671 | D | BB+CCB | D+BB | CCB |
| 672 | D | BB+CCB | D+BB | ACEI/ARB |
| 673 | D | BB+CCB | D+BB | D+CCB |
| 674 | D | BB+CCB | D+BB | D+ACEI/ARB |
| 675 | D | BB+CCB | D+BB | BB+ACEI/ARB |
| 676 | D | BB+CCB | D+BB | CCB+ACEI/ARB |
| 677 | D | BB+CCB | D+BB | D+BB+CCB |
| 678 | D | BB+CCB | D+BB | D+BB+ACEI/ARB |
| 679 | D | BB+CCB | D+BB | D+CCB+ACEI/ARB |
| 680 | D | BB+CCB | D+BB | BB+CCB+ACEI/ARB |
| 681 | D | BB+CCB | D+CCB | BB |
| 682 | D | BB+CCB | D+CCB | CCB |
| 683 | D | BB+CCB | D+CCB | ACEI/ARB |
| 684 | D | BB+CCB | D+CCB | D+BB |
| 685 | D | BB+CCB | D+CCB | D+ACEI/ARB |
| 686 | D | BB+CCB | D+CCB | BB+ACEI/ARB |
| 687 | D | BB+CCB | D+CCB | CCB+ACEI/ARB |
| 688 | D | BB+CCB | D+CCB | D+BB+CCB |
| 689 | D | BB+CCB | D+CCB | D+BB+ACEI/ARB |
| 690 | D | BB+CCB | D+CCB | D+CCB+ACEI/ARB |
| 691 | D | BB+CCB | D+CCB | BB+CCB+ACEI/ARB |
| 692 | D | BB+CCB | D+ACEIs/ARB | BB |
| 693 | D | BB+CCB | D+ACEIs/ARB | CCB |
| 694 | D | BB+CCB | D+ACEIs/ARB | ACEI/ARB |
| 695 | D | BB+CCB | D+ACEIs/ARB | D+BB |
| 696 | D | BB+CCB | D+ACEIs/ARB | D+CCB |
| 697 | D | BB+CCB | D+ACEIs/ARB | BB+ACEI/ARB |
| 698 | D | BB+CCB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 699 | D | BB+CCB | D+ACEIs/ARB | D+BB+CCB |
| 700 | D | BB+CCB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 701 | D | BB+CCB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 702 | D | BB+CCB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 703 | D | BB+CCB | BB+ACEI/ARB | BB |
| 704 | D | BB+CCB | BB+ACEI/ARB | CCB |
| 705 | D | BB+CCB | BB+ACEI/ARB | ACEI/ARB |
| 706 | D | BB+CCB | BB+ACEI/ARB | D+BB |
| 707 | D | BB+CCB | BB+ACEI/ARB | D+CCB |
| 708 | D | BB+CCB | BB+ACEI/ARB | D+ACEI/ARB |
| 709 | D | BB+CCB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 710 | D | BB+CCB | BB+ACEI/ARB | D+BB+CCB |
| 711 | D | BB+CCB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 712 | D | BB+CCB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 713 | D | BB+CCB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 714 | D | BB+CCB | CCB+ACEI/ARB | BB |
| 715 | D | BB+CCB | CCB+ACEI/ARB | CCB |
| 716 | D | BB+CCB | CCB+ACEI/ARB | ACEI/ARB |
| 717 | D | BB+CCB | CCB+ACEI/ARB | D+BB |
| 718 | D | BB+CCB | CCB+ACEI/ARB | D+CCB |
| 719 | D | BB+CCB | CCB+ACEI/ARB | D+ACEI/ARB |
| 720 | D | BB+CCB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 721 | D | BB+CCB | CCB+ACEI/ARB | D+BB+CCB |
| 722 | D | BB+CCB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 723 | D | BB+CCB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 724 | D | BB+CCB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 725 | D | BB+CCB | D+BB+CCB | BB |
| 726 | D | BB+CCB | D+BB+CCB | CCB |
| 727 | D | BB+CCB | D+BB+CCB | ACEI/ARB |
| 728 | D | BB+CCB | D+BB+CCB | D+BB |
| 729 | D | BB+CCB | D+BB+CCB | D+CCB |
| 730 | D | BB+CCB | D+BB+CCB | D+ACEI/ARB |
| 731 | D | BB+CCB | D+BB+CCB | BB+ACEI/ARB |
| 732 | D | BB+CCB | D+BB+CCB | CCB+ACEI/ARB |
| 733 | D | BB+CCB | D+BB+CCB | D+BB+ACEI/ARB |
| 734 | D | BB+CCB | D+BB+CCB | D+CCB+ACEI/ARB |
| 735 | D | BB+CCB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 736 | D | BB+CCB | D+BB+ACEI/ARB | BB |
| 737 | D | BB+CCB | D+BB+ACEI/ARB | CCB |
| 738 | D | BB+CCB | D+BB+ACEI/ARB | ACEI/ARB |
| 739 | D | BB+CCB | D+BB+ACEI/ARB | D+BB |
| 740 | D | BB+CCB | D+BB+ACEI/ARB | D+CCB |
| 741 | D | BB+CCB | D+BB+ACEI/ARB | D+ACEI/ARB |
| 742 | D | BB+CCB | D+BB+ACEI/ARB | BB+ACEI/ARB |
| 743 | D | BB+CCB | D+BB+ACEI/ARB | CCB+ACEI/ARB |
| 744 | D | BB+CCB | D+BB+ACEI/ARB | D+BB+CCB |
| 745 | D | BB+CCB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 746 | D | BB+CCB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 747 | D | BB+CCB | D+CCB+ACEI/ARB | BB |
| 748 | D | BB+CCB | D+CCB+ACEI/ARB | CCB |
| 749 | D | BB+CCB | D+CCB+ACEI/ARB | ACEI/ARB |
| 750 | D | BB+CCB | D+CCB+ACEI/ARB | D+BB |
| 751 | D | BB+CCB | D+CCB+ACEI/ARB | D+CCB |
| 752 | D | BB+CCB | D+CCB+ACEI/ARB | D+ACEI/ARB |
| 753 | D | BB+CCB | D+CCB+ACEI/ARB | BB+ACEI/ARB |
| 754 | D | BB+CCB | D+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 755 | D | BB+CCB | D+CCB+ACEI/ARB | D+BB+CCB |
| 756 | D | BB+CCB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 757 | D | BB+CCB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 758 | D | BB+CCB | BB+CCB+ACEI/ARB | BB |
| 759 | D | BB+CCB | BB+CCB+ACEI/ARB | CCB |
| 760 | D | BB+CCB | BB+CCB+ACEI/ARB | ACEI/ARB |
| 761 | D | BB+CCB | BB+CCB+ACEI/ARB | D+BB |
| 762 | D | BB+CCB | BB+CCB+ACEI/ARB | D+CCB |
| 763 | D | BB+CCB | BB+CCB+ACEI/ARB | D+ACEI/ARB |
| 764 | D | BB+CCB | BB+CCB+ACEI/ARB | BB+ACEI/ARB |
| 765 | D | BB+CCB | BB+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 766 | D | BB+CCB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 767 | D | BB+CCB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 768 | D | BB+CCB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 769 | D | BB+ACEI/ARB | BB | CCB |
| 770 | D | BB+ACEI/ARB | BB | ACEI/ARB |
| 771 | D | BB+ACEI/ARB | BB | D+BB |
| 772 | D | BB+ACEI/ARB | BB | D+CCB |
| 773 | D | BB+ACEI/ARB | BB | D+ACEI/ARB |
| 774 | D | BB+ACEI/ARB | BB | BB+CCB |
| 775 | D | BB+ACEI/ARB | BB | CCB+ACEI/ARB |
| 776 | D | BB+ACEI/ARB | BB | D+BB+CCB |
| 777 | D | BB+ACEI/ARB | BB | D+BB+ACEI/ARB |
| 778 | D | BB+ACEI/ARB | BB | D+CCB+ACEI/ARB |
| 779 | D | BB+ACEI/ARB | BB | BB+CCB+ACEI/ARB |
| 780 | D | BB+ACEI/ARB | CCB | BB |
| 781 | D | BB+ACEI/ARB | CCB | ACEI/ARB |
| 782 | D | BB+ACEI/ARB | CCB | D+BB |
| 783 | D | BB+ACEI/ARB | CCB | D+CCB |
| 784 | D | BB+ACEI/ARB | CCB | D+ACEI/ARB |
| 785 | D | BB+ACEI/ARB | CCB | BB+CCB |
| 786 | D | BB+ACEI/ARB | CCB | CCB+ACEI/ARB |
| 787 | D | BB+ACEI/ARB | CCB | D+BB+CCB |
| 788 | D | BB+ACEI/ARB | CCB | D+BB+ACEI/ARB |
| 789 | D | BB+ACEI/ARB | CCB | D+CCB+ACEI/ARB |
| 790 | D | BB+ACEI/ARB | CCB | BB+CCB+ACEI/ARB |
| 791 | D | BB+ACEI/ARB | ACEI/ARB | BB |
| 792 | D | BB+ACEI/ARB | ACEI/ARB | CCB |
| 793 | D | BB+ACEI/ARB | ACEI/ARB | D+BB |
| 794 | D | BB+ACEI/ARB | ACEI/ARB | D+CCB |
| 795 | D | BB+ACEI/ARB | ACEI/ARB | D+ACEI/ARB |
| 796 | D | BB+ACEI/ARB | ACEI/ARB | BB+CCB |
| 797 | D | BB+ACEI/ARB | ACEI/ARB | CCB+ACEI/ARB |
| 798 | D | BB+ACEI/ARB | ACEI/ARB | D+BB+CCB |
| 799 | D | BB+ACEI/ARB | ACEI/ARB | D+BB+ACEI/ARB |
| 800 | D | BB+ACEI/ARB | ACEI/ARB | D+CCB+ACEI/ARB |
| 801 | D | BB+ACEI/ARB | ACEI/ARB | BB+CCB+ACEI/ARB |
| 802 | D | BB+ACEI/ARB | D+BB | BB |
| 803 | D | BB+ACEI/ARB | D+BB | CCB |
| 804 | D | BB+ACEI/ARB | D+BB | ACEI/ARB |
| 805 | D | BB+ACEI/ARB | D+BB | D+CCB |
| 806 | D | BB+ACEI/ARB | D+BB | D+ACEI/ARB |
| 807 | D | BB+ACEI/ARB | D+BB | BB+CCB |
| 808 | D | BB+ACEI/ARB | D+BB | CCB+ACEI/ARB |
| 809 | D | BB+ACEI/ARB | D+BB | D+BB+CCB |
| 810 | D | BB+ACEI/ARB | D+BB | D+BB+ACEI/ARB |
| 811 | D | BB+ACEI/ARB | D+BB | D+CCB+ACEI/ARB |
| 812 | D | BB+ACEI/ARB | D+BB | BB+CCB+ACEI/ARB |
| 813 | D | BB+ACEI/ARB | D+CCB | BB |
| 814 | D | BB+ACEI/ARB | D+CCB | CCB |
| 815 | D | BB+ACEI/ARB | D+CCB | ACEI/ARB |
| 816 | D | BB+ACEI/ARB | D+CCB | D+BB |
| 817 | D | BB+ACEI/ARB | D+CCB | D+ACEI/ARB |
| 818 | D | BB+ACEI/ARB | D+CCB | BB+CCB |
| 819 | D | BB+ACEI/ARB | D+CCB | CCB+ACEI/ARB |
| 820 | D | BB+ACEI/ARB | D+CCB | D+BB+CCB |
| 821 | D | BB+ACEI/ARB | D+CCB | D+BB+ACEI/ARB |
| 822 | D | BB+ACEI/ARB | D+CCB | D+CCB+ACEI/ARB |
| 823 | D | BB+ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB |
| 824 | D | BB+ACEI/ARB | D+ACEIs/ARB | BB |
| 825 | D | BB+ACEI/ARB | D+ACEIs/ARB | CCB |
| 826 | D | BB+ACEI/ARB | D+ACEIs/ARB | ACEI/ARB |
| 827 | D | BB+ACEI/ARB | D+ACEIs/ARB | D+BB |
| 828 | D | BB+ACEI/ARB | D+ACEIs/ARB | D+CCB |
| 829 | D | BB+ACEI/ARB | D+ACEIs/ARB | BB+CCB |
| 830 | D | BB+ACEI/ARB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 831 | D | BB+ACEI/ARB | D+ACEIs/ARB | D+BB+CCB |
| 832 | D | BB+ACEI/ARB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 833 | D | BB+ACEI/ARB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 834 | D | BB+ACEI/ARB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 835 | D | BB+ACEI/ARB | BB+CCB | BB |
| 836 | D | BB+ACEI/ARB | BB+CCB | CCB |
| 837 | D | BB+ACEI/ARB | BB+CCB | ACEI/ARB |
| 838 | D | BB+ACEI/ARB | BB+CCB | D+BB |
| 839 | D | BB+ACEI/ARB | BB+CCB | D+CCB |
| 840 | D | BB+ACEI/ARB | BB+CCB | D+ACEI/ARB |
| 841 | D | BB+ACEI/ARB | BB+CCB | CCB+ACEI/ARB |
| 842 | D | BB+ACEI/ARB | BB+CCB | D+BB+CCB |
| 843 | D | BB+ACEI/ARB | BB+CCB | D+BB+ACEI/ARB |
| 844 | D | BB+ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB |
| 845 | D | BB+ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB |
| 846 | D | BB+ACEI/ARB | CCB+ACEI/ARB | BB |
| 847 | D | BB+ACEI/ARB | CCB+ACEI/ARB | CCB |
| 848 | D | BB+ACEI/ARB | CCB+ACEI/ARB | ACEI/ARB |
| 849 | D | BB+ACEI/ARB | CCB+ACEI/ARB | D+BB |
| 850 | D | BB+ACEI/ARB | CCB+ACEI/ARB | D+CCB |
| 851 | D | BB+ACEI/ARB | CCB+ACEI/ARB | D+ACEI/ARB |
| 852 | D | BB+ACEI/ARB | CCB+ACEI/ARB | BB+CCB |
| 853 | D | BB+ACEI/ARB | CCB+ACEI/ARB | D+BB+CCB |
| 854 | D | BB+ACEI/ARB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 855 | D | BB+ACEI/ARB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 856 | D | BB+ACEI/ARB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 857 | D | BB+ACEI/ARB | D+BB+CCB | BB |
| 858 | D | BB+ACEI/ARB | D+BB+CCB | CCB |
| 859 | D | BB+ACEI/ARB | D+BB+CCB | ACEI/ARB |
| 860 | D | BB+ACEI/ARB | D+BB+CCB | D+BB |
| 861 | D | BB+ACEI/ARB | D+BB+CCB | D+CCB |
| 862 | D | BB+ACEI/ARB | D+BB+CCB | D+ACEI/ARB |
| 863 | D | BB+ACEI/ARB | D+BB+CCB | BB+CCB |
| 864 | D | BB+ACEI/ARB | D+BB+CCB | CCB+ACEI/ARB |
| 865 | D | BB+ACEI/ARB | D+BB+CCB | D+BB+ACEI/ARB |
| 866 | D | BB+ACEI/ARB | D+BB+CCB | D+CCB+ACEI/ARB |
| 867 | D | BB+ACEI/ARB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 868 | D | BB+ACEI/ARB | D+BB+ACEI/ARB | BB |
| 869 | D | BB+ACEI/ARB | D+BB+ACEI/ARB | CCB |
| 870 | D | BB+ACEI/ARB | D+BB+ACEI/ARB | ACEI/ARB |
| 871 | D | BB+ACEI/ARB | D+BB+ACEI/ARB | D+BB |
| 872 | D | BB+ACEI/ARB | D+BB+ACEI/ARB | D+CCB |
| 873 | D | BB+ACEI/ARB | D+BB+ACEI/ARB | D+ACEI/ARB |
| 874 | D | BB+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB |
| 875 | D | BB+ACEI/ARB | D+BB+ACEI/ARB | CCB+ACEI/ARB |
| 876 | D | BB+ACEI/ARB | D+BB+ACEI/ARB | D+BB+CCB |
| 877 | D | BB+ACEI/ARB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 878 | D | BB+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 879 | D | BB+ACEI/ARB | D+CCB+ACEI/ARB | BB |
| 880 | D | BB+ACEI/ARB | D+CCB+ACEI/ARB | CCB |
| 881 | D | BB+ACEI/ARB | D+CCB+ACEI/ARB | ACEI/ARB |
| 882 | D | BB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB |
| 883 | D | BB+ACEI/ARB | D+CCB+ACEI/ARB | D+CCB |
| 884 | D | BB+ACEI/ARB | D+CCB+ACEI/ARB | D+ACEI/ARB |
| 885 | D | BB+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB |
| 886 | D | BB+ACEI/ARB | D+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 887 | D | BB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+CCB |
| 888 | D | BB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 889 | D | BB+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 890 | D | BB+ACEI/ARB | BB+CCB+ACEI/ARB | BB |
| 891 | D | BB+ACEI/ARB | BB+CCB+ACEI/ARB | CCB |
| 892 | D | BB+ACEI/ARB | BB+CCB+ACEI/ARB | ACEI/ARB |
| 893 | D | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB |
| 894 | D | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB |
| 895 | D | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+ACEI/ARB |
| 896 | D | BB+ACEI/ARB | BB+CCB+ACEI/ARB | BB+CCB |
| 897 | D | BB+ACEI/ARB | BB+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 898 | D | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 899 | D | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 900 | D | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 901 | D | CCB+ACEI/ARB | BB | CCB |
| 902 | D | CCB+ACEI/ARB | BB | ACEI/ARB |
| 903 | D | CCB+ACEI/ARB | BB | D+BB |
| 904 | D | CCB+ACEI/ARB | BB | D+CCB |
| 905 | D | CCB+ACEI/ARB | BB | D+ACEI/ARB |
| 906 | D | CCB+ACEI/ARB | BB | BB+CCB |
| 907 | D | CCB+ACEI/ARB | BB | BB+ACEI/ARB |
| 908 | D | CCB+ACEI/ARB | BB | D+BB+CCB |
| 909 | D | CCB+ACEI/ARB | BB | D+BB+ACEI/ARB |
| 910 | D | CCB+ACEI/ARB | BB | D+CCB+ACEI/ARB |
| 911 | D | CCB+ACEI/ARB | BB | BB+CCB+ACEI/ARB |
| 912 | D | CCB+ACEI/ARB | CCB | BB |
| 913 | D | CCB+ACEI/ARB | CCB | ACEI/ARB |
| 914 | D | CCB+ACEI/ARB | CCB | D+BB |
| 915 | D | CCB+ACEI/ARB | CCB | D+CCB |
| 916 | D | CCB+ACEI/ARB | CCB | D+ACEI/ARB |
| 917 | D | CCB+ACEI/ARB | CCB | BB+CCB |
| 918 | D | CCB+ACEI/ARB | CCB | BB+ACEI/ARB |
| 919 | D | CCB+ACEI/ARB | CCB | D+BB+CCB |
| 920 | D | CCB+ACEI/ARB | CCB | D+BB+ACEI/ARB |
| 921 | D | CCB+ACEI/ARB | CCB | D+CCB+ACEI/ARB |
| 922 | D | CCB+ACEI/ARB | CCB | BB+CCB+ACEI/ARB |
| 923 | D | CCB+ACEI/ARB | ACEI/ARB | BB |
| 924 | D | CCB+ACEI/ARB | ACEI/ARB | CCB |
| 925 | D | CCB+ACEI/ARB | ACEI/ARB | D+BB |
| 926 | D | CCB+ACEI/ARB | ACEI/ARB | D+CCB |
| 927 | D | CCB+ACEI/ARB | ACEI/ARB | D+ACEI/ARB |
| 928 | D | CCB+ACEI/ARB | ACEI/ARB | BB+CCB |
| 929 | D | CCB+ACEI/ARB | ACEI/ARB | BB+ACEI/ARB |
| 930 | D | CCB+ACEI/ARB | ACEI/ARB | D+BB+CCB |
| 931 | D | CCB+ACEI/ARB | ACEI/ARB | D+BB+ACEI/ARB |
| 932 | D | CCB+ACEI/ARB | ACEI/ARB | D+CCB+ACEI/ARB |
| 933 | D | CCB+ACEI/ARB | ACEI/ARB | BB+CCB+ACEI/ARB |
| 934 | D | CCB+ACEI/ARB | D+BB | BB |
| 935 | D | CCB+ACEI/ARB | D+BB | CCB |
| 936 | D | CCB+ACEI/ARB | D+BB | ACEI/ARB |
| 937 | D | CCB+ACEI/ARB | D+BB | D+CCB |
| 938 | D | CCB+ACEI/ARB | D+BB | D+ACEI/ARB |
| 939 | D | CCB+ACEI/ARB | D+BB | BB+CCB |
| 940 | D | CCB+ACEI/ARB | D+BB | BB+ACEI/ARB |
| 941 | D | CCB+ACEI/ARB | D+BB | D+BB+CCB |
| 942 | D | CCB+ACEI/ARB | D+BB | D+BB+ACEI/ARB |
| 943 | D | CCB+ACEI/ARB | D+BB | D+CCB+ACEI/ARB |
| 944 | D | CCB+ACEI/ARB | D+BB | BB+CCB+ACEI/ARB |
| 945 | D | CCB+ACEI/ARB | D+CCB | BB |
| 946 | D | CCB+ACEI/ARB | D+CCB | CCB |
| 947 | D | CCB+ACEI/ARB | D+CCB | ACEI/ARB |
| 948 | D | CCB+ACEI/ARB | D+CCB | D+BB |
| 949 | D | CCB+ACEI/ARB | D+CCB | D+ACEI/ARB |
| 950 | D | CCB+ACEI/ARB | D+CCB | BB+CCB |
| 951 | D | CCB+ACEI/ARB | D+CCB | BB+ACEI/ARB |
| 952 | D | CCB+ACEI/ARB | D+CCB | D+BB+CCB |
| 953 | D | CCB+ACEI/ARB | D+CCB | D+BB+ACEI/ARB |
| 954 | D | CCB+ACEI/ARB | D+CCB | D+CCB+ACEI/ARB |
| 955 | D | CCB+ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB |
| 956 | D | CCB+ACEI/ARB | D+ACEIs/ARB | BB |
| 957 | D | CCB+ACEI/ARB | D+ACEIs/ARB | CCB |
| 958 | D | CCB+ACEI/ARB | D+ACEIs/ARB | ACEI/ARB |
| 959 | D | CCB+ACEI/ARB | D+ACEIs/ARB | D+BB |
| 960 | D | CCB+ACEI/ARB | D+ACEIs/ARB | D+CCB |
| 961 | D | CCB+ACEI/ARB | D+ACEIs/ARB | BB+CCB |
| 962 | D | CCB+ACEI/ARB | D+ACEIs/ARB | BB+ACEI/ARB |
| 963 | D | CCB+ACEI/ARB | D+ACEIs/ARB | D+BB+CCB |
| 964 | D | CCB+ACEI/ARB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 965 | D | CCB+ACEI/ARB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 966 | D | CCB+ACEI/ARB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 967 | D | CCB+ACEI/ARB | BB+CCB | BB |
| 968 | D | CCB+ACEI/ARB | BB+CCB | CCB |
| 969 | D | CCB+ACEI/ARB | BB+CCB | ACEI/ARB |
| 970 | D | CCB+ACEI/ARB | BB+CCB | D+BB |
| 971 | D | CCB+ACEI/ARB | BB+CCB | D+CCB |
| 972 | D | CCB+ACEI/ARB | BB+CCB | D+ACEI/ARB |
| 973 | D | CCB+ACEI/ARB | BB+CCB | BB+ACEI/ARB |
| 974 | D | CCB+ACEI/ARB | BB+CCB | D+BB+CCB |
| 975 | D | CCB+ACEI/ARB | BB+CCB | D+BB+ACEI/ARB |
| 976 | D | CCB+ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB |
| 977 | D | CCB+ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB |
| 978 | D | CCB+ACEI/ARB | BB+ACEI/ARB | BB |
| 979 | D | CCB+ACEI/ARB | BB+ACEI/ARB | CCB |
| 980 | D | CCB+ACEI/ARB | BB+ACEI/ARB | ACEI/ARB |
| 981 | D | CCB+ACEI/ARB | BB+ACEI/ARB | D+BB |
| 982 | D | CCB+ACEI/ARB | BB+ACEI/ARB | D+CCB |
| 983 | D | CCB+ACEI/ARB | BB+ACEI/ARB | D+ACEI/ARB |
| 984 | D | CCB+ACEI/ARB | BB+ACEI/ARB | BB+CCB |
| 985 | D | CCB+ACEI/ARB | BB+ACEI/ARB | D+BB+CCB |
| 986 | D | CCB+ACEI/ARB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 987 | D | CCB+ACEI/ARB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 988 | D | CCB+ACEI/ARB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 989 | D | CCB+ACEI/ARB | D+BB+CCB | BB |
| 990 | D | CCB+ACEI/ARB | D+BB+CCB | CCB |
| 991 | D | CCB+ACEI/ARB | D+BB+CCB | ACEI/ARB |
| 992 | D | CCB+ACEI/ARB | D+BB+CCB | D+BB |
| 993 | D | CCB+ACEI/ARB | D+BB+CCB | D+CCB |
| 994 | D | CCB+ACEI/ARB | D+BB+CCB | D+ACEI/ARB |
| 995 | D | CCB+ACEI/ARB | D+BB+CCB | BB+CCB |
| 996 | D | CCB+ACEI/ARB | D+BB+CCB | BB+ACEI/ARB |
| 997 | D | CCB+ACEI/ARB | D+BB+CCB | D+BB+ACEI/ARB |
| 998 | D | CCB+ACEI/ARB | D+BB+CCB | D+CCB+ACEI/ARB |
| 999 | D | CCB+ACEI/ARB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 1000 | D | CCB+ACEI/ARB | D+BB+ACEI/ARB | BB |
| 1001 | D | CCB+ACEI/ARB | D+BB+ACEI/ARB | CCB |
| 1002 | D | CCB+ACEI/ARB | D+BB+ACEI/ARB | ACEI/ARB |
| 1003 | D | CCB+ACEI/ARB | D+BB+ACEI/ARB | D+BB |
| 1004 | D | CCB+ACEI/ARB | D+BB+ACEI/ARB | D+CCB |
| 1005 | D | CCB+ACEI/ARB | D+BB+ACEI/ARB | D+ACEI/ARB |
| 1006 | D | CCB+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB |
| 1007 | D | CCB+ACEI/ARB | D+BB+ACEI/ARB | BB+ACEI/ARB |
| 1008 | D | CCB+ACEI/ARB | D+BB+ACEI/ARB | D+BB+CCB |
| 1009 | D | CCB+ACEI/ARB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1010 | D | CCB+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1011 | D | CCB+ACEI/ARB | D+CCB+ACEI/ARB | BB |
| 1012 | D | CCB+ACEI/ARB | D+CCB+ACEI/ARB | CCB |
| 1013 | D | CCB+ACEI/ARB | D+CCB+ACEI/ARB | ACEI/ARB |
| 1014 | D | CCB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB |
| 1015 | D | CCB+ACEI/ARB | D+CCB+ACEI/ARB | D+CCB |
| 1016 | D | CCB+ACEI/ARB | D+CCB+ACEI/ARB | D+ACEI/ARB |
| 1017 | D | CCB+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB |
| 1018 | D | CCB+ACEI/ARB | D+CCB+ACEI/ARB | BB+ACEI/ARB |
| 1019 | D | CCB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+CCB |
| 1020 | D | CCB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 1021 | D | CCB+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1022 | D | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | BB |
| 1023 | D | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | CCB |
| 1024 | D | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | ACEI/ARB |
| 1025 | D | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB |
| 1026 | D | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB |
| 1027 | D | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+ACEI/ARB |
| 1028 | D | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | BB+CCB |
| 1029 | D | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | BB+ACEI/ARB |
| 1030 | D | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 1031 | D | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 1032 | D | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1033 | BB | D | CCB | ACEI/ARB |
| 1034 | BB | D | CCB | D+BB |
| 1035 | BB | D | CCB | D+CCB |
| 1036 | BB | D | CCB | D+ACEI/ARB |
| 1037 | BB | D | CCB | BB+CCB |
| 1038 | BB | D | CCB | BB+ACEI/ARB |
| 1039 | BB | D | CCB | CCB+ACEI/ARB |
| 1040 | BB | D | ACEI/ARB | CCB |
| 1041 | BB | D | ACEI/ARB | D+BB |
| 1042 | BB | D | ACEI/ARB | D+CCB |
| 1043 | BB | D | ACEI/ARB | D+ACEI/ARB |
| 1044 | BB | D | ACEI/ARB | BB+CCB |
| 1045 | BB | D | ACEI/ARB | BB+ACEI/ARB |
| 1046 | BB | D | ACEI/ARB | CCB+ACEI/ARB |
| 1047 | BB | D | D+BB | CCB |
| 1048 | BB | D | D+BB | ACEI/ARB |
| 1049 | BB | D | D+BB | D+CCB |
| 1050 | BB | D | D+BB | D+ACEI/ARB |
| 1051 | BB | D | D+BB | BB+CCB |
| 1052 | BB | D | D+BB | BB+ACEI/ARB |
| 1053 | BB | D | D+BB | CCB+ACEI/ARB |
| 1054 | BB | D | D+BB | D+BB+CCB |
| 1055 | BB | D | D+BB | D+BB+ACEI/ARB |
| 1056 | BB | D | D+BB | D+CCB+ACEI/ARB |
| 1057 | BB | D | D+BB | BB+CCB+ACEI/ARB |
| 1058 | BB | D | D+CCB | CCB |
| 1059 | BB | D | D+CCB | ACEI/ARB |
| 1060 | BB | D | D+CCB | D+BB |
| 1061 | BB | D | D+CCB | D+ACEI/ARB |
| 1062 | BB | D | D+CCB | BB+CCB |
| 1063 | BB | D | D+CCB | BB+ACEI/ARB |
| 1064 | BB | D | D+CCB | CCB+ACEI/ARB |
| 1065 | BB | D | D+CCB | D+BB+CCB |
| 1066 | BB | D | D+CCB | D+BB+ACEI/ARB |
| 1067 | BB | D | D+CCB | D+CCB+ACEI/ARB |
| 1068 | BB | D | D+CCB | BB+CCB+ACEI/ARB |
| 1069 | BB | D | D+ACEIs/ARB | CCB |
| 1070 | BB | D | D+ACEIs/ARB | ACEI/ARB |
| 1071 | BB | D | D+ACEIs/ARB | D+BB |
| 1072 | BB | D | D+ACEIs/ARB | D+CCB |
| 1073 | BB | D | D+ACEIs/ARB | BB+CCB |
| 1074 | BB | D | D+ACEIs/ARB | BB+ACEI/ARB |
| 1075 | BB | D | D+ACEIs/ARB | CCB+ACEI/ARB |
| 1076 | BB | D | D+ACEIs/ARB | D+BB+CCB |
| 1077 | BB | D | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 1078 | BB | D | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 1079 | BB | D | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 1080 | BB | D | BB+CCB | CCB |
| 1081 | BB | D | BB+CCB | ACEI/ARB |
| 1082 | BB | D | BB+CCB | D+BB |
| 1083 | BB | D | BB+CCB | D+CCB |
| 1084 | BB | D | BB+CCB | D+ACEI/ARB |
| 1085 | BB | D | BB+CCB | BB+ACEI/ARB |
| 1086 | BB | D | BB+CCB | CCB+ACEI/ARB |
| 1087 | BB | D | BB+CCB | D+BB+CCB |
| 1088 | BB | D | BB+CCB | D+BB+ACEI/ARB |
| 1089 | BB | D | BB+CCB | D+CCB+ACEI/ARB |
| 1090 | BB | D | BB+CCB | BB+CCB+ACEI/ARB |
| 1091 | BB | D | BB+ACEI/ARB | CCB |
| 1092 | BB | D | BB+ACEI/ARB | ACEI/ARB |
| 1093 | BB | D | BB+ACEI/ARB | D+BB |
| 1094 | BB | D | BB+ACEI/ARB | D+CCB |
| 1095 | BB | D | BB+ACEI/ARB | D+ACEI/ARB |
| 1096 | BB | D | BB+ACEI/ARB | BB+CCB |
| 1097 | BB | D | BB+ACEI/ARB | CCB+ACEI/ARB |
| 1098 | BB | D | BB+ACEI/ARB | D+BB+CCB |
| 1099 | BB | D | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 1100 | BB | D | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1101 | BB | D | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1102 | BB | D | CCB+ACEI/ARB | CCB |
| 1103 | BB | D | CCB+ACEI/ARB | ACEI/ARB |
| 1104 | BB | D | CCB+ACEI/ARB | D+BB |
| 1105 | BB | D | CCB+ACEI/ARB | D+CCB |
| 1106 | BB | D | CCB+ACEI/ARB | D+ACEI/ARB |
| 1107 | BB | D | CCB+ACEI/ARB | BB+CCB |
| 1108 | BB | D | CCB+ACEI/ARB | BB+ACEI/ARB |
| 1109 | BB | D | CCB+ACEI/ARB | D+BB+CCB |
| 1110 | BB | D | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 1111 | BB | D | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1112 | BB | D | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1113 | BB | CCB | D | ACEI/ARB |
| 1114 | BB | CCB | D | D+BB |
| 1115 | BB | CCB | D | D+CCB |
| 1116 | BB | CCB | D | D+ACEI/ARB |
| 1117 | BB | CCB | D | BB+CCB |
| 1118 | BB | CCB | D | BB+ACEI/ARB |
| 1119 | BB | CCB | D | CCB+ACEI/ARB |
| 1120 | BB | CCB | ACEI/ARB | D |
| 1121 | BB | CCB | ACEI/ARB | D+BB |
| 1122 | BB | CCB | ACEI/ARB | D+CCB |
| 1123 | BB | CCB | ACEI/ARB | D+ACEI/ARB |
| 1124 | BB | CCB | ACEI/ARB | BB+CCB |
| 1125 | BB | CCB | ACEI/ARB | BB+ACEI/ARB |
| 1126 | BB | CCB | ACEI/ARB | CCB+ACEI/ARB |
| 1127 | BB | CCB | D+BB | D |
| 1128 | BB | CCB | D+BB | ACEI/ARB |
| 1129 | BB | CCB | D+BB | D+CCB |
| 1130 | BB | CCB | D+BB | D+ACEI/ARB |
| 1131 | BB | CCB | D+BB | BB+CCB |
| 1132 | BB | CCB | D+BB | BB+ACEI/ARB |
| 1133 | BB | CCB | D+BB | CCB+ACEI/ARB |
| 1134 | BB | CCB | D+BB | D+BB+CCB |
| 1135 | BB | CCB | D+BB | D+BB+ACEI/ARB |
| 1136 | BB | CCB | D+BB | D+CCB+ACEI/ARB |
| 1137 | BB | CCB | D+BB | BB+CCB+ACEI/ARB |
| 1138 | BB | CCB | D+CCB | D |
| 1139 | BB | CCB | D+CCB | ACEI/ARB |
| 1140 | BB | CCB | D+CCB | D+BB |
| 1141 | BB | CCB | D+CCB | D+ACEI/ARB |
| 1142 | BB | CCB | D+CCB | BB+CCB |
| 1143 | BB | CCB | D+CCB | BB+ACEI/ARB |
| 1144 | BB | CCB | D+CCB | CCB+ACEI/ARB |
| 1145 | BB | CCB | D+CCB | D+BB+CCB |
| 1146 | BB | CCB | D+CCB | D+BB+ACEI/ARB |
| 1147 | BB | CCB | D+CCB | D+CCB+ACEI/ARB |
| 1148 | BB | CCB | D+CCB | BB+CCB+ACEI/ARB |
| 1149 | BB | CCB | D+ACEIs/ARB | D |
| 1150 | BB | CCB | D+ACEIs/ARB | ACEI/ARB |
| 1151 | BB | CCB | D+ACEIs/ARB | D+BB |
| 1152 | BB | CCB | D+ACEIs/ARB | D+CCB |
| 1153 | BB | CCB | D+ACEIs/ARB | BB+CCB |
| 1154 | BB | CCB | D+ACEIs/ARB | BB+ACEI/ARB |
| 1155 | BB | CCB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 1156 | BB | CCB | D+ACEIs/ARB | D+BB+CCB |
| 1157 | BB | CCB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 1158 | BB | CCB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 1159 | BB | CCB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 1160 | BB | CCB | BB+CCB | D |
| 1161 | BB | CCB | BB+CCB | ACEI/ARB |
| 1162 | BB | CCB | BB+CCB | D+BB |
| 1163 | BB | CCB | BB+CCB | D+CCB |
| 1164 | BB | CCB | BB+CCB | D+ACEI/ARB |
| 1165 | BB | CCB | BB+CCB | BB+ACEI/ARB |
| 1166 | BB | CCB | BB+CCB | CCB+ACEI/ARB |
| 1167 | BB | CCB | BB+CCB | D+BB+CCB |
| 1168 | BB | CCB | BB+CCB | D+BB+ACEI/ARB |
| 1169 | BB | CCB | BB+CCB | D+CCB+ACEI/ARB |
| 1170 | BB | CCB | BB+CCB | BB+CCB+ACEI/ARB |
| 1171 | BB | CCB | BB+ACEI/ARB | D |
| 1172 | BB | CCB | BB+ACEI/ARB | ACEI/ARB |
| 1173 | BB | CCB | BB+ACEI/ARB | D+BB |
| 1174 | BB | CCB | BB+ACEI/ARB | D+CCB |
| 1175 | BB | CCB | BB+ACEI/ARB | D+ACEI/ARB |
| 1176 | BB | CCB | BB+ACEI/ARB | BB+CCB |
| 1177 | BB | CCB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 1178 | BB | CCB | BB+ACEI/ARB | D+BB+CCB |
| 1179 | BB | CCB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 1180 | BB | CCB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1181 | BB | CCB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1182 | BB | CCB | CCB+ACEI/ARB | D |
| 1183 | BB | CCB | CCB+ACEI/ARB | ACEI/ARB |
| 1184 | BB | CCB | CCB+ACEI/ARB | D+BB |
| 1185 | BB | CCB | CCB+ACEI/ARB | D+CCB |
| 1186 | BB | CCB | CCB+ACEI/ARB | D+ACEI/ARB |
| 1187 | BB | CCB | CCB+ACEI/ARB | BB+CCB |
| 1188 | BB | CCB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 1189 | BB | CCB | CCB+ACEI/ARB | D+BB+CCB |
| 1190 | BB | CCB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 1191 | BB | CCB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1192 | BB | CCB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1193 | BB | ACEI/ARB | D | CCB |
| 1194 | BB | ACEI/ARB | D | D+BB |
| 1195 | BB | ACEI/ARB | D | D+CCB |
| 1196 | BB | ACEI/ARB | D | D+ACEI/ARB |
| 1197 | BB | ACEI/ARB | D | BB+CCB |
| 1198 | BB | ACEI/ARB | D | BB+ACEI/ARB |
| 1199 | BB | ACEI/ARB | D | CCB+ACEI/ARB |
| 1200 | BB | ACEI/ARB | CCB | D |
| 1201 | BB | ACEI/ARB | CCB | D+BB |
| 1202 | BB | ACEI/ARB | CCB | D+CCB |
| 1203 | BB | ACEI/ARB | CCB | D+ACEI/ARB |
| 1204 | BB | ACEI/ARB | CCB | BB+CCB |
| 1205 | BB | ACEI/ARB | CCB | BB+ACEI/ARB |
| 1206 | BB | ACEI/ARB | CCB | CCB+ACEI/ARB |
| 1207 | BB | ACEI/ARB | D+BB | D |
| 1208 | BB | ACEI/ARB | D+BB | CCB |
| 1209 | BB | ACEI/ARB | D+BB | D+CCB |
| 1210 | BB | ACEI/ARB | D+BB | D+ACEI/ARB |
| 1211 | BB | ACEI/ARB | D+BB | BB+CCB |
| 1212 | BB | ACEI/ARB | D+BB | BB+ACEI/ARB |
| 1213 | BB | ACEI/ARB | D+BB | CCB+ACEI/ARB |
| 1214 | BB | ACEI/ARB | D+BB | D+BB+CCB |
| 1215 | BB | ACEI/ARB | D+BB | D+BB+ACEI/ARB |
| 1216 | BB | ACEI/ARB | D+BB | D+CCB+ACEI/ARB |
| 1217 | BB | ACEI/ARB | D+BB | BB+CCB+ACEI/ARB |
| 1218 | BB | ACEI/ARB | D+CCB | D |
| 1219 | BB | ACEI/ARB | D+CCB | CCB |
| 1220 | BB | ACEI/ARB | D+CCB | D+BB |
| 1221 | BB | ACEI/ARB | D+CCB | D+ACEI/ARB |
| 1222 | BB | ACEI/ARB | D+CCB | BB+CCB |
| 1223 | BB | ACEI/ARB | D+CCB | BB+ACEI/ARB |
| 1224 | BB | ACEI/ARB | D+CCB | CCB+ACEI/ARB |
| 1225 | BB | ACEI/ARB | D+CCB | D+BB+CCB |
| 1226 | BB | ACEI/ARB | D+CCB | D+BB+ACEI/ARB |
| 1227 | BB | ACEI/ARB | D+CCB | D+CCB+ACEI/ARB |
| 1228 | BB | ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB |
| 1229 | BB | ACEI/ARB | D+ACEIs/ARB | D |
| 1230 | BB | ACEI/ARB | D+ACEIs/ARB | CCB |
| 1231 | BB | ACEI/ARB | D+ACEIs/ARB | D+BB |
| 1232 | BB | ACEI/ARB | D+ACEIs/ARB | D+CCB |
| 1233 | BB | ACEI/ARB | D+ACEIs/ARB | BB+CCB |
| 1234 | BB | ACEI/ARB | D+ACEIs/ARB | BB+ACEI/ARB |
| 1235 | BB | ACEI/ARB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 1236 | BB | ACEI/ARB | D+ACEIs/ARB | D+BB+CCB |
| 1237 | BB | ACEI/ARB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 1238 | BB | ACEI/ARB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 1239 | BB | ACEI/ARB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 1240 | BB | ACEI/ARB | BB+CCB | D |
| 1241 | BB | ACEI/ARB | BB+CCB | CCB |
| 1242 | BB | ACEI/ARB | BB+CCB | D+BB |
| 1243 | BB | ACEI/ARB | BB+CCB | D+CCB |
| 1244 | BB | ACEI/ARB | BB+CCB | D+ACEI/ARB |
| 1245 | BB | ACEI/ARB | BB+CCB | BB+ACEI/ARB |
| 1246 | BB | ACEI/ARB | BB+CCB | CCB+ACEI/ARB |
| 1247 | BB | ACEI/ARB | BB+CCB | D+BB+CCB |
| 1248 | BB | ACEI/ARB | BB+CCB | D+BB+ACEI/ARB |
| 1249 | BB | ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB |
| 1250 | BB | ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB |
| 1251 | BB | ACEI/ARB | BB+ACEI/ARB | D |
| 1252 | BB | ACEI/ARB | BB+ACEI/ARB | CCB |
| 1253 | BB | ACEI/ARB | BB+ACEI/ARB | D+BB |
| 1254 | BB | ACEI/ARB | BB+ACEI/ARB | D+CCB |
| 1255 | BB | ACEI/ARB | BB+ACEI/ARB | D+ACEI/ARB |
| 1256 | BB | ACEI/ARB | BB+ACEI/ARB | BB+CCB |
| 1257 | BB | ACEI/ARB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 1258 | BB | ACEI/ARB | BB+ACEI/ARB | D+BB+CCB |
| 1259 | BB | ACEI/ARB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 1260 | BB | ACEI/ARB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1261 | BB | ACEI/ARB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1262 | BB | ACEI/ARB | CCB+ACEI/ARB | D |
| 1263 | BB | ACEI/ARB | CCB+ACEI/ARB | CCB |
| 1264 | BB | ACEI/ARB | CCB+ACEI/ARB | D+BB |
| 1265 | BB | ACEI/ARB | CCB+ACEI/ARB | D+CCB |
| 1266 | BB | ACEI/ARB | CCB+ACEI/ARB | D+ACEI/ARB |
| 1267 | BB | ACEI/ARB | CCB+ACEI/ARB | BB+CCB |
| 1268 | BB | ACEI/ARB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 1269 | BB | ACEI/ARB | CCB+ACEI/ARB | D+BB+CCB |
| 1270 | BB | ACEI/ARB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 1271 | BB | ACEI/ARB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1272 | BB | ACEI/ARB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1273 | BB | D+BB | D | CCB |
| 1274 | BB | D+BB | D | ACEI/ARB |
| 1275 | BB | D+BB | D | D+CCB |
| 1276 | BB | D+BB | D | D+ACEI/ARB |
| 1277 | BB | D+BB | D | BB+CCB |
| 1278 | BB | D+BB | D | BB+ACEI/ARB |
| 1279 | BB | D+BB | D | CCB+ACEI/ARB |
| 1280 | BB | D+BB | D | D+BB+CCB |
| 1281 | BB | D+BB | D | D+BB+ACEI/ARB |
| 1282 | BB | D+BB | D | D+CCB+ACEI/ARB |
| 1283 | BB | D+BB | D | BB+CCB+ACEI/ARB |
| 1284 | BB | D+BB | CCB | D |
| 1285 | BB | D+BB | CCB | ACEI/ARB |
| 1286 | BB | D+BB | CCB | D+CCB |
| 1287 | BB | D+BB | CCB | D+ACEI/ARB |
| 1288 | BB | D+BB | CCB | BB+CCB |
| 1289 | BB | D+BB | CCB | BB+ACEI/ARB |
| 1290 | BB | D+BB | CCB | CCB+ACEI/ARB |
| 1291 | BB | D+BB | CCB | D+BB+CCB |
| 1292 | BB | D+BB | CCB | D+BB+ACEI/ARB |
| 1293 | BB | D+BB | CCB | D+CCB+ACEI/ARB |
| 1294 | BB | D+BB | CCB | BB+CCB+ACEI/ARB |
| 1295 | BB | D+BB | ACEI/ARB | D |
| 1296 | BB | D+BB | ACEI/ARB | CCB |
| 1297 | BB | D+BB | ACEI/ARB | D+CCB |
| 1298 | BB | D+BB | ACEI/ARB | D+ACEI/ARB |
| 1299 | BB | D+BB | ACEI/ARB | BB+CCB |
| 1300 | BB | D+BB | ACEI/ARB | BB+ACEI/ARB |
| 1301 | BB | D+BB | ACEI/ARB | CCB+ACEI/ARB |
| 1302 | BB | D+BB | ACEI/ARB | D+BB+CCB |
| 1303 | BB | D+BB | ACEI/ARB | D+BB+ACEI/ARB |
| 1304 | BB | D+BB | ACEI/ARB | D+CCB+ACEI/ARB |
| 1305 | BB | D+BB | ACEI/ARB | BB+CCB+ACEI/ARB |
| 1306 | BB | D+BB | D+CCB | D |
| 1307 | BB | D+BB | D+CCB | CCB |
| 1308 | BB | D+BB | D+CCB | ACEI/ARB |
| 1309 | BB | D+BB | D+CCB | D+ACEI/ARB |
| 1310 | BB | D+BB | D+CCB | BB+CCB |
| 1311 | BB | D+BB | D+CCB | BB+ACEI/ARB |
| 1312 | BB | D+BB | D+CCB | CCB+ACEI/ARB |
| 1313 | BB | D+BB | D+CCB | D+BB+CCB |
| 1314 | BB | D+BB | D+CCB | D+BB+ACEI/ARB |
| 1315 | BB | D+BB | D+CCB | D+CCB+ACEI/ARB |
| 1316 | BB | D+BB | D+CCB | BB+CCB+ACEI/ARB |
| 1317 | BB | D+BB | D+ACEIs/ARB | D |
| 1318 | BB | D+BB | D+ACEIs/ARB | CCB |
| 1319 | BB | D+BB | D+ACEIs/ARB | ACEI/ARB |
| 1320 | BB | D+BB | D+ACEIs/ARB | D+CCB |
| 1321 | BB | D+BB | D+ACEIs/ARB | BB+CCB |
| 1322 | BB | D+BB | D+ACEIs/ARB | BB+ACEI/ARB |
| 1323 | BB | D+BB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 1324 | BB | D+BB | D+ACEIs/ARB | D+BB+CCB |
| 1325 | BB | D+BB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 1326 | BB | D+BB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 1327 | BB | D+BB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 1328 | BB | D+BB | BB+CCB | D |
| 1329 | BB | D+BB | BB+CCB | CCB |
| 1330 | BB | D+BB | BB+CCB | ACEI/ARB |
| 1331 | BB | D+BB | BB+CCB | D+CCB |
| 1332 | BB | D+BB | BB+CCB | D+ACEI/ARB |
| 1333 | BB | D+BB | BB+CCB | BB+ACEI/ARB |
| 1334 | BB | D+BB | BB+CCB | CCB+ACEI/ARB |
| 1335 | BB | D+BB | BB+CCB | D+BB+CCB |
| 1336 | BB | D+BB | BB+CCB | D+BB+ACEI/ARB |
| 1337 | BB | D+BB | BB+CCB | D+CCB+ACEI/ARB |
| 1338 | BB | D+BB | BB+CCB | BB+CCB+ACEI/ARB |
| 1339 | BB | D+BB | BB+ACEI/ARB | D |
| 1340 | BB | D+BB | BB+ACEI/ARB | CCB |
| 1341 | BB | D+BB | BB+ACEI/ARB | ACEI/ARB |
| 1342 | BB | D+BB | BB+ACEI/ARB | D+CCB |
| 1343 | BB | D+BB | BB+ACEI/ARB | D+ACEI/ARB |
| 1344 | BB | D+BB | BB+ACEI/ARB | BB+CCB |
| 1345 | BB | D+BB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 1346 | BB | D+BB | BB+ACEI/ARB | D+BB+CCB |
| 1347 | BB | D+BB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 1348 | BB | D+BB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1349 | BB | D+BB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1350 | BB | D+BB | CCB+ACEI/ARB | D |
| 1351 | BB | D+BB | CCB+ACEI/ARB | CCB |
| 1352 | BB | D+BB | CCB+ACEI/ARB | ACEI/ARB |
| 1353 | BB | D+BB | CCB+ACEI/ARB | D+CCB |
| 1354 | BB | D+BB | CCB+ACEI/ARB | D+ACEI/ARB |
| 1355 | BB | D+BB | CCB+ACEI/ARB | BB+CCB |
| 1356 | BB | D+BB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 1357 | BB | D+BB | CCB+ACEI/ARB | D+BB+CCB |
| 1358 | BB | D+BB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 1359 | BB | D+BB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1360 | BB | D+BB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1361 | BB | D+BB | D+BB+CCB | D |
| 1362 | BB | D+BB | D+BB+CCB | CCB |
| 1363 | BB | D+BB | D+BB+CCB | ACEI/ARB |
| 1364 | BB | D+BB | D+BB+CCB | D+CCB |
| 1365 | BB | D+BB | D+BB+CCB | D+ACEI/ARB |
| 1366 | BB | D+BB | D+BB+CCB | BB+CCB |
| 1367 | BB | D+BB | D+BB+CCB | BB+ACEI/ARB |
| 1368 | BB | D+BB | D+BB+CCB | CCB+ACEI/ARB |
| 1369 | BB | D+BB | D+BB+CCB | D+BB+ACEI/ARB |
| 1370 | BB | D+BB | D+BB+CCB | D+CCB+ACEI/ARB |
| 1371 | BB | D+BB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 1372 | BB | D+BB | D+BB+ACEI/ARB | D |
| 1373 | BB | D+BB | D+BB+ACEI/ARB | CCB |
| 1374 | BB | D+BB | D+BB+ACEI/ARB | ACEI/ARB |
| 1375 | BB | D+BB | D+BB+ACEI/ARB | D+CCB |
| 1376 | BB | D+BB | D+BB+ACEI/ARB | D+ACEI/ARB |
| 1377 | BB | D+BB | D+BB+ACEI/ARB | BB+CCB |
| 1378 | BB | D+BB | D+BB+ACEI/ARB | BB+ACEI/ARB |
| 1379 | BB | D+BB | D+BB+ACEI/ARB | CCB+ACEI/ARB |
| 1380 | BB | D+BB | D+BB+ACEI/ARB | D+BB+CCB |
| 1381 | BB | D+BB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1382 | BB | D+BB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1383 | BB | D+BB | D+CCB+ACEI/ARB | D |
| 1384 | BB | D+BB | D+CCB+ACEI/ARB | CCB |
| 1385 | BB | D+BB | D+CCB+ACEI/ARB | ACEI/ARB |
| 1386 | BB | D+BB | D+CCB+ACEI/ARB | D+CCB |
| 1387 | BB | D+BB | D+CCB+ACEI/ARB | D+ACEI/ARB |
| 1388 | BB | D+BB | D+CCB+ACEI/ARB | BB+CCB |
| 1389 | BB | D+BB | D+CCB+ACEI/ARB | BB+ACEI/ARB |
| 1390 | BB | D+BB | D+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 1391 | BB | D+BB | D+CCB+ACEI/ARB | D+BB+CCB |
| 1392 | BB | D+BB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 1393 | BB | D+BB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1394 | BB | D+BB | BB+CCB+ACEI/ARB | D |
| 1395 | BB | D+BB | BB+CCB+ACEI/ARB | CCB |
| 1396 | BB | D+BB | BB+CCB+ACEI/ARB | ACEI/ARB |
| 1397 | BB | D+BB | BB+CCB+ACEI/ARB | D+CCB |
| 1398 | BB | D+BB | BB+CCB+ACEI/ARB | D+ACEI/ARB |
| 1399 | BB | D+BB | BB+CCB+ACEI/ARB | BB+CCB |
| 1400 | BB | D+BB | BB+CCB+ACEI/ARB | BB+ACEI/ARB |
| 1401 | BB | D+BB | BB+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 1402 | BB | D+BB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 1403 | BB | D+BB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 1404 | BB | D+BB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1405 | BB | D+CCB | D | CCB |
| 1406 | BB | D+CCB | D | ACEI/ARB |
| 1407 | BB | D+CCB | D | D+BB |
| 1408 | BB | D+CCB | D | D+ACEI/ARB |
| 1409 | BB | D+CCB | D | BB+CCB |
| 1410 | BB | D+CCB | D | BB+ACEI/ARB |
| 1411 | BB | D+CCB | D | CCB+ACEI/ARB |
| 1412 | BB | D+CCB | D | D+BB+CCB |
| 1413 | BB | D+CCB | D | D+BB+ACEI/ARB |
| 1414 | BB | D+CCB | D | D+CCB+ACEI/ARB |
| 1415 | BB | D+CCB | D | BB+CCB+ACEI/ARB |
| 1416 | BB | D+CCB | CCB | D |
| 1417 | BB | D+CCB | CCB | ACEI/ARB |
| 1418 | BB | D+CCB | CCB | D+BB |
| 1419 | BB | D+CCB | CCB | D+ACEI/ARB |
| 1420 | BB | D+CCB | CCB | BB+CCB |
| 1421 | BB | D+CCB | CCB | BB+ACEI/ARB |
| 1422 | BB | D+CCB | CCB | CCB+ACEI/ARB |
| 1423 | BB | D+CCB | CCB | D+BB+CCB |
| 1424 | BB | D+CCB | CCB | D+BB+ACEI/ARB |
| 1425 | BB | D+CCB | CCB | D+CCB+ACEI/ARB |
| 1426 | BB | D+CCB | CCB | BB+CCB+ACEI/ARB |
| 1427 | BB | D+CCB | ACEI/ARB | D |
| 1428 | BB | D+CCB | ACEI/ARB | CCB |
| 1429 | BB | D+CCB | ACEI/ARB | D+BB |
| 1430 | BB | D+CCB | ACEI/ARB | D+ACEI/ARB |
| 1431 | BB | D+CCB | ACEI/ARB | BB+CCB |
| 1432 | BB | D+CCB | ACEI/ARB | BB+ACEI/ARB |
| 1433 | BB | D+CCB | ACEI/ARB | CCB+ACEI/ARB |
| 1434 | BB | D+CCB | ACEI/ARB | D+BB+CCB |
| 1435 | BB | D+CCB | ACEI/ARB | D+BB+ACEI/ARB |
| 1436 | BB | D+CCB | ACEI/ARB | D+CCB+ACEI/ARB |
| 1437 | BB | D+CCB | ACEI/ARB | BB+CCB+ACEI/ARB |
| 1438 | BB | D+CCB | D+BB | D |
| 1439 | BB | D+CCB | D+BB | CCB |
| 1440 | BB | D+CCB | D+BB | ACEI/ARB |
| 1441 | BB | D+CCB | D+BB | D+ACEI/ARB |
| 1442 | BB | D+CCB | D+BB | BB+CCB |
| 1443 | BB | D+CCB | D+BB | BB+ACEI/ARB |
| 1444 | BB | D+CCB | D+BB | CCB+ACEI/ARB |
| 1445 | BB | D+CCB | D+BB | D+BB+CCB |
| 1446 | BB | D+CCB | D+BB | D+BB+ACEI/ARB |
| 1447 | BB | D+CCB | D+BB | D+CCB+ACEI/ARB |
| 1448 | BB | D+CCB | D+BB | BB+CCB+ACEI/ARB |
| 1449 | BB | D+CCB | D+ACEIs/ARB | D |
| 1450 | BB | D+CCB | D+ACEIs/ARB | CCB |
| 1451 | BB | D+CCB | D+ACEIs/ARB | ACEI/ARB |
| 1452 | BB | D+CCB | D+ACEIs/ARB | D+BB |
| 1453 | BB | D+CCB | D+ACEIs/ARB | BB+CCB |
| 1454 | BB | D+CCB | D+ACEIs/ARB | BB+ACEI/ARB |
| 1455 | BB | D+CCB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 1456 | BB | D+CCB | D+ACEIs/ARB | D+BB+CCB |
| 1457 | BB | D+CCB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 1458 | BB | D+CCB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 1459 | BB | D+CCB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 1460 | BB | D+CCB | BB+CCB | D |
| 1461 | BB | D+CCB | BB+CCB | CCB |
| 1462 | BB | D+CCB | BB+CCB | ACEI/ARB |
| 1463 | BB | D+CCB | BB+CCB | D+BB |
| 1464 | BB | D+CCB | BB+CCB | D+ACEI/ARB |
| 1465 | BB | D+CCB | BB+CCB | BB+ACEI/ARB |
| 1466 | BB | D+CCB | BB+CCB | CCB+ACEI/ARB |
| 1467 | BB | D+CCB | BB+CCB | D+BB+CCB |
| 1468 | BB | D+CCB | BB+CCB | D+BB+ACEI/ARB |
| 1469 | BB | D+CCB | BB+CCB | D+CCB+ACEI/ARB |
| 1470 | BB | D+CCB | BB+CCB | BB+CCB+ACEI/ARB |
| 1471 | BB | D+CCB | BB+ACEI/ARB | D |
| 1472 | BB | D+CCB | BB+ACEI/ARB | CCB |
| 1473 | BB | D+CCB | BB+ACEI/ARB | ACEI/ARB |
| 1474 | BB | D+CCB | BB+ACEI/ARB | D+BB |
| 1475 | BB | D+CCB | BB+ACEI/ARB | D+ACEI/ARB |
| 1476 | BB | D+CCB | BB+ACEI/ARB | BB+CCB |
| 1477 | BB | D+CCB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 1478 | BB | D+CCB | BB+ACEI/ARB | D+BB+CCB |
| 1479 | BB | D+CCB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 1480 | BB | D+CCB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1481 | BB | D+CCB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1482 | BB | D+CCB | CCB+ACEI/ARB | D |
| 1483 | BB | D+CCB | CCB+ACEI/ARB | CCB |
| 1484 | BB | D+CCB | CCB+ACEI/ARB | ACEI/ARB |
| 1485 | BB | D+CCB | CCB+ACEI/ARB | D+BB |
| 1486 | BB | D+CCB | CCB+ACEI/ARB | D+ACEI/ARB |
| 1487 | BB | D+CCB | CCB+ACEI/ARB | BB+CCB |
| 1488 | BB | D+CCB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 1489 | BB | D+CCB | CCB+ACEI/ARB | D+BB+CCB |
| 1490 | BB | D+CCB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 1491 | BB | D+CCB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1492 | BB | D+CCB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1493 | BB | D+CCB | D+BB+CCB | D |
| 1494 | BB | D+CCB | D+BB+CCB | CCB |
| 1495 | BB | D+CCB | D+BB+CCB | ACEI/ARB |
| 1496 | BB | D+CCB | D+BB+CCB | D+BB |
| 1497 | BB | D+CCB | D+BB+CCB | D+ACEI/ARB |
| 1498 | BB | D+CCB | D+BB+CCB | BB+CCB |
| 1499 | BB | D+CCB | D+BB+CCB | BB+ACEI/ARB |
| 1500 | BB | D+CCB | D+BB+CCB | CCB+ACEI/ARB |
| 1501 | BB | D+CCB | D+BB+CCB | D+BB+ACEI/ARB |
| 1502 | BB | D+CCB | D+BB+CCB | D+CCB+ACEI/ARB |
| 1503 | BB | D+CCB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 1504 | BB | D+CCB | D+BB+ACEI/ARB | D |
| 1505 | BB | D+CCB | D+BB+ACEI/ARB | CCB |
| 1506 | BB | D+CCB | D+BB+ACEI/ARB | ACEI/ARB |
| 1507 | BB | D+CCB | D+BB+ACEI/ARB | D+BB |
| 1508 | BB | D+CCB | D+BB+ACEI/ARB | D+ACEI/ARB |
| 1509 | BB | D+CCB | D+BB+ACEI/ARB | BB+CCB |
| 1510 | BB | D+CCB | D+BB+ACEI/ARB | BB+ACEI/ARB |
| 1511 | BB | D+CCB | D+BB+ACEI/ARB | CCB+ACEI/ARB |
| 1512 | BB | D+CCB | D+BB+ACEI/ARB | D+BB+CCB |
| 1513 | BB | D+CCB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1514 | BB | D+CCB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1515 | BB | D+CCB | D+CCB+ACEI/ARB | D |
| 1516 | BB | D+CCB | D+CCB+ACEI/ARB | CCB |
| 1517 | BB | D+CCB | D+CCB+ACEI/ARB | ACEI/ARB |
| 1518 | BB | D+CCB | D+CCB+ACEI/ARB | D+BB |
| 1519 | BB | D+CCB | D+CCB+ACEI/ARB | D+ACEI/ARB |
| 1520 | BB | D+CCB | D+CCB+ACEI/ARB | BB+CCB |
| 1521 | BB | D+CCB | D+CCB+ACEI/ARB | BB+ACEI/ARB |
| 1522 | BB | D+CCB | D+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 1523 | BB | D+CCB | D+CCB+ACEI/ARB | D+BB+CCB |
| 1524 | BB | D+CCB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 1525 | BB | D+CCB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1526 | BB | D+CCB | BB+CCB+ACEI/ARB | D |
| 1527 | BB | D+CCB | BB+CCB+ACEI/ARB | CCB |
| 1528 | BB | D+CCB | BB+CCB+ACEI/ARB | ACEI/ARB |
| 1529 | BB | D+CCB | BB+CCB+ACEI/ARB | D+BB |
| 1530 | BB | D+CCB | BB+CCB+ACEI/ARB | D+ACEI/ARB |
| 1531 | BB | D+CCB | BB+CCB+ACEI/ARB | BB+CCB |
| 1532 | BB | D+CCB | BB+CCB+ACEI/ARB | BB+ACEI/ARB |
| 1533 | BB | D+CCB | BB+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 1534 | BB | D+CCB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 1535 | BB | D+CCB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 1536 | BB | D+CCB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1537 | BB | D+ACEI/ARB | D | CCB |
| 1538 | BB | D+ACEI/ARB | D | ACEI/ARB |
| 1539 | BB | D+ACEI/ARB | D | D+BB |
| 1540 | BB | D+ACEI/ARB | D | D+CCB |
| 1541 | BB | D+ACEI/ARB | D | BB+CCB |
| 1542 | BB | D+ACEI/ARB | D | BB+ACEI/ARB |
| 1543 | BB | D+ACEI/ARB | D | CCB+ACEI/ARB |
| 1544 | BB | D+ACEI/ARB | D | D+BB+CCB |
| 1545 | BB | D+ACEI/ARB | D | D+BB+ACEI/ARB |
| 1546 | BB | D+ACEI/ARB | D | D+CCB+ACEI/ARB |
| 1547 | BB | D+ACEI/ARB | D | BB+CCB+ACEI/ARB |
| 1548 | BB | D+ACEI/ARB | CCB | D |
| 1549 | BB | D+ACEI/ARB | CCB | ACEI/ARB |
| 1550 | BB | D+ACEI/ARB | CCB | D+BB |
| 1551 | BB | D+ACEI/ARB | CCB | D+CCB |
| 1552 | BB | D+ACEI/ARB | CCB | BB+CCB |
| 1553 | BB | D+ACEI/ARB | CCB | BB+ACEI/ARB |
| 1554 | BB | D+ACEI/ARB | CCB | CCB+ACEI/ARB |
| 1555 | BB | D+ACEI/ARB | CCB | D+BB+CCB |
| 1556 | BB | D+ACEI/ARB | CCB | D+BB+ACEI/ARB |
| 1557 | BB | D+ACEI/ARB | CCB | D+CCB+ACEI/ARB |
| 1558 | BB | D+ACEI/ARB | CCB | BB+CCB+ACEI/ARB |
| 1559 | BB | D+ACEI/ARB | ACEI/ARB | D |
| 1560 | BB | D+ACEI/ARB | ACEI/ARB | CCB |
| 1561 | BB | D+ACEI/ARB | ACEI/ARB | D+BB |
| 1562 | BB | D+ACEI/ARB | ACEI/ARB | D+CCB |
| 1563 | BB | D+ACEI/ARB | ACEI/ARB | BB+CCB |
| 1564 | BB | D+ACEI/ARB | ACEI/ARB | BB+ACEI/ARB |
| 1565 | BB | D+ACEI/ARB | ACEI/ARB | CCB+ACEI/ARB |
| 1566 | BB | D+ACEI/ARB | ACEI/ARB | D+BB+CCB |
| 1567 | BB | D+ACEI/ARB | ACEI/ARB | D+BB+ACEI/ARB |
| 1568 | BB | D+ACEI/ARB | ACEI/ARB | D+CCB+ACEI/ARB |
| 1569 | BB | D+ACEI/ARB | ACEI/ARB | BB+CCB+ACEI/ARB |
| 1570 | BB | D+ACEI/ARB | D+BB | D |
| 1571 | BB | D+ACEI/ARB | D+BB | CCB |
| 1572 | BB | D+ACEI/ARB | D+BB | ACEI/ARB |
| 1573 | BB | D+ACEI/ARB | D+BB | D+CCB |
| 1574 | BB | D+ACEI/ARB | D+BB | BB+CCB |
| 1575 | BB | D+ACEI/ARB | D+BB | BB+ACEI/ARB |
| 1576 | BB | D+ACEI/ARB | D+BB | CCB+ACEI/ARB |
| 1577 | BB | D+ACEI/ARB | D+BB | D+BB+CCB |
| 1578 | BB | D+ACEI/ARB | D+BB | D+BB+ACEI/ARB |
| 1579 | BB | D+ACEI/ARB | D+BB | D+CCB+ACEI/ARB |
| 1580 | BB | D+ACEI/ARB | D+BB | BB+CCB+ACEI/ARB |
| 1581 | BB | D+ACEI/ARB | D+CCB | D |
| 1582 | BB | D+ACEI/ARB | D+CCB | CCB |
| 1583 | BB | D+ACEI/ARB | D+CCB | ACEI/ARB |
| 1584 | BB | D+ACEI/ARB | D+CCB | D+BB |
| 1585 | BB | D+ACEI/ARB | D+CCB | BB+CCB |
| 1586 | BB | D+ACEI/ARB | D+CCB | BB+ACEI/ARB |
| 1587 | BB | D+ACEI/ARB | D+CCB | CCB+ACEI/ARB |
| 1588 | BB | D+ACEI/ARB | D+CCB | D+BB+CCB |
| 1589 | BB | D+ACEI/ARB | D+CCB | D+BB+ACEI/ARB |
| 1590 | BB | D+ACEI/ARB | D+CCB | D+CCB+ACEI/ARB |
| 1591 | BB | D+ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB |
| 1592 | BB | D+ACEI/ARB | BB+CCB | D |
| 1593 | BB | D+ACEI/ARB | BB+CCB | CCB |
| 1594 | BB | D+ACEI/ARB | BB+CCB | ACEI/ARB |
| 1595 | BB | D+ACEI/ARB | BB+CCB | D+BB |
| 1596 | BB | D+ACEI/ARB | BB+CCB | D+CCB |
| 1597 | BB | D+ACEI/ARB | BB+CCB | BB+ACEI/ARB |
| 1598 | BB | D+ACEI/ARB | BB+CCB | CCB+ACEI/ARB |
| 1599 | BB | D+ACEI/ARB | BB+CCB | D+BB+CCB |
| 1600 | BB | D+ACEI/ARB | BB+CCB | D+BB+ACEI/ARB |
| 1601 | BB | D+ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB |
| 1602 | BB | D+ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB |
| 1603 | BB | D+ACEI/ARB | BB+ACEI/ARB | D |
| 1604 | BB | D+ACEI/ARB | BB+ACEI/ARB | CCB |
| 1605 | BB | D+ACEI/ARB | BB+ACEI/ARB | ACEI/ARB |
| 1606 | BB | D+ACEI/ARB | BB+ACEI/ARB | D+BB |
| 1607 | BB | D+ACEI/ARB | BB+ACEI/ARB | D+CCB |
| 1608 | BB | D+ACEI/ARB | BB+ACEI/ARB | BB+CCB |
| 1609 | BB | D+ACEI/ARB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 1610 | BB | D+ACEI/ARB | BB+ACEI/ARB | D+BB+CCB |
| 1611 | BB | D+ACEI/ARB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 1612 | BB | D+ACEI/ARB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1613 | BB | D+ACEI/ARB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1614 | BB | D+ACEI/ARB | CCB+ACEI/ARB | D |
| 1615 | BB | D+ACEI/ARB | CCB+ACEI/ARB | CCB |
| 1616 | BB | D+ACEI/ARB | CCB+ACEI/ARB | ACEI/ARB |
| 1617 | BB | D+ACEI/ARB | CCB+ACEI/ARB | D+BB |
| 1618 | BB | D+ACEI/ARB | CCB+ACEI/ARB | D+CCB |
| 1619 | BB | D+ACEI/ARB | CCB+ACEI/ARB | BB+CCB |
| 1620 | BB | D+ACEI/ARB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 1621 | BB | D+ACEI/ARB | CCB+ACEI/ARB | D+BB+CCB |
| 1622 | BB | D+ACEI/ARB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 1623 | BB | D+ACEI/ARB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1624 | BB | D+ACEI/ARB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1625 | BB | D+ACEI/ARB | D+BB+CCB | D |
| 1626 | BB | D+ACEI/ARB | D+BB+CCB | CCB |
| 1627 | BB | D+ACEI/ARB | D+BB+CCB | ACEI/ARB |
| 1628 | BB | D+ACEI/ARB | D+BB+CCB | D+BB |
| 1629 | BB | D+ACEI/ARB | D+BB+CCB | D+CCB |
| 1630 | BB | D+ACEI/ARB | D+BB+CCB | BB+CCB |
| 1631 | BB | D+ACEI/ARB | D+BB+CCB | BB+ACEI/ARB |
| 1632 | BB | D+ACEI/ARB | D+BB+CCB | CCB+ACEI/ARB |
| 1633 | BB | D+ACEI/ARB | D+BB+CCB | D+BB+ACEI/ARB |
| 1634 | BB | D+ACEI/ARB | D+BB+CCB | D+CCB+ACEI/ARB |
| 1635 | BB | D+ACEI/ARB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 1636 | BB | D+ACEI/ARB | D+BB+ACEI/ARB | D |
| 1637 | BB | D+ACEI/ARB | D+BB+ACEI/ARB | CCB |
| 1638 | BB | D+ACEI/ARB | D+BB+ACEI/ARB | ACEI/ARB |
| 1639 | BB | D+ACEI/ARB | D+BB+ACEI/ARB | D+BB |
| 1640 | BB | D+ACEI/ARB | D+BB+ACEI/ARB | D+CCB |
| 1641 | BB | D+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB |
| 1642 | BB | D+ACEI/ARB | D+BB+ACEI/ARB | BB+ACEI/ARB |
| 1643 | BB | D+ACEI/ARB | D+BB+ACEI/ARB | CCB+ACEI/ARB |
| 1644 | BB | D+ACEI/ARB | D+BB+ACEI/ARB | D+BB+CCB |
| 1645 | BB | D+ACEI/ARB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1646 | BB | D+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1647 | BB | D+ACEI/ARB | D+CCB+ACEI/ARB | D |
| 1648 | BB | D+ACEI/ARB | D+CCB+ACEI/ARB | CCB |
| 1649 | BB | D+ACEI/ARB | D+CCB+ACEI/ARB | ACEI/ARB |
| 1650 | BB | D+ACEI/ARB | D+CCB+ACEI/ARB | D+BB |
| 1651 | BB | D+ACEI/ARB | D+CCB+ACEI/ARB | D+CCB |
| 1652 | BB | D+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB |
| 1653 | BB | D+ACEI/ARB | D+CCB+ACEI/ARB | BB+ACEI/ARB |
| 1654 | BB | D+ACEI/ARB | D+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 1655 | BB | D+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+CCB |
| 1656 | BB | D+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 1657 | BB | D+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1658 | BB | D+ACEI/ARB | BB+CCB+ACEI/ARB | D |
| 1659 | BB | D+ACEI/ARB | BB+CCB+ACEI/ARB | CCB |
| 1660 | BB | D+ACEI/ARB | BB+CCB+ACEI/ARB | ACEI/ARB |
| 1661 | BB | D+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB |
| 1662 | BB | D+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB |
| 1663 | BB | D+ACEI/ARB | BB+CCB+ACEI/ARB | BB+CCB |
| 1664 | BB | D+ACEI/ARB | BB+CCB+ACEI/ARB | BB+ACEI/ARB |
| 1665 | BB | D+ACEI/ARB | BB+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 1666 | BB | D+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 1667 | BB | D+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 1668 | BB | D+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1669 | BB | BB+CCB | D | CCB |
| 1670 | BB | BB+CCB | D | ACEI/ARB |
| 1671 | BB | BB+CCB | D | D+BB |
| 1672 | BB | BB+CCB | D | D+CCB |
| 1673 | BB | BB+CCB | D | D+ACEI/ARB |
| 1674 | BB | BB+CCB | D | BB+ACEI/ARB |
| 1675 | BB | BB+CCB | D | CCB+ACEI/ARB |
| 1676 | BB | BB+CCB | D | D+BB+CCB |
| 1677 | BB | BB+CCB | D | D+BB+ACEI/ARB |
| 1678 | BB | BB+CCB | D | D+CCB+ACEI/ARB |
| 1679 | BB | BB+CCB | D | BB+CCB+ACEI/ARB |
| 1680 | BB | BB+CCB | CCB | D |
| 1681 | BB | BB+CCB | CCB | ACEI/ARB |
| 1682 | BB | BB+CCB | CCB | D+BB |
| 1683 | BB | BB+CCB | CCB | D+CCB |
| 1684 | BB | BB+CCB | CCB | D+ACEI/ARB |
| 1685 | BB | BB+CCB | CCB | BB+ACEI/ARB |
| 1686 | BB | BB+CCB | CCB | CCB+ACEI/ARB |
| 1687 | BB | BB+CCB | CCB | D+BB+CCB |
| 1688 | BB | BB+CCB | CCB | D+BB+ACEI/ARB |
| 1689 | BB | BB+CCB | CCB | D+CCB+ACEI/ARB |
| 1690 | BB | BB+CCB | CCB | BB+CCB+ACEI/ARB |
| 1691 | BB | BB+CCB | ACEI/ARB | D |
| 1692 | BB | BB+CCB | ACEI/ARB | CCB |
| 1693 | BB | BB+CCB | ACEI/ARB | D+BB |
| 1694 | BB | BB+CCB | ACEI/ARB | D+CCB |
| 1695 | BB | BB+CCB | ACEI/ARB | D+ACEI/ARB |
| 1696 | BB | BB+CCB | ACEI/ARB | BB+ACEI/ARB |
| 1697 | BB | BB+CCB | ACEI/ARB | CCB+ACEI/ARB |
| 1698 | BB | BB+CCB | ACEI/ARB | D+BB+CCB |
| 1699 | BB | BB+CCB | ACEI/ARB | D+BB+ACEI/ARB |
| 1700 | BB | BB+CCB | ACEI/ARB | D+CCB+ACEI/ARB |
| 1701 | BB | BB+CCB | ACEI/ARB | BB+CCB+ACEI/ARB |
| 1702 | BB | BB+CCB | D+BB | D |
| 1703 | BB | BB+CCB | D+BB | CCB |
| 1704 | BB | BB+CCB | D+BB | ACEI/ARB |
| 1705 | BB | BB+CCB | D+BB | D+CCB |
| 1706 | BB | BB+CCB | D+BB | D+ACEI/ARB |
| 1707 | BB | BB+CCB | D+BB | BB+ACEI/ARB |
| 1708 | BB | BB+CCB | D+BB | CCB+ACEI/ARB |
| 1709 | BB | BB+CCB | D+BB | D+BB+CCB |
| 1710 | BB | BB+CCB | D+BB | D+BB+ACEI/ARB |
| 1711 | BB | BB+CCB | D+BB | D+CCB+ACEI/ARB |
| 1712 | BB | BB+CCB | D+BB | BB+CCB+ACEI/ARB |
| 1713 | BB | BB+CCB | D+CCB | D |
| 1714 | BB | BB+CCB | D+CCB | CCB |
| 1715 | BB | BB+CCB | D+CCB | ACEI/ARB |
| 1716 | BB | BB+CCB | D+CCB | D+BB |
| 1717 | BB | BB+CCB | D+CCB | D+ACEI/ARB |
| 1718 | BB | BB+CCB | D+CCB | BB+ACEI/ARB |
| 1719 | BB | BB+CCB | D+CCB | CCB+ACEI/ARB |
| 1720 | BB | BB+CCB | D+CCB | D+BB+CCB |
| 1721 | BB | BB+CCB | D+CCB | D+BB+ACEI/ARB |
| 1722 | BB | BB+CCB | D+CCB | D+CCB+ACEI/ARB |
| 1723 | BB | BB+CCB | D+CCB | BB+CCB+ACEI/ARB |
| 1724 | BB | BB+CCB | D+ACEIs/ARB | D |
| 1725 | BB | BB+CCB | D+ACEIs/ARB | CCB |
| 1726 | BB | BB+CCB | D+ACEIs/ARB | ACEI/ARB |
| 1727 | BB | BB+CCB | D+ACEIs/ARB | D+BB |
| 1728 | BB | BB+CCB | D+ACEIs/ARB | D+CCB |
| 1729 | BB | BB+CCB | D+ACEIs/ARB | BB+ACEI/ARB |
| 1730 | BB | BB+CCB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 1731 | BB | BB+CCB | D+ACEIs/ARB | D+BB+CCB |
| 1732 | BB | BB+CCB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 1733 | BB | BB+CCB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 1734 | BB | BB+CCB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 1735 | BB | BB+CCB | BB+ACEI/ARB | D |
| 1736 | BB | BB+CCB | BB+ACEI/ARB | CCB |
| 1737 | BB | BB+CCB | BB+ACEI/ARB | ACEI/ARB |
| 1738 | BB | BB+CCB | BB+ACEI/ARB | D+BB |
| 1739 | BB | BB+CCB | BB+ACEI/ARB | D+CCB |
| 1740 | BB | BB+CCB | BB+ACEI/ARB | D+ACEI/ARB |
| 1741 | BB | BB+CCB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 1742 | BB | BB+CCB | BB+ACEI/ARB | D+BB+CCB |
| 1743 | BB | BB+CCB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 1744 | BB | BB+CCB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1745 | BB | BB+CCB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1746 | BB | BB+CCB | CCB+ACEI/ARB | D |
| 1747 | BB | BB+CCB | CCB+ACEI/ARB | CCB |
| 1748 | BB | BB+CCB | CCB+ACEI/ARB | ACEI/ARB |
| 1749 | BB | BB+CCB | CCB+ACEI/ARB | D+BB |
| 1750 | BB | BB+CCB | CCB+ACEI/ARB | D+CCB |
| 1751 | BB | BB+CCB | CCB+ACEI/ARB | D+ACEI/ARB |
| 1752 | BB | BB+CCB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 1753 | BB | BB+CCB | CCB+ACEI/ARB | D+BB+CCB |
| 1754 | BB | BB+CCB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 1755 | BB | BB+CCB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1756 | BB | BB+CCB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1757 | BB | BB+CCB | D+BB+CCB | D |
| 1758 | BB | BB+CCB | D+BB+CCB | CCB |
| 1759 | BB | BB+CCB | D+BB+CCB | ACEI/ARB |
| 1760 | BB | BB+CCB | D+BB+CCB | D+BB |
| 1761 | BB | BB+CCB | D+BB+CCB | D+CCB |
| 1762 | BB | BB+CCB | D+BB+CCB | D+ACEI/ARB |
| 1763 | BB | BB+CCB | D+BB+CCB | BB+ACEI/ARB |
| 1764 | BB | BB+CCB | D+BB+CCB | CCB+ACEI/ARB |
| 1765 | BB | BB+CCB | D+BB+CCB | D+BB+ACEI/ARB |
| 1766 | BB | BB+CCB | D+BB+CCB | D+CCB+ACEI/ARB |
| 1767 | BB | BB+CCB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 1768 | BB | BB+CCB | D+BB+ACEI/ARB | D |
| 1769 | BB | BB+CCB | D+BB+ACEI/ARB | CCB |
| 1770 | BB | BB+CCB | D+BB+ACEI/ARB | ACEI/ARB |
| 1771 | BB | BB+CCB | D+BB+ACEI/ARB | D+BB |
| 1772 | BB | BB+CCB | D+BB+ACEI/ARB | D+CCB |
| 1773 | BB | BB+CCB | D+BB+ACEI/ARB | D+ACEI/ARB |
| 1774 | BB | BB+CCB | D+BB+ACEI/ARB | BB+ACEI/ARB |
| 1775 | BB | BB+CCB | D+BB+ACEI/ARB | CCB+ACEI/ARB |
| 1776 | BB | BB+CCB | D+BB+ACEI/ARB | D+BB+CCB |
| 1777 | BB | BB+CCB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1778 | BB | BB+CCB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1779 | BB | BB+CCB | D+CCB+ACEI/ARB | D |
| 1780 | BB | BB+CCB | D+CCB+ACEI/ARB | CCB |
| 1781 | BB | BB+CCB | D+CCB+ACEI/ARB | ACEI/ARB |
| 1782 | BB | BB+CCB | D+CCB+ACEI/ARB | D+BB |
| 1783 | BB | BB+CCB | D+CCB+ACEI/ARB | D+CCB |
| 1784 | BB | BB+CCB | D+CCB+ACEI/ARB | D+ACEI/ARB |
| 1785 | BB | BB+CCB | D+CCB+ACEI/ARB | BB+ACEI/ARB |
| 1786 | BB | BB+CCB | D+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 1787 | BB | BB+CCB | D+CCB+ACEI/ARB | D+BB+CCB |
| 1788 | BB | BB+CCB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 1789 | BB | BB+CCB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1790 | BB | BB+CCB | BB+CCB+ACEI/ARB | D |
| 1791 | BB | BB+CCB | BB+CCB+ACEI/ARB | CCB |
| 1792 | BB | BB+CCB | BB+CCB+ACEI/ARB | ACEI/ARB |
| 1793 | BB | BB+CCB | BB+CCB+ACEI/ARB | D+BB |
| 1794 | BB | BB+CCB | BB+CCB+ACEI/ARB | D+CCB |
| 1795 | BB | BB+CCB | BB+CCB+ACEI/ARB | D+ACEI/ARB |
| 1796 | BB | BB+CCB | BB+CCB+ACEI/ARB | BB+ACEI/ARB |
| 1797 | BB | BB+CCB | BB+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 1798 | BB | BB+CCB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 1799 | BB | BB+CCB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 1800 | BB | BB+CCB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1801 | BB | BB+ACEI/ARB | D | CCB |
| 1802 | BB | BB+ACEI/ARB | D | ACEI/ARB |
| 1803 | BB | BB+ACEI/ARB | D | D+BB |
| 1804 | BB | BB+ACEI/ARB | D | D+CCB |
| 1805 | BB | BB+ACEI/ARB | D | D+ACEI/ARB |
| 1806 | BB | BB+ACEI/ARB | D | BB+CCB |
| 1807 | BB | BB+ACEI/ARB | D | CCB+ACEI/ARB |
| 1808 | BB | BB+ACEI/ARB | D | D+BB+CCB |
| 1809 | BB | BB+ACEI/ARB | D | D+BB+ACEI/ARB |
| 1810 | BB | BB+ACEI/ARB | D | D+CCB+ACEI/ARB |
| 1811 | BB | BB+ACEI/ARB | D | BB+CCB+ACEI/ARB |
| 1812 | BB | BB+ACEI/ARB | CCB | D |
| 1813 | BB | BB+ACEI/ARB | CCB | ACEI/ARB |
| 1814 | BB | BB+ACEI/ARB | CCB | D+BB |
| 1815 | BB | BB+ACEI/ARB | CCB | D+CCB |
| 1816 | BB | BB+ACEI/ARB | CCB | D+ACEI/ARB |
| 1817 | BB | BB+ACEI/ARB | CCB | BB+CCB |
| 1818 | BB | BB+ACEI/ARB | CCB | CCB+ACEI/ARB |
| 1819 | BB | BB+ACEI/ARB | CCB | D+BB+CCB |
| 1820 | BB | BB+ACEI/ARB | CCB | D+BB+ACEI/ARB |
| 1821 | BB | BB+ACEI/ARB | CCB | D+CCB+ACEI/ARB |
| 1822 | BB | BB+ACEI/ARB | CCB | BB+CCB+ACEI/ARB |
| 1823 | BB | BB+ACEI/ARB | ACEI/ARB | D |
| 1824 | BB | BB+ACEI/ARB | ACEI/ARB | CCB |
| 1825 | BB | BB+ACEI/ARB | ACEI/ARB | D+BB |
| 1826 | BB | BB+ACEI/ARB | ACEI/ARB | D+CCB |
| 1827 | BB | BB+ACEI/ARB | ACEI/ARB | D+ACEI/ARB |
| 1828 | BB | BB+ACEI/ARB | ACEI/ARB | BB+CCB |
| 1829 | BB | BB+ACEI/ARB | ACEI/ARB | CCB+ACEI/ARB |
| 1830 | BB | BB+ACEI/ARB | ACEI/ARB | D+BB+CCB |
| 1831 | BB | BB+ACEI/ARB | ACEI/ARB | D+BB+ACEI/ARB |
| 1832 | BB | BB+ACEI/ARB | ACEI/ARB | D+CCB+ACEI/ARB |
| 1833 | BB | BB+ACEI/ARB | ACEI/ARB | BB+CCB+ACEI/ARB |
| 1834 | BB | BB+ACEI/ARB | D+BB | D |
| 1835 | BB | BB+ACEI/ARB | D+BB | CCB |
| 1836 | BB | BB+ACEI/ARB | D+BB | ACEI/ARB |
| 1837 | BB | BB+ACEI/ARB | D+BB | D+CCB |
| 1838 | BB | BB+ACEI/ARB | D+BB | D+ACEI/ARB |
| 1839 | BB | BB+ACEI/ARB | D+BB | BB+CCB |
| 1840 | BB | BB+ACEI/ARB | D+BB | CCB+ACEI/ARB |
| 1841 | BB | BB+ACEI/ARB | D+BB | D+BB+CCB |
| 1842 | BB | BB+ACEI/ARB | D+BB | D+BB+ACEI/ARB |
| 1843 | BB | BB+ACEI/ARB | D+BB | D+CCB+ACEI/ARB |
| 1844 | BB | BB+ACEI/ARB | D+BB | BB+CCB+ACEI/ARB |
| 1845 | BB | BB+ACEI/ARB | D+CCB | D |
| 1846 | BB | BB+ACEI/ARB | D+CCB | CCB |
| 1847 | BB | BB+ACEI/ARB | D+CCB | ACEI/ARB |
| 1848 | BB | BB+ACEI/ARB | D+CCB | D+BB |
| 1849 | BB | BB+ACEI/ARB | D+CCB | D+ACEI/ARB |
| 1850 | BB | BB+ACEI/ARB | D+CCB | BB+CCB |
| 1851 | BB | BB+ACEI/ARB | D+CCB | CCB+ACEI/ARB |
| 1852 | BB | BB+ACEI/ARB | D+CCB | D+BB+CCB |
| 1853 | BB | BB+ACEI/ARB | D+CCB | D+BB+ACEI/ARB |
| 1854 | BB | BB+ACEI/ARB | D+CCB | D+CCB+ACEI/ARB |
| 1855 | BB | BB+ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB |
| 1856 | BB | BB+ACEI/ARB | D+ACEIs/ARB | D |
| 1857 | BB | BB+ACEI/ARB | D+ACEIs/ARB | CCB |
| 1858 | BB | BB+ACEI/ARB | D+ACEIs/ARB | ACEI/ARB |
| 1859 | BB | BB+ACEI/ARB | D+ACEIs/ARB | D+BB |
| 1860 | BB | BB+ACEI/ARB | D+ACEIs/ARB | D+CCB |
| 1861 | BB | BB+ACEI/ARB | D+ACEIs/ARB | BB+CCB |
| 1862 | BB | BB+ACEI/ARB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 1863 | BB | BB+ACEI/ARB | D+ACEIs/ARB | D+BB+CCB |
| 1864 | BB | BB+ACEI/ARB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 1865 | BB | BB+ACEI/ARB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 1866 | BB | BB+ACEI/ARB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 1867 | BB | BB+ACEI/ARB | BB+CCB | D |
| 1868 | BB | BB+ACEI/ARB | BB+CCB | CCB |
| 1869 | BB | BB+ACEI/ARB | BB+CCB | ACEI/ARB |
| 1870 | BB | BB+ACEI/ARB | BB+CCB | D+BB |
| 1871 | BB | BB+ACEI/ARB | BB+CCB | D+CCB |
| 1872 | BB | BB+ACEI/ARB | BB+CCB | D+ACEI/ARB |
| 1873 | BB | BB+ACEI/ARB | BB+CCB | CCB+ACEI/ARB |
| 1874 | BB | BB+ACEI/ARB | BB+CCB | D+BB+CCB |
| 1875 | BB | BB+ACEI/ARB | BB+CCB | D+BB+ACEI/ARB |
| 1876 | BB | BB+ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB |
| 1877 | BB | BB+ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB |
| 1878 | BB | BB+ACEI/ARB | CCB+ACEI/ARB | D |
| 1879 | BB | BB+ACEI/ARB | CCB+ACEI/ARB | CCB |
| 1880 | BB | BB+ACEI/ARB | CCB+ACEI/ARB | ACEI/ARB |
| 1881 | BB | BB+ACEI/ARB | CCB+ACEI/ARB | D+BB |
| 1882 | BB | BB+ACEI/ARB | CCB+ACEI/ARB | D+CCB |
| 1883 | BB | BB+ACEI/ARB | CCB+ACEI/ARB | D+ACEI/ARB |
| 1884 | BB | BB+ACEI/ARB | CCB+ACEI/ARB | BB+CCB |
| 1885 | BB | BB+ACEI/ARB | CCB+ACEI/ARB | D+BB+CCB |
| 1886 | BB | BB+ACEI/ARB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 1887 | BB | BB+ACEI/ARB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1888 | BB | BB+ACEI/ARB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1889 | BB | BB+ACEI/ARB | D+BB+CCB | D |
| 1890 | BB | BB+ACEI/ARB | D+BB+CCB | CCB |
| 1891 | BB | BB+ACEI/ARB | D+BB+CCB | ACEI/ARB |
| 1892 | BB | BB+ACEI/ARB | D+BB+CCB | D+BB |
| 1893 | BB | BB+ACEI/ARB | D+BB+CCB | D+CCB |
| 1894 | BB | BB+ACEI/ARB | D+BB+CCB | D+ACEI/ARB |
| 1895 | BB | BB+ACEI/ARB | D+BB+CCB | BB+CCB |
| 1896 | BB | BB+ACEI/ARB | D+BB+CCB | CCB+ACEI/ARB |
| 1897 | BB | BB+ACEI/ARB | D+BB+CCB | D+BB+ACEI/ARB |
| 1898 | BB | BB+ACEI/ARB | D+BB+CCB | D+CCB+ACEI/ARB |
| 1899 | BB | BB+ACEI/ARB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 1900 | BB | BB+ACEI/ARB | D+BB+ACEI/ARB | D |
| 1901 | BB | BB+ACEI/ARB | D+BB+ACEI/ARB | CCB |
| 1902 | BB | BB+ACEI/ARB | D+BB+ACEI/ARB | ACEI/ARB |
| 1903 | BB | BB+ACEI/ARB | D+BB+ACEI/ARB | D+BB |
| 1904 | BB | BB+ACEI/ARB | D+BB+ACEI/ARB | D+CCB |
| 1905 | BB | BB+ACEI/ARB | D+BB+ACEI/ARB | D+ACEI/ARB |
| 1906 | BB | BB+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB |
| 1907 | BB | BB+ACEI/ARB | D+BB+ACEI/ARB | CCB+ACEI/ARB |
| 1908 | BB | BB+ACEI/ARB | D+BB+ACEI/ARB | D+BB+CCB |
| 1909 | BB | BB+ACEI/ARB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1910 | BB | BB+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1911 | BB | BB+ACEI/ARB | D+CCB+ACEI/ARB | D |
| 1912 | BB | BB+ACEI/ARB | D+CCB+ACEI/ARB | CCB |
| 1913 | BB | BB+ACEI/ARB | D+CCB+ACEI/ARB | ACEI/ARB |
| 1914 | BB | BB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB |
| 1915 | BB | BB+ACEI/ARB | D+CCB+ACEI/ARB | D+CCB |
| 1916 | BB | BB+ACEI/ARB | D+CCB+ACEI/ARB | D+ACEI/ARB |
| 1917 | BB | BB+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB |
| 1918 | BB | BB+ACEI/ARB | D+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 1919 | BB | BB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+CCB |
| 1920 | BB | BB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 1921 | BB | BB+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 1922 | BB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D |
| 1923 | BB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | CCB |
| 1924 | BB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | ACEI/ARB |
| 1925 | BB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB |
| 1926 | BB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB |
| 1927 | BB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+ACEI/ARB |
| 1928 | BB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | BB+CCB |
| 1929 | BB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 1930 | BB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 1931 | BB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 1932 | BB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 1933 | BB | CCB+ACEI/ARB | D | CCB |
| 1934 | BB | CCB+ACEI/ARB | D | ACEI/ARB |
| 1935 | BB | CCB+ACEI/ARB | D | D+BB |
| 1936 | BB | CCB+ACEI/ARB | D | D+CCB |
| 1937 | BB | CCB+ACEI/ARB | D | D+ACEI/ARB |
| 1938 | BB | CCB+ACEI/ARB | D | BB+CCB |
| 1939 | BB | CCB+ACEI/ARB | D | BB+ACEI/ARB |
| 1940 | BB | CCB+ACEI/ARB | D | D+BB+CCB |
| 1941 | BB | CCB+ACEI/ARB | D | D+BB+ACEI/ARB |
| 1942 | BB | CCB+ACEI/ARB | D | D+CCB+ACEI/ARB |
| 1943 | BB | CCB+ACEI/ARB | D | BB+CCB+ACEI/ARB |
| 1944 | BB | CCB+ACEI/ARB | CCB | D |
| 1945 | BB | CCB+ACEI/ARB | CCB | ACEI/ARB |
| 1946 | BB | CCB+ACEI/ARB | CCB | D+BB |
| 1947 | BB | CCB+ACEI/ARB | CCB | D+CCB |
| 1948 | BB | CCB+ACEI/ARB | CCB | D+ACEI/ARB |
| 1949 | BB | CCB+ACEI/ARB | CCB | BB+CCB |
| 1950 | BB | CCB+ACEI/ARB | CCB | BB+ACEI/ARB |
| 1951 | BB | CCB+ACEI/ARB | CCB | D+BB+CCB |
| 1952 | BB | CCB+ACEI/ARB | CCB | D+BB+ACEI/ARB |
| 1953 | BB | CCB+ACEI/ARB | CCB | D+CCB+ACEI/ARB |
| 1954 | BB | CCB+ACEI/ARB | CCB | BB+CCB+ACEI/ARB |
| 1955 | BB | CCB+ACEI/ARB | ACEI/ARB | D |
| 1956 | BB | CCB+ACEI/ARB | ACEI/ARB | CCB |
| 1957 | BB | CCB+ACEI/ARB | ACEI/ARB | D+BB |
| 1958 | BB | CCB+ACEI/ARB | ACEI/ARB | D+CCB |
| 1959 | BB | CCB+ACEI/ARB | ACEI/ARB | D+ACEI/ARB |
| 1960 | BB | CCB+ACEI/ARB | ACEI/ARB | BB+CCB |
| 1961 | BB | CCB+ACEI/ARB | ACEI/ARB | BB+ACEI/ARB |
| 1962 | BB | CCB+ACEI/ARB | ACEI/ARB | D+BB+CCB |
| 1963 | BB | CCB+ACEI/ARB | ACEI/ARB | D+BB+ACEI/ARB |
| 1964 | BB | CCB+ACEI/ARB | ACEI/ARB | D+CCB+ACEI/ARB |
| 1965 | BB | CCB+ACEI/ARB | ACEI/ARB | BB+CCB+ACEI/ARB |
| 1966 | BB | CCB+ACEI/ARB | D+BB | D |
| 1967 | BB | CCB+ACEI/ARB | D+BB | CCB |
| 1968 | BB | CCB+ACEI/ARB | D+BB | ACEI/ARB |
| 1969 | BB | CCB+ACEI/ARB | D+BB | D+CCB |
| 1970 | BB | CCB+ACEI/ARB | D+BB | D+ACEI/ARB |
| 1971 | BB | CCB+ACEI/ARB | D+BB | BB+CCB |
| 1972 | BB | CCB+ACEI/ARB | D+BB | BB+ACEI/ARB |
| 1973 | BB | CCB+ACEI/ARB | D+BB | D+BB+CCB |
| 1974 | BB | CCB+ACEI/ARB | D+BB | D+BB+ACEI/ARB |
| 1975 | BB | CCB+ACEI/ARB | D+BB | D+CCB+ACEI/ARB |
| 1976 | BB | CCB+ACEI/ARB | D+BB | BB+CCB+ACEI/ARB |
| 1977 | BB | CCB+ACEI/ARB | D+CCB | D |
| 1978 | BB | CCB+ACEI/ARB | D+CCB | CCB |
| 1979 | BB | CCB+ACEI/ARB | D+CCB | ACEI/ARB |
| 1980 | BB | CCB+ACEI/ARB | D+CCB | D+BB |
| 1981 | BB | CCB+ACEI/ARB | D+CCB | D+ACEI/ARB |
| 1982 | BB | CCB+ACEI/ARB | D+CCB | BB+CCB |
| 1983 | BB | CCB+ACEI/ARB | D+CCB | BB+ACEI/ARB |
| 1984 | BB | CCB+ACEI/ARB | D+CCB | D+BB+CCB |
| 1985 | BB | CCB+ACEI/ARB | D+CCB | D+BB+ACEI/ARB |
| 1986 | BB | CCB+ACEI/ARB | D+CCB | D+CCB+ACEI/ARB |
| 1987 | BB | CCB+ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB |
| 1988 | BB | CCB+ACEI/ARB | D+ACEIs/ARB | D |
| 1989 | BB | CCB+ACEI/ARB | D+ACEIs/ARB | CCB |
| 1990 | BB | CCB+ACEI/ARB | D+ACEIs/ARB | ACEI/ARB |
| 1991 | BB | CCB+ACEI/ARB | D+ACEIs/ARB | D+BB |
| 1992 | BB | CCB+ACEI/ARB | D+ACEIs/ARB | D+CCB |
| 1993 | BB | CCB+ACEI/ARB | D+ACEIs/ARB | BB+CCB |
| 1994 | BB | CCB+ACEI/ARB | D+ACEIs/ARB | BB+ACEI/ARB |
| 1995 | BB | CCB+ACEI/ARB | D+ACEIs/ARB | D+BB+CCB |
| 1996 | BB | CCB+ACEI/ARB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 1997 | BB | CCB+ACEI/ARB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 1998 | BB | CCB+ACEI/ARB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 1999 | BB | CCB+ACEI/ARB | BB+CCB | D |
| 2000 | BB | CCB+ACEI/ARB | BB+CCB | CCB |
| 2001 | BB | CCB+ACEI/ARB | BB+CCB | ACEI/ARB |
| 2002 | BB | CCB+ACEI/ARB | BB+CCB | D+BB |
| 2003 | BB | CCB+ACEI/ARB | BB+CCB | D+CCB |
| 2004 | BB | CCB+ACEI/ARB | BB+CCB | D+ACEI/ARB |
| 2005 | BB | CCB+ACEI/ARB | BB+CCB | BB+ACEI/ARB |
| 2006 | BB | CCB+ACEI/ARB | BB+CCB | D+BB+CCB |
| 2007 | BB | CCB+ACEI/ARB | BB+CCB | D+BB+ACEI/ARB |
| 2008 | BB | CCB+ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB |
| 2009 | BB | CCB+ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB |
| 2010 | BB | CCB+ACEI/ARB | BB+ACEI/ARB | D |
| 2011 | BB | CCB+ACEI/ARB | BB+ACEI/ARB | CCB |
| 2012 | BB | CCB+ACEI/ARB | BB+ACEI/ARB | ACEI/ARB |
| 2013 | BB | CCB+ACEI/ARB | BB+ACEI/ARB | D+BB |
| 2014 | BB | CCB+ACEI/ARB | BB+ACEI/ARB | D+CCB |
| 2015 | BB | CCB+ACEI/ARB | BB+ACEI/ARB | D+ACEI/ARB |
| 2016 | BB | CCB+ACEI/ARB | BB+ACEI/ARB | BB+CCB |
| 2017 | BB | CCB+ACEI/ARB | BB+ACEI/ARB | D+BB+CCB |
| 2018 | BB | CCB+ACEI/ARB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 2019 | BB | CCB+ACEI/ARB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2020 | BB | CCB+ACEI/ARB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2021 | BB | CCB+ACEI/ARB | D+BB+CCB | D |
| 2022 | BB | CCB+ACEI/ARB | D+BB+CCB | CCB |
| 2023 | BB | CCB+ACEI/ARB | D+BB+CCB | ACEI/ARB |
| 2024 | BB | CCB+ACEI/ARB | D+BB+CCB | D+BB |
| 2025 | BB | CCB+ACEI/ARB | D+BB+CCB | D+CCB |
| 2026 | BB | CCB+ACEI/ARB | D+BB+CCB | D+ACEI/ARB |
| 2027 | BB | CCB+ACEI/ARB | D+BB+CCB | BB+CCB |
| 2028 | BB | CCB+ACEI/ARB | D+BB+CCB | BB+ACEI/ARB |
| 2029 | BB | CCB+ACEI/ARB | D+BB+CCB | D+BB+ACEI/ARB |
| 2030 | BB | CCB+ACEI/ARB | D+BB+CCB | D+CCB+ACEI/ARB |
| 2031 | BB | CCB+ACEI/ARB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 2032 | BB | CCB+ACEI/ARB | D+BB+ACEI/ARB | D |
| 2033 | BB | CCB+ACEI/ARB | D+BB+ACEI/ARB | CCB |
| 2034 | BB | CCB+ACEI/ARB | D+BB+ACEI/ARB | ACEI/ARB |
| 2035 | BB | CCB+ACEI/ARB | D+BB+ACEI/ARB | D+BB |
| 2036 | BB | CCB+ACEI/ARB | D+BB+ACEI/ARB | D+CCB |
| 2037 | BB | CCB+ACEI/ARB | D+BB+ACEI/ARB | D+ACEI/ARB |
| 2038 | BB | CCB+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB |
| 2039 | BB | CCB+ACEI/ARB | D+BB+ACEI/ARB | BB+ACEI/ARB |
| 2040 | BB | CCB+ACEI/ARB | D+BB+ACEI/ARB | D+BB+CCB |
| 2041 | BB | CCB+ACEI/ARB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2042 | BB | CCB+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2043 | BB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | D |
| 2044 | BB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | CCB |
| 2045 | BB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | ACEI/ARB |
| 2046 | BB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB |
| 2047 | BB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | D+CCB |
| 2048 | BB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | D+ACEI/ARB |
| 2049 | BB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB |
| 2050 | BB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | BB+ACEI/ARB |
| 2051 | BB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+CCB |
| 2052 | BB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 2053 | BB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2054 | BB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D |
| 2055 | BB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | CCB |
| 2056 | BB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | ACEI/ARB |
| 2057 | BB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB |
| 2058 | BB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB |
| 2059 | BB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+ACEI/ARB |
| 2060 | BB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | BB+CCB |
| 2061 | BB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | BB+ACEI/ARB |
| 2062 | BB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 2063 | BB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 2064 | BB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2065 | CCB | D | BB | ACEI/ARB |
| 2066 | CCB | D | BB | D+BB |
| 2067 | CCB | D | BB | D+CCB |
| 2068 | CCB | D | BB | D+ACEI/ARB |
| 2069 | CCB | D | BB | BB+CCB |
| 2070 | CCB | D | BB | BB+ACEI/ARB |
| 2071 | CCB | D | BB | CCB+ACEI/ARB |
| 2072 | CCB | D | ACEI/ARB | BB |
| 2073 | CCB | D | ACEI/ARB | D+BB |
| 2074 | CCB | D | ACEI/ARB | D+CCB |
| 2075 | CCB | D | ACEI/ARB | D+ACEI/ARB |
| 2076 | CCB | D | ACEI/ARB | BB+CCB |
| 2077 | CCB | D | ACEI/ARB | BB+ACEI/ARB |
| 2078 | CCB | D | ACEI/ARB | CCB+ACEI/ARB |
| 2079 | CCB | D | D+BB | BB |
| 2080 | CCB | D | D+BB | ACEI/ARB |
| 2081 | CCB | D | D+BB | D+CCB |
| 2082 | CCB | D | D+BB | D+ACEI/ARB |
| 2083 | CCB | D | D+BB | BB+CCB |
| 2084 | CCB | D | D+BB | BB+ACEI/ARB |
| 2085 | CCB | D | D+BB | CCB+ACEI/ARB |
| 2086 | CCB | D | D+BB | D+BB+CCB |
| 2087 | CCB | D | D+BB | D+BB+ACEI/ARB |
| 2088 | CCB | D | D+BB | D+CCB+ACEI/ARB |
| 2089 | CCB | D | D+BB | BB+CCB+ACEI/ARB |
| 2090 | CCB | D | D+CCB | BB |
| 2091 | CCB | D | D+CCB | ACEI/ARB |
| 2092 | CCB | D | D+CCB | D+BB |
| 2093 | CCB | D | D+CCB | D+ACEI/ARB |
| 2094 | CCB | D | D+CCB | BB+CCB |
| 2095 | CCB | D | D+CCB | BB+ACEI/ARB |
| 2096 | CCB | D | D+CCB | CCB+ACEI/ARB |
| 2097 | CCB | D | D+CCB | D+BB+CCB |
| 2098 | CCB | D | D+CCB | D+BB+ACEI/ARB |
| 2099 | CCB | D | D+CCB | D+CCB+ACEI/ARB |
| 2100 | CCB | D | D+CCB | BB+CCB+ACEI/ARB |
| 2101 | CCB | D | D+ACEIs/ARB | BB |
| 2102 | CCB | D | D+ACEIs/ARB | ACEI/ARB |
| 2103 | CCB | D | D+ACEIs/ARB | D+BB |
| 2104 | CCB | D | D+ACEIs/ARB | D+CCB |
| 2105 | CCB | D | D+ACEIs/ARB | BB+CCB |
| 2106 | CCB | D | D+ACEIs/ARB | BB+ACEI/ARB |
| 2107 | CCB | D | D+ACEIs/ARB | CCB+ACEI/ARB |
| 2108 | CCB | D | D+ACEIs/ARB | D+BB+CCB |
| 2109 | CCB | D | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 2110 | CCB | D | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 2111 | CCB | D | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 2112 | CCB | D | BB+CCB | BB |
| 2113 | CCB | D | BB+CCB | ACEI/ARB |
| 2114 | CCB | D | BB+CCB | D+BB |
| 2115 | CCB | D | BB+CCB | D+CCB |
| 2116 | CCB | D | BB+CCB | D+ACEI/ARB |
| 2117 | CCB | D | BB+CCB | BB+ACEI/ARB |
| 2118 | CCB | D | BB+CCB | CCB+ACEI/ARB |
| 2119 | CCB | D | BB+CCB | D+BB+CCB |
| 2120 | CCB | D | BB+CCB | D+BB+ACEI/ARB |
| 2121 | CCB | D | BB+CCB | D+CCB+ACEI/ARB |
| 2122 | CCB | D | BB+CCB | BB+CCB+ACEI/ARB |
| 2123 | CCB | D | BB+ACEI/ARB | BB |
| 2124 | CCB | D | BB+ACEI/ARB | ACEI/ARB |
| 2125 | CCB | D | BB+ACEI/ARB | D+BB |
| 2126 | CCB | D | BB+ACEI/ARB | D+CCB |
| 2127 | CCB | D | BB+ACEI/ARB | D+ACEI/ARB |
| 2128 | CCB | D | BB+ACEI/ARB | BB+CCB |
| 2129 | CCB | D | BB+ACEI/ARB | CCB+ACEI/ARB |
| 2130 | CCB | D | BB+ACEI/ARB | D+BB+CCB |
| 2131 | CCB | D | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 2132 | CCB | D | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2133 | CCB | D | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2134 | CCB | D | CCB+ACEI/ARB | BB |
| 2135 | CCB | D | CCB+ACEI/ARB | ACEI/ARB |
| 2136 | CCB | D | CCB+ACEI/ARB | D+BB |
| 2137 | CCB | D | CCB+ACEI/ARB | D+CCB |
| 2138 | CCB | D | CCB+ACEI/ARB | D+ACEI/ARB |
| 2139 | CCB | D | CCB+ACEI/ARB | BB+CCB |
| 2140 | CCB | D | CCB+ACEI/ARB | BB+ACEI/ARB |
| 2141 | CCB | D | CCB+ACEI/ARB | D+BB+CCB |
| 2142 | CCB | D | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 2143 | CCB | D | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2144 | CCB | D | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2145 | CCB | BB | D | ACEI/ARB |
| 2146 | CCB | BB | D | D+BB |
| 2147 | CCB | BB | D | D+CCB |
| 2148 | CCB | BB | D | D+ACEI/ARB |
| 2149 | CCB | BB | D | BB+CCB |
| 2150 | CCB | BB | D | BB+ACEI/ARB |
| 2151 | CCB | BB | D | CCB+ACEI/ARB |
| 2152 | CCB | BB | ACEI/ARB | D |
| 2153 | CCB | BB | ACEI/ARB | D+BB |
| 2154 | CCB | BB | ACEI/ARB | D+CCB |
| 2155 | CCB | BB | ACEI/ARB | D+ACEI/ARB |
| 2156 | CCB | BB | ACEI/ARB | BB+CCB |
| 2157 | CCB | BB | ACEI/ARB | BB+ACEI/ARB |
| 2158 | CCB | BB | ACEI/ARB | CCB+ACEI/ARB |
| 2159 | CCB | BB | D+BB | D |
| 2160 | CCB | BB | D+BB | ACEI/ARB |
| 2161 | CCB | BB | D+BB | D+CCB |
| 2162 | CCB | BB | D+BB | D+ACEI/ARB |
| 2163 | CCB | BB | D+BB | BB+CCB |
| 2164 | CCB | BB | D+BB | BB+ACEI/ARB |
| 2165 | CCB | BB | D+BB | CCB+ACEI/ARB |
| 2166 | CCB | BB | D+BB | D+BB+CCB |
| 2167 | CCB | BB | D+BB | D+BB+ACEI/ARB |
| 2168 | CCB | BB | D+BB | D+CCB+ACEI/ARB |
| 2169 | CCB | BB | D+BB | BB+CCB+ACEI/ARB |
| 2170 | CCB | BB | D+CCB | D |
| 2171 | CCB | BB | D+CCB | ACEI/ARB |
| 2172 | CCB | BB | D+CCB | D+BB |
| 2173 | CCB | BB | D+CCB | D+ACEI/ARB |
| 2174 | CCB | BB | D+CCB | BB+CCB |
| 2175 | CCB | BB | D+CCB | BB+ACEI/ARB |
| 2176 | CCB | BB | D+CCB | CCB+ACEI/ARB |
| 2177 | CCB | BB | D+CCB | D+BB+CCB |
| 2178 | CCB | BB | D+CCB | D+BB+ACEI/ARB |
| 2179 | CCB | BB | D+CCB | D+CCB+ACEI/ARB |
| 2180 | CCB | BB | D+CCB | BB+CCB+ACEI/ARB |
| 2181 | CCB | BB | D+ACEIs/ARB | D |
| 2182 | CCB | BB | D+ACEIs/ARB | ACEI/ARB |
| 2183 | CCB | BB | D+ACEIs/ARB | D+BB |
| 2184 | CCB | BB | D+ACEIs/ARB | D+CCB |
| 2185 | CCB | BB | D+ACEIs/ARB | BB+CCB |
| 2186 | CCB | BB | D+ACEIs/ARB | BB+ACEI/ARB |
| 2187 | CCB | BB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 2188 | CCB | BB | D+ACEIs/ARB | D+BB+CCB |
| 2189 | CCB | BB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 2190 | CCB | BB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 2191 | CCB | BB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 2192 | CCB | BB | BB+CCB | D |
| 2193 | CCB | BB | BB+CCB | ACEI/ARB |
| 2194 | CCB | BB | BB+CCB | D+BB |
| 2195 | CCB | BB | BB+CCB | D+CCB |
| 2196 | CCB | BB | BB+CCB | D+ACEI/ARB |
| 2197 | CCB | BB | BB+CCB | BB+ACEI/ARB |
| 2198 | CCB | BB | BB+CCB | CCB+ACEI/ARB |
| 2199 | CCB | BB | BB+CCB | D+BB+CCB |
| 2200 | CCB | BB | BB+CCB | D+BB+ACEI/ARB |
| 2201 | CCB | BB | BB+CCB | D+CCB+ACEI/ARB |
| 2202 | CCB | BB | BB+CCB | BB+CCB+ACEI/ARB |
| 2203 | CCB | BB | BB+ACEI/ARB | D |
| 2204 | CCB | BB | BB+ACEI/ARB | ACEI/ARB |
| 2205 | CCB | BB | BB+ACEI/ARB | D+BB |
| 2206 | CCB | BB | BB+ACEI/ARB | D+CCB |
| 2207 | CCB | BB | BB+ACEI/ARB | D+ACEI/ARB |
| 2208 | CCB | BB | BB+ACEI/ARB | BB+CCB |
| 2209 | CCB | BB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 2210 | CCB | BB | BB+ACEI/ARB | D+BB+CCB |
| 2211 | CCB | BB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 2212 | CCB | BB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2213 | CCB | BB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2214 | CCB | BB | CCB+ACEI/ARB | D |
| 2215 | CCB | BB | CCB+ACEI/ARB | ACEI/ARB |
| 2216 | CCB | BB | CCB+ACEI/ARB | D+BB |
| 2217 | CCB | BB | CCB+ACEI/ARB | D+CCB |
| 2218 | CCB | BB | CCB+ACEI/ARB | D+ACEI/ARB |
| 2219 | CCB | BB | CCB+ACEI/ARB | BB+CCB |
| 2220 | CCB | BB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 2221 | CCB | BB | CCB+ACEI/ARB | D+BB+CCB |
| 2222 | CCB | BB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 2223 | CCB | BB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2224 | CCB | BB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2225 | CCB | ACEI/ARB | D | BB |
| 2226 | CCB | ACEI/ARB | D | D+BB |
| 2227 | CCB | ACEI/ARB | D | D+CCB |
| 2228 | CCB | ACEI/ARB | D | D+ACEI/ARB |
| 2229 | CCB | ACEI/ARB | D | BB+CCB |
| 2230 | CCB | ACEI/ARB | D | BB+ACEI/ARB |
| 2231 | CCB | ACEI/ARB | D | CCB+ACEI/ARB |
| 2232 | CCB | ACEI/ARB | BB | D |
| 2233 | CCB | ACEI/ARB | BB | D+BB |
| 2234 | CCB | ACEI/ARB | BB | D+CCB |
| 2235 | CCB | ACEI/ARB | BB | D+ACEI/ARB |
| 2236 | CCB | ACEI/ARB | BB | BB+CCB |
| 2237 | CCB | ACEI/ARB | BB | BB+ACEI/ARB |
| 2238 | CCB | ACEI/ARB | BB | CCB+ACEI/ARB |
| 2239 | CCB | ACEI/ARB | D+BB | D |
| 2240 | CCB | ACEI/ARB | D+BB | BB |
| 2241 | CCB | ACEI/ARB | D+BB | D+CCB |
| 2242 | CCB | ACEI/ARB | D+BB | D+ACEI/ARB |
| 2243 | CCB | ACEI/ARB | D+BB | BB+CCB |
| 2244 | CCB | ACEI/ARB | D+BB | BB+ACEI/ARB |
| 2245 | CCB | ACEI/ARB | D+BB | CCB+ACEI/ARB |
| 2246 | CCB | ACEI/ARB | D+BB | D+BB+CCB |
| 2247 | CCB | ACEI/ARB | D+BB | D+BB+ACEI/ARB |
| 2248 | CCB | ACEI/ARB | D+BB | D+CCB+ACEI/ARB |
| 2249 | CCB | ACEI/ARB | D+BB | BB+CCB+ACEI/ARB |
| 2250 | CCB | ACEI/ARB | D+CCB | D |
| 2251 | CCB | ACEI/ARB | D+CCB | BB |
| 2252 | CCB | ACEI/ARB | D+CCB | D+BB |
| 2253 | CCB | ACEI/ARB | D+CCB | D+ACEI/ARB |
| 2254 | CCB | ACEI/ARB | D+CCB | BB+CCB |
| 2255 | CCB | ACEI/ARB | D+CCB | BB+ACEI/ARB |
| 2256 | CCB | ACEI/ARB | D+CCB | CCB+ACEI/ARB |
| 2257 | CCB | ACEI/ARB | D+CCB | D+BB+CCB |
| 2258 | CCB | ACEI/ARB | D+CCB | D+BB+ACEI/ARB |
| 2259 | CCB | ACEI/ARB | D+CCB | D+CCB+ACEI/ARB |
| 2260 | CCB | ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB |
| 2261 | CCB | ACEI/ARB | D+ACEIs/ARB | D |
| 2262 | CCB | ACEI/ARB | D+ACEIs/ARB | BB |
| 2263 | CCB | ACEI/ARB | D+ACEIs/ARB | D+BB |
| 2264 | CCB | ACEI/ARB | D+ACEIs/ARB | D+CCB |
| 2265 | CCB | ACEI/ARB | D+ACEIs/ARB | BB+CCB |
| 2266 | CCB | ACEI/ARB | D+ACEIs/ARB | BB+ACEI/ARB |
| 2267 | CCB | ACEI/ARB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 2268 | CCB | ACEI/ARB | D+ACEIs/ARB | D+BB+CCB |
| 2269 | CCB | ACEI/ARB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 2270 | CCB | ACEI/ARB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 2271 | CCB | ACEI/ARB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 2272 | CCB | ACEI/ARB | BB+CCB | D |
| 2273 | CCB | ACEI/ARB | BB+CCB | BB |
| 2274 | CCB | ACEI/ARB | BB+CCB | D+BB |
| 2275 | CCB | ACEI/ARB | BB+CCB | D+CCB |
| 2276 | CCB | ACEI/ARB | BB+CCB | D+ACEI/ARB |
| 2277 | CCB | ACEI/ARB | BB+CCB | BB+ACEI/ARB |
| 2278 | CCB | ACEI/ARB | BB+CCB | CCB+ACEI/ARB |
| 2279 | CCB | ACEI/ARB | BB+CCB | D+BB+CCB |
| 2280 | CCB | ACEI/ARB | BB+CCB | D+BB+ACEI/ARB |
| 2281 | CCB | ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB |
| 2282 | CCB | ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB |
| 2283 | CCB | ACEI/ARB | BB+ACEI/ARB | D |
| 2284 | CCB | ACEI/ARB | BB+ACEI/ARB | BB |
| 2285 | CCB | ACEI/ARB | BB+ACEI/ARB | D+BB |
| 2286 | CCB | ACEI/ARB | BB+ACEI/ARB | D+CCB |
| 2287 | CCB | ACEI/ARB | BB+ACEI/ARB | D+ACEI/ARB |
| 2288 | CCB | ACEI/ARB | BB+ACEI/ARB | BB+CCB |
| 2289 | CCB | ACEI/ARB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 2290 | CCB | ACEI/ARB | BB+ACEI/ARB | D+BB+CCB |
| 2291 | CCB | ACEI/ARB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 2292 | CCB | ACEI/ARB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2293 | CCB | ACEI/ARB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2294 | CCB | ACEI/ARB | CCB+ACEI/ARB | D |
| 2295 | CCB | ACEI/ARB | CCB+ACEI/ARB | BB |
| 2296 | CCB | ACEI/ARB | CCB+ACEI/ARB | D+BB |
| 2297 | CCB | ACEI/ARB | CCB+ACEI/ARB | D+CCB |
| 2298 | CCB | ACEI/ARB | CCB+ACEI/ARB | D+ACEI/ARB |
| 2299 | CCB | ACEI/ARB | CCB+ACEI/ARB | BB+CCB |
| 2300 | CCB | ACEI/ARB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 2301 | CCB | ACEI/ARB | CCB+ACEI/ARB | D+BB+CCB |
| 2302 | CCB | ACEI/ARB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 2303 | CCB | ACEI/ARB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2304 | CCB | ACEI/ARB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2305 | CCB | D+BB | D | BB |
| 2306 | CCB | D+BB | D | ACEI/ARB |
| 2307 | CCB | D+BB | D | D+CCB |
| 2308 | CCB | D+BB | D | D+ACEI/ARB |
| 2309 | CCB | D+BB | D | BB+CCB |
| 2310 | CCB | D+BB | D | BB+ACEI/ARB |
| 2311 | CCB | D+BB | D | CCB+ACEI/ARB |
| 2312 | CCB | D+BB | D | D+BB+CCB |
| 2313 | CCB | D+BB | D | D+BB+ACEI/ARB |
| 2314 | CCB | D+BB | D | D+CCB+ACEI/ARB |
| 2315 | CCB | D+BB | D | BB+CCB+ACEI/ARB |
| 2316 | CCB | D+BB | BB | D |
| 2317 | CCB | D+BB | BB | ACEI/ARB |
| 2318 | CCB | D+BB | BB | D+CCB |
| 2319 | CCB | D+BB | BB | D+ACEI/ARB |
| 2320 | CCB | D+BB | BB | BB+CCB |
| 2321 | CCB | D+BB | BB | BB+ACEI/ARB |
| 2322 | CCB | D+BB | BB | CCB+ACEI/ARB |
| 2323 | CCB | D+BB | BB | D+BB+CCB |
| 2324 | CCB | D+BB | BB | D+BB+ACEI/ARB |
| 2325 | CCB | D+BB | BB | D+CCB+ACEI/ARB |
| 2326 | CCB | D+BB | BB | BB+CCB+ACEI/ARB |
| 2327 | CCB | D+BB | ACEI/ARB | D |
| 2328 | CCB | D+BB | ACEI/ARB | BB |
| 2329 | CCB | D+BB | ACEI/ARB | D+CCB |
| 2330 | CCB | D+BB | ACEI/ARB | D+ACEI/ARB |
| 2331 | CCB | D+BB | ACEI/ARB | BB+CCB |
| 2332 | CCB | D+BB | ACEI/ARB | BB+ACEI/ARB |
| 2333 | CCB | D+BB | ACEI/ARB | CCB+ACEI/ARB |
| 2334 | CCB | D+BB | ACEI/ARB | D+BB+CCB |
| 2335 | CCB | D+BB | ACEI/ARB | D+BB+ACEI/ARB |
| 2336 | CCB | D+BB | ACEI/ARB | D+CCB+ACEI/ARB |
| 2337 | CCB | D+BB | ACEI/ARB | BB+CCB+ACEI/ARB |
| 2338 | CCB | D+BB | D+CCB | D |
| 2339 | CCB | D+BB | D+CCB | BB |
| 2340 | CCB | D+BB | D+CCB | ACEI/ARB |
| 2341 | CCB | D+BB | D+CCB | D+ACEI/ARB |
| 2342 | CCB | D+BB | D+CCB | BB+CCB |
| 2343 | CCB | D+BB | D+CCB | BB+ACEI/ARB |
| 2344 | CCB | D+BB | D+CCB | CCB+ACEI/ARB |
| 2345 | CCB | D+BB | D+CCB | D+BB+CCB |
| 2346 | CCB | D+BB | D+CCB | D+BB+ACEI/ARB |
| 2347 | CCB | D+BB | D+CCB | D+CCB+ACEI/ARB |
| 2348 | CCB | D+BB | D+CCB | BB+CCB+ACEI/ARB |
| 2349 | CCB | D+BB | D+ACEIs/ARB | D |
| 2350 | CCB | D+BB | D+ACEIs/ARB | BB |
| 2351 | CCB | D+BB | D+ACEIs/ARB | ACEI/ARB |
| 2352 | CCB | D+BB | D+ACEIs/ARB | D+CCB |
| 2353 | CCB | D+BB | D+ACEIs/ARB | BB+CCB |
| 2354 | CCB | D+BB | D+ACEIs/ARB | BB+ACEI/ARB |
| 2355 | CCB | D+BB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 2356 | CCB | D+BB | D+ACEIs/ARB | D+BB+CCB |
| 2357 | CCB | D+BB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 2358 | CCB | D+BB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 2359 | CCB | D+BB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 2360 | CCB | D+BB | BB+CCB | D |
| 2361 | CCB | D+BB | BB+CCB | BB |
| 2362 | CCB | D+BB | BB+CCB | ACEI/ARB |
| 2363 | CCB | D+BB | BB+CCB | D+CCB |
| 2364 | CCB | D+BB | BB+CCB | D+ACEI/ARB |
| 2365 | CCB | D+BB | BB+CCB | BB+ACEI/ARB |
| 2366 | CCB | D+BB | BB+CCB | CCB+ACEI/ARB |
| 2367 | CCB | D+BB | BB+CCB | D+BB+CCB |
| 2368 | CCB | D+BB | BB+CCB | D+BB+ACEI/ARB |
| 2369 | CCB | D+BB | BB+CCB | D+CCB+ACEI/ARB |
| 2370 | CCB | D+BB | BB+CCB | BB+CCB+ACEI/ARB |
| 2371 | CCB | D+BB | BB+ACEI/ARB | D |
| 2372 | CCB | D+BB | BB+ACEI/ARB | BB |
| 2373 | CCB | D+BB | BB+ACEI/ARB | ACEI/ARB |
| 2374 | CCB | D+BB | BB+ACEI/ARB | D+CCB |
| 2375 | CCB | D+BB | BB+ACEI/ARB | D+ACEI/ARB |
| 2376 | CCB | D+BB | BB+ACEI/ARB | BB+CCB |
| 2377 | CCB | D+BB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 2378 | CCB | D+BB | BB+ACEI/ARB | D+BB+CCB |
| 2379 | CCB | D+BB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 2380 | CCB | D+BB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2381 | CCB | D+BB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2382 | CCB | D+BB | CCB+ACEI/ARB | D |
| 2383 | CCB | D+BB | CCB+ACEI/ARB | BB |
| 2384 | CCB | D+BB | CCB+ACEI/ARB | ACEI/ARB |
| 2385 | CCB | D+BB | CCB+ACEI/ARB | D+CCB |
| 2386 | CCB | D+BB | CCB+ACEI/ARB | D+ACEI/ARB |
| 2387 | CCB | D+BB | CCB+ACEI/ARB | BB+CCB |
| 2388 | CCB | D+BB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 2389 | CCB | D+BB | CCB+ACEI/ARB | D+BB+CCB |
| 2390 | CCB | D+BB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 2391 | CCB | D+BB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2392 | CCB | D+BB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2393 | CCB | D+BB | D+BB+CCB | D |
| 2394 | CCB | D+BB | D+BB+CCB | BB |
| 2395 | CCB | D+BB | D+BB+CCB | ACEI/ARB |
| 2396 | CCB | D+BB | D+BB+CCB | D+CCB |
| 2397 | CCB | D+BB | D+BB+CCB | D+ACEI/ARB |
| 2398 | CCB | D+BB | D+BB+CCB | BB+CCB |
| 2399 | CCB | D+BB | D+BB+CCB | BB+ACEI/ARB |
| 2400 | CCB | D+BB | D+BB+CCB | CCB+ACEI/ARB |
| 2401 | CCB | D+BB | D+BB+CCB | D+BB+ACEI/ARB |
| 2402 | CCB | D+BB | D+BB+CCB | D+CCB+ACEI/ARB |
| 2403 | CCB | D+BB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 2404 | CCB | D+BB | D+BB+ACEI/ARB | D |
| 2405 | CCB | D+BB | D+BB+ACEI/ARB | BB |
| 2406 | CCB | D+BB | D+BB+ACEI/ARB | ACEI/ARB |
| 2407 | CCB | D+BB | D+BB+ACEI/ARB | D+CCB |
| 2408 | CCB | D+BB | D+BB+ACEI/ARB | D+ACEI/ARB |
| 2409 | CCB | D+BB | D+BB+ACEI/ARB | BB+CCB |
| 2410 | CCB | D+BB | D+BB+ACEI/ARB | BB+ACEI/ARB |
| 2411 | CCB | D+BB | D+BB+ACEI/ARB | CCB+ACEI/ARB |
| 2412 | CCB | D+BB | D+BB+ACEI/ARB | D+BB+CCB |
| 2413 | CCB | D+BB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2414 | CCB | D+BB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2415 | CCB | D+BB | D+CCB+ACEI/ARB | D |
| 2416 | CCB | D+BB | D+CCB+ACEI/ARB | BB |
| 2417 | CCB | D+BB | D+CCB+ACEI/ARB | ACEI/ARB |
| 2418 | CCB | D+BB | D+CCB+ACEI/ARB | D+CCB |
| 2419 | CCB | D+BB | D+CCB+ACEI/ARB | D+ACEI/ARB |
| 2420 | CCB | D+BB | D+CCB+ACEI/ARB | BB+CCB |
| 2421 | CCB | D+BB | D+CCB+ACEI/ARB | BB+ACEI/ARB |
| 2422 | CCB | D+BB | D+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 2423 | CCB | D+BB | D+CCB+ACEI/ARB | D+BB+CCB |
| 2424 | CCB | D+BB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 2425 | CCB | D+BB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2426 | CCB | D+BB | BB+CCB+ACEI/ARB | D |
| 2427 | CCB | D+BB | BB+CCB+ACEI/ARB | BB |
| 2428 | CCB | D+BB | BB+CCB+ACEI/ARB | ACEI/ARB |
| 2429 | CCB | D+BB | BB+CCB+ACEI/ARB | D+CCB |
| 2430 | CCB | D+BB | BB+CCB+ACEI/ARB | D+ACEI/ARB |
| 2431 | CCB | D+BB | BB+CCB+ACEI/ARB | BB+CCB |
| 2432 | CCB | D+BB | BB+CCB+ACEI/ARB | BB+ACEI/ARB |
| 2433 | CCB | D+BB | BB+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 2434 | CCB | D+BB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 2435 | CCB | D+BB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 2436 | CCB | D+BB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2437 | CCB | D+CCB | D | BB |
| 2438 | CCB | D+CCB | D | ACEI/ARB |
| 2439 | CCB | D+CCB | D | D+BB |
| 2440 | CCB | D+CCB | D | D+ACEI/ARB |
| 2441 | CCB | D+CCB | D | BB+CCB |
| 2442 | CCB | D+CCB | D | BB+ACEI/ARB |
| 2443 | CCB | D+CCB | D | CCB+ACEI/ARB |
| 2444 | CCB | D+CCB | D | D+BB+CCB |
| 2445 | CCB | D+CCB | D | D+BB+ACEI/ARB |
| 2446 | CCB | D+CCB | D | D+CCB+ACEI/ARB |
| 2447 | CCB | D+CCB | D | BB+CCB+ACEI/ARB |
| 2448 | CCB | D+CCB | BB | D |
| 2449 | CCB | D+CCB | BB | ACEI/ARB |
| 2450 | CCB | D+CCB | BB | D+BB |
| 2451 | CCB | D+CCB | BB | D+ACEI/ARB |
| 2452 | CCB | D+CCB | BB | BB+CCB |
| 2453 | CCB | D+CCB | BB | BB+ACEI/ARB |
| 2454 | CCB | D+CCB | BB | CCB+ACEI/ARB |
| 2455 | CCB | D+CCB | BB | D+BB+CCB |
| 2456 | CCB | D+CCB | BB | D+BB+ACEI/ARB |
| 2457 | CCB | D+CCB | BB | D+CCB+ACEI/ARB |
| 2458 | CCB | D+CCB | BB | BB+CCB+ACEI/ARB |
| 2459 | CCB | D+CCB | ACEI/ARB | D |
| 2460 | CCB | D+CCB | ACEI/ARB | BB |
| 2461 | CCB | D+CCB | ACEI/ARB | D+BB |
| 2462 | CCB | D+CCB | ACEI/ARB | D+ACEI/ARB |
| 2463 | CCB | D+CCB | ACEI/ARB | BB+CCB |
| 2464 | CCB | D+CCB | ACEI/ARB | BB+ACEI/ARB |
| 2465 | CCB | D+CCB | ACEI/ARB | CCB+ACEI/ARB |
| 2466 | CCB | D+CCB | ACEI/ARB | D+BB+CCB |
| 2467 | CCB | D+CCB | ACEI/ARB | D+BB+ACEI/ARB |
| 2468 | CCB | D+CCB | ACEI/ARB | D+CCB+ACEI/ARB |
| 2469 | CCB | D+CCB | ACEI/ARB | BB+CCB+ACEI/ARB |
| 2470 | CCB | D+CCB | D+BB | D |
| 2471 | CCB | D+CCB | D+BB | BB |
| 2472 | CCB | D+CCB | D+BB | ACEI/ARB |
| 2473 | CCB | D+CCB | D+BB | D+ACEI/ARB |
| 2474 | CCB | D+CCB | D+BB | BB+CCB |
| 2475 | CCB | D+CCB | D+BB | BB+ACEI/ARB |
| 2476 | CCB | D+CCB | D+BB | CCB+ACEI/ARB |
| 2477 | CCB | D+CCB | D+BB | D+BB+CCB |
| 2478 | CCB | D+CCB | D+BB | D+BB+ACEI/ARB |
| 2479 | CCB | D+CCB | D+BB | D+CCB+ACEI/ARB |
| 2480 | CCB | D+CCB | D+BB | BB+CCB+ACEI/ARB |
| 2481 | CCB | D+CCB | D+ACEIs/ARB | D |
| 2482 | CCB | D+CCB | D+ACEIs/ARB | BB |
| 2483 | CCB | D+CCB | D+ACEIs/ARB | ACEI/ARB |
| 2484 | CCB | D+CCB | D+ACEIs/ARB | D+BB |
| 2485 | CCB | D+CCB | D+ACEIs/ARB | BB+CCB |
| 2486 | CCB | D+CCB | D+ACEIs/ARB | BB+ACEI/ARB |
| 2487 | CCB | D+CCB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 2488 | CCB | D+CCB | D+ACEIs/ARB | D+BB+CCB |
| 2489 | CCB | D+CCB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 2490 | CCB | D+CCB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 2491 | CCB | D+CCB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 2492 | CCB | D+CCB | BB+CCB | D |
| 2493 | CCB | D+CCB | BB+CCB | BB |
| 2494 | CCB | D+CCB | BB+CCB | ACEI/ARB |
| 2495 | CCB | D+CCB | BB+CCB | D+BB |
| 2496 | CCB | D+CCB | BB+CCB | D+ACEI/ARB |
| 2497 | CCB | D+CCB | BB+CCB | BB+ACEI/ARB |
| 2498 | CCB | D+CCB | BB+CCB | CCB+ACEI/ARB |
| 2499 | CCB | D+CCB | BB+CCB | D+BB+CCB |
| 2500 | CCB | D+CCB | BB+CCB | D+BB+ACEI/ARB |
| 2501 | CCB | D+CCB | BB+CCB | D+CCB+ACEI/ARB |
| 2502 | CCB | D+CCB | BB+CCB | BB+CCB+ACEI/ARB |
| 2503 | CCB | D+CCB | BB+ACEI/ARB | D |
| 2504 | CCB | D+CCB | BB+ACEI/ARB | BB |
| 2505 | CCB | D+CCB | BB+ACEI/ARB | ACEI/ARB |
| 2506 | CCB | D+CCB | BB+ACEI/ARB | D+BB |
| 2507 | CCB | D+CCB | BB+ACEI/ARB | D+ACEI/ARB |
| 2508 | CCB | D+CCB | BB+ACEI/ARB | BB+CCB |
| 2509 | CCB | D+CCB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 2510 | CCB | D+CCB | BB+ACEI/ARB | D+BB+CCB |
| 2511 | CCB | D+CCB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 2512 | CCB | D+CCB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2513 | CCB | D+CCB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2514 | CCB | D+CCB | CCB+ACEI/ARB | D |
| 2515 | CCB | D+CCB | CCB+ACEI/ARB | BB |
| 2516 | CCB | D+CCB | CCB+ACEI/ARB | ACEI/ARB |
| 2517 | CCB | D+CCB | CCB+ACEI/ARB | D+BB |
| 2518 | CCB | D+CCB | CCB+ACEI/ARB | D+ACEI/ARB |
| 2519 | CCB | D+CCB | CCB+ACEI/ARB | BB+CCB |
| 2520 | CCB | D+CCB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 2521 | CCB | D+CCB | CCB+ACEI/ARB | D+BB+CCB |
| 2522 | CCB | D+CCB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 2523 | CCB | D+CCB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2524 | CCB | D+CCB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2525 | CCB | D+CCB | D+BB+CCB | D |
| 2526 | CCB | D+CCB | D+BB+CCB | BB |
| 2527 | CCB | D+CCB | D+BB+CCB | ACEI/ARB |
| 2528 | CCB | D+CCB | D+BB+CCB | D+BB |
| 2529 | CCB | D+CCB | D+BB+CCB | D+ACEI/ARB |
| 2530 | CCB | D+CCB | D+BB+CCB | BB+CCB |
| 2531 | CCB | D+CCB | D+BB+CCB | BB+ACEI/ARB |
| 2532 | CCB | D+CCB | D+BB+CCB | CCB+ACEI/ARB |
| 2533 | CCB | D+CCB | D+BB+CCB | D+BB+ACEI/ARB |
| 2534 | CCB | D+CCB | D+BB+CCB | D+CCB+ACEI/ARB |
| 2535 | CCB | D+CCB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 2536 | CCB | D+CCB | D+BB+ACEI/ARB | D |
| 2537 | CCB | D+CCB | D+BB+ACEI/ARB | BB |
| 2538 | CCB | D+CCB | D+BB+ACEI/ARB | ACEI/ARB |
| 2539 | CCB | D+CCB | D+BB+ACEI/ARB | D+BB |
| 2540 | CCB | D+CCB | D+BB+ACEI/ARB | D+ACEI/ARB |
| 2541 | CCB | D+CCB | D+BB+ACEI/ARB | BB+CCB |
| 2542 | CCB | D+CCB | D+BB+ACEI/ARB | BB+ACEI/ARB |
| 2543 | CCB | D+CCB | D+BB+ACEI/ARB | CCB+ACEI/ARB |
| 2544 | CCB | D+CCB | D+BB+ACEI/ARB | D+BB+CCB |
| 2545 | CCB | D+CCB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2546 | CCB | D+CCB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2547 | CCB | D+CCB | D+CCB+ACEI/ARB | D |
| 2548 | CCB | D+CCB | D+CCB+ACEI/ARB | BB |
| 2549 | CCB | D+CCB | D+CCB+ACEI/ARB | ACEI/ARB |
| 2550 | CCB | D+CCB | D+CCB+ACEI/ARB | D+BB |
| 2551 | CCB | D+CCB | D+CCB+ACEI/ARB | D+ACEI/ARB |
| 2552 | CCB | D+CCB | D+CCB+ACEI/ARB | BB+CCB |
| 2553 | CCB | D+CCB | D+CCB+ACEI/ARB | BB+ACEI/ARB |
| 2554 | CCB | D+CCB | D+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 2555 | CCB | D+CCB | D+CCB+ACEI/ARB | D+BB+CCB |
| 2556 | CCB | D+CCB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 2557 | CCB | D+CCB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2558 | CCB | D+CCB | BB+CCB+ACEI/ARB | D |
| 2559 | CCB | D+CCB | BB+CCB+ACEI/ARB | BB |
| 2560 | CCB | D+CCB | BB+CCB+ACEI/ARB | ACEI/ARB |
| 2561 | CCB | D+CCB | BB+CCB+ACEI/ARB | D+BB |
| 2562 | CCB | D+CCB | BB+CCB+ACEI/ARB | D+ACEI/ARB |
| 2563 | CCB | D+CCB | BB+CCB+ACEI/ARB | BB+CCB |
| 2564 | CCB | D+CCB | BB+CCB+ACEI/ARB | BB+ACEI/ARB |
| 2565 | CCB | D+CCB | BB+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 2566 | CCB | D+CCB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 2567 | CCB | D+CCB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 2568 | CCB | D+CCB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2569 | CCB | D+ACEI/ARB | D | BB |
| 2570 | CCB | D+ACEI/ARB | D | ACEI/ARB |
| 2571 | CCB | D+ACEI/ARB | D | D+BB |
| 2572 | CCB | D+ACEI/ARB | D | D+CCB |
| 2573 | CCB | D+ACEI/ARB | D | BB+CCB |
| 2574 | CCB | D+ACEI/ARB | D | BB+ACEI/ARB |
| 2575 | CCB | D+ACEI/ARB | D | CCB+ACEI/ARB |
| 2576 | CCB | D+ACEI/ARB | D | D+BB+CCB |
| 2577 | CCB | D+ACEI/ARB | D | D+BB+ACEI/ARB |
| 2578 | CCB | D+ACEI/ARB | D | D+CCB+ACEI/ARB |
| 2579 | CCB | D+ACEI/ARB | D | BB+CCB+ACEI/ARB |
| 2580 | CCB | D+ACEI/ARB | BB | D |
| 2581 | CCB | D+ACEI/ARB | BB | ACEI/ARB |
| 2582 | CCB | D+ACEI/ARB | BB | D+BB |
| 2583 | CCB | D+ACEI/ARB | BB | D+CCB |
| 2584 | CCB | D+ACEI/ARB | BB | BB+CCB |
| 2585 | CCB | D+ACEI/ARB | BB | BB+ACEI/ARB |
| 2586 | CCB | D+ACEI/ARB | BB | CCB+ACEI/ARB |
| 2587 | CCB | D+ACEI/ARB | BB | D+BB+CCB |
| 2588 | CCB | D+ACEI/ARB | BB | D+BB+ACEI/ARB |
| 2589 | CCB | D+ACEI/ARB | BB | D+CCB+ACEI/ARB |
| 2590 | CCB | D+ACEI/ARB | BB | BB+CCB+ACEI/ARB |
| 2591 | CCB | D+ACEI/ARB | ACEI/ARB | D |
| 2592 | CCB | D+ACEI/ARB | ACEI/ARB | BB |
| 2593 | CCB | D+ACEI/ARB | ACEI/ARB | D+BB |
| 2594 | CCB | D+ACEI/ARB | ACEI/ARB | D+CCB |
| 2595 | CCB | D+ACEI/ARB | ACEI/ARB | BB+CCB |
| 2596 | CCB | D+ACEI/ARB | ACEI/ARB | BB+ACEI/ARB |
| 2597 | CCB | D+ACEI/ARB | ACEI/ARB | CCB+ACEI/ARB |
| 2598 | CCB | D+ACEI/ARB | ACEI/ARB | D+BB+CCB |
| 2599 | CCB | D+ACEI/ARB | ACEI/ARB | D+BB+ACEI/ARB |
| 2600 | CCB | D+ACEI/ARB | ACEI/ARB | D+CCB+ACEI/ARB |
| 2601 | CCB | D+ACEI/ARB | ACEI/ARB | BB+CCB+ACEI/ARB |
| 2602 | CCB | D+ACEI/ARB | D+BB | D |
| 2603 | CCB | D+ACEI/ARB | D+BB | BB |
| 2604 | CCB | D+ACEI/ARB | D+BB | ACEI/ARB |
| 2605 | CCB | D+ACEI/ARB | D+BB | D+CCB |
| 2606 | CCB | D+ACEI/ARB | D+BB | BB+CCB |
| 2607 | CCB | D+ACEI/ARB | D+BB | BB+ACEI/ARB |
| 2608 | CCB | D+ACEI/ARB | D+BB | CCB+ACEI/ARB |
| 2609 | CCB | D+ACEI/ARB | D+BB | D+BB+CCB |
| 2610 | CCB | D+ACEI/ARB | D+BB | D+BB+ACEI/ARB |
| 2611 | CCB | D+ACEI/ARB | D+BB | D+CCB+ACEI/ARB |
| 2612 | CCB | D+ACEI/ARB | D+BB | BB+CCB+ACEI/ARB |
| 2613 | CCB | D+ACEI/ARB | D+CCB | D |
| 2614 | CCB | D+ACEI/ARB | D+CCB | BB |
| 2615 | CCB | D+ACEI/ARB | D+CCB | ACEI/ARB |
| 2616 | CCB | D+ACEI/ARB | D+CCB | D+BB |
| 2617 | CCB | D+ACEI/ARB | D+CCB | BB+CCB |
| 2618 | CCB | D+ACEI/ARB | D+CCB | BB+ACEI/ARB |
| 2619 | CCB | D+ACEI/ARB | D+CCB | CCB+ACEI/ARB |
| 2620 | CCB | D+ACEI/ARB | D+CCB | D+BB+CCB |
| 2621 | CCB | D+ACEI/ARB | D+CCB | D+BB+ACEI/ARB |
| 2622 | CCB | D+ACEI/ARB | D+CCB | D+CCB+ACEI/ARB |
| 2623 | CCB | D+ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB |
| 2624 | CCB | D+ACEI/ARB | BB+CCB | D |
| 2625 | CCB | D+ACEI/ARB | BB+CCB | BB |
| 2626 | CCB | D+ACEI/ARB | BB+CCB | ACEI/ARB |
| 2627 | CCB | D+ACEI/ARB | BB+CCB | D+BB |
| 2628 | CCB | D+ACEI/ARB | BB+CCB | D+CCB |
| 2629 | CCB | D+ACEI/ARB | BB+CCB | BB+ACEI/ARB |
| 2630 | CCB | D+ACEI/ARB | BB+CCB | CCB+ACEI/ARB |
| 2631 | CCB | D+ACEI/ARB | BB+CCB | D+BB+CCB |
| 2632 | CCB | D+ACEI/ARB | BB+CCB | D+BB+ACEI/ARB |
| 2633 | CCB | D+ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB |
| 2634 | CCB | D+ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB |
| 2635 | CCB | D+ACEI/ARB | BB+ACEI/ARB | D |
| 2636 | CCB | D+ACEI/ARB | BB+ACEI/ARB | BB |
| 2637 | CCB | D+ACEI/ARB | BB+ACEI/ARB | ACEI/ARB |
| 2638 | CCB | D+ACEI/ARB | BB+ACEI/ARB | D+BB |
| 2639 | CCB | D+ACEI/ARB | BB+ACEI/ARB | D+CCB |
| 2640 | CCB | D+ACEI/ARB | BB+ACEI/ARB | BB+CCB |
| 2641 | CCB | D+ACEI/ARB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 2642 | CCB | D+ACEI/ARB | BB+ACEI/ARB | D+BB+CCB |
| 2643 | CCB | D+ACEI/ARB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 2644 | CCB | D+ACEI/ARB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2645 | CCB | D+ACEI/ARB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2646 | CCB | D+ACEI/ARB | CCB+ACEI/ARB | D |
| 2647 | CCB | D+ACEI/ARB | CCB+ACEI/ARB | BB |
| 2648 | CCB | D+ACEI/ARB | CCB+ACEI/ARB | ACEI/ARB |
| 2649 | CCB | D+ACEI/ARB | CCB+ACEI/ARB | D+BB |
| 2650 | CCB | D+ACEI/ARB | CCB+ACEI/ARB | D+CCB |
| 2651 | CCB | D+ACEI/ARB | CCB+ACEI/ARB | BB+CCB |
| 2652 | CCB | D+ACEI/ARB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 2653 | CCB | D+ACEI/ARB | CCB+ACEI/ARB | D+BB+CCB |
| 2654 | CCB | D+ACEI/ARB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 2655 | CCB | D+ACEI/ARB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2656 | CCB | D+ACEI/ARB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2657 | CCB | D+ACEI/ARB | D+BB+CCB | D |
| 2658 | CCB | D+ACEI/ARB | D+BB+CCB | BB |
| 2659 | CCB | D+ACEI/ARB | D+BB+CCB | ACEI/ARB |
| 2660 | CCB | D+ACEI/ARB | D+BB+CCB | D+BB |
| 2661 | CCB | D+ACEI/ARB | D+BB+CCB | D+CCB |
| 2662 | CCB | D+ACEI/ARB | D+BB+CCB | BB+CCB |
| 2663 | CCB | D+ACEI/ARB | D+BB+CCB | BB+ACEI/ARB |
| 2664 | CCB | D+ACEI/ARB | D+BB+CCB | CCB+ACEI/ARB |
| 2665 | CCB | D+ACEI/ARB | D+BB+CCB | D+BB+ACEI/ARB |
| 2666 | CCB | D+ACEI/ARB | D+BB+CCB | D+CCB+ACEI/ARB |
| 2667 | CCB | D+ACEI/ARB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 2668 | CCB | D+ACEI/ARB | D+BB+ACEI/ARB | D |
| 2669 | CCB | D+ACEI/ARB | D+BB+ACEI/ARB | BB |
| 2670 | CCB | D+ACEI/ARB | D+BB+ACEI/ARB | ACEI/ARB |
| 2671 | CCB | D+ACEI/ARB | D+BB+ACEI/ARB | D+BB |
| 2672 | CCB | D+ACEI/ARB | D+BB+ACEI/ARB | D+CCB |
| 2673 | CCB | D+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB |
| 2674 | CCB | D+ACEI/ARB | D+BB+ACEI/ARB | BB+ACEI/ARB |
| 2675 | CCB | D+ACEI/ARB | D+BB+ACEI/ARB | CCB+ACEI/ARB |
| 2676 | CCB | D+ACEI/ARB | D+BB+ACEI/ARB | D+BB+CCB |
| 2677 | CCB | D+ACEI/ARB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2678 | CCB | D+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2679 | CCB | D+ACEI/ARB | D+CCB+ACEI/ARB | D |
| 2680 | CCB | D+ACEI/ARB | D+CCB+ACEI/ARB | BB |
| 2681 | CCB | D+ACEI/ARB | D+CCB+ACEI/ARB | ACEI/ARB |
| 2682 | CCB | D+ACEI/ARB | D+CCB+ACEI/ARB | D+BB |
| 2683 | CCB | D+ACEI/ARB | D+CCB+ACEI/ARB | D+CCB |
| 2684 | CCB | D+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB |
| 2685 | CCB | D+ACEI/ARB | D+CCB+ACEI/ARB | BB+ACEI/ARB |
| 2686 | CCB | D+ACEI/ARB | D+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 2687 | CCB | D+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+CCB |
| 2688 | CCB | D+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 2689 | CCB | D+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2690 | CCB | D+ACEI/ARB | BB+CCB+ACEI/ARB | D |
| 2691 | CCB | D+ACEI/ARB | BB+CCB+ACEI/ARB | BB |
| 2692 | CCB | D+ACEI/ARB | BB+CCB+ACEI/ARB | ACEI/ARB |
| 2693 | CCB | D+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB |
| 2694 | CCB | D+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB |
| 2695 | CCB | D+ACEI/ARB | BB+CCB+ACEI/ARB | BB+CCB |
| 2696 | CCB | D+ACEI/ARB | BB+CCB+ACEI/ARB | BB+ACEI/ARB |
| 2697 | CCB | D+ACEI/ARB | BB+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 2698 | CCB | D+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 2699 | CCB | D+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 2700 | CCB | D+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2701 | CCB | BB+CCB | D | BB |
| 2702 | CCB | BB+CCB | D | ACEI/ARB |
| 2703 | CCB | BB+CCB | D | D+BB |
| 2704 | CCB | BB+CCB | D | D+CCB |
| 2705 | CCB | BB+CCB | D | D+ACEI/ARB |
| 2706 | CCB | BB+CCB | D | BB+ACEI/ARB |
| 2707 | CCB | BB+CCB | D | CCB+ACEI/ARB |
| 2708 | CCB | BB+CCB | D | D+BB+CCB |
| 2709 | CCB | BB+CCB | D | D+BB+ACEI/ARB |
| 2710 | CCB | BB+CCB | D | D+CCB+ACEI/ARB |
| 2711 | CCB | BB+CCB | D | BB+CCB+ACEI/ARB |
| 2712 | CCB | BB+CCB | BB | D |
| 2713 | CCB | BB+CCB | BB | ACEI/ARB |
| 2714 | CCB | BB+CCB | BB | D+BB |
| 2715 | CCB | BB+CCB | BB | D+CCB |
| 2716 | CCB | BB+CCB | BB | D+ACEI/ARB |
| 2717 | CCB | BB+CCB | BB | BB+ACEI/ARB |
| 2718 | CCB | BB+CCB | BB | CCB+ACEI/ARB |
| 2719 | CCB | BB+CCB | BB | D+BB+CCB |
| 2720 | CCB | BB+CCB | BB | D+BB+ACEI/ARB |
| 2721 | CCB | BB+CCB | BB | D+CCB+ACEI/ARB |
| 2722 | CCB | BB+CCB | BB | BB+CCB+ACEI/ARB |
| 2723 | CCB | BB+CCB | ACEI/ARB | D |
| 2724 | CCB | BB+CCB | ACEI/ARB | BB |
| 2725 | CCB | BB+CCB | ACEI/ARB | D+BB |
| 2726 | CCB | BB+CCB | ACEI/ARB | D+CCB |
| 2727 | CCB | BB+CCB | ACEI/ARB | D+ACEI/ARB |
| 2728 | CCB | BB+CCB | ACEI/ARB | BB+ACEI/ARB |
| 2729 | CCB | BB+CCB | ACEI/ARB | CCB+ACEI/ARB |
| 2730 | CCB | BB+CCB | ACEI/ARB | D+BB+CCB |
| 2731 | CCB | BB+CCB | ACEI/ARB | D+BB+ACEI/ARB |
| 2732 | CCB | BB+CCB | ACEI/ARB | D+CCB+ACEI/ARB |
| 2733 | CCB | BB+CCB | ACEI/ARB | BB+CCB+ACEI/ARB |
| 2734 | CCB | BB+CCB | D+BB | D |
| 2735 | CCB | BB+CCB | D+BB | BB |
| 2736 | CCB | BB+CCB | D+BB | ACEI/ARB |
| 2737 | CCB | BB+CCB | D+BB | D+CCB |
| 2738 | CCB | BB+CCB | D+BB | D+ACEI/ARB |
| 2739 | CCB | BB+CCB | D+BB | BB+ACEI/ARB |
| 2740 | CCB | BB+CCB | D+BB | CCB+ACEI/ARB |
| 2741 | CCB | BB+CCB | D+BB | D+BB+CCB |
| 2742 | CCB | BB+CCB | D+BB | D+BB+ACEI/ARB |
| 2743 | CCB | BB+CCB | D+BB | D+CCB+ACEI/ARB |
| 2744 | CCB | BB+CCB | D+BB | BB+CCB+ACEI/ARB |
| 2745 | CCB | BB+CCB | D+CCB | D |
| 2746 | CCB | BB+CCB | D+CCB | BB |
| 2747 | CCB | BB+CCB | D+CCB | ACEI/ARB |
| 2748 | CCB | BB+CCB | D+CCB | D+BB |
| 2749 | CCB | BB+CCB | D+CCB | D+ACEI/ARB |
| 2750 | CCB | BB+CCB | D+CCB | BB+ACEI/ARB |
| 2751 | CCB | BB+CCB | D+CCB | CCB+ACEI/ARB |
| 2752 | CCB | BB+CCB | D+CCB | D+BB+CCB |
| 2753 | CCB | BB+CCB | D+CCB | D+BB+ACEI/ARB |
| 2754 | CCB | BB+CCB | D+CCB | D+CCB+ACEI/ARB |
| 2755 | CCB | BB+CCB | D+CCB | BB+CCB+ACEI/ARB |
| 2756 | CCB | BB+CCB | D+ACEIs/ARB | D |
| 2757 | CCB | BB+CCB | D+ACEIs/ARB | BB |
| 2758 | CCB | BB+CCB | D+ACEIs/ARB | ACEI/ARB |
| 2759 | CCB | BB+CCB | D+ACEIs/ARB | D+BB |
| 2760 | CCB | BB+CCB | D+ACEIs/ARB | D+CCB |
| 2761 | CCB | BB+CCB | D+ACEIs/ARB | BB+ACEI/ARB |
| 2762 | CCB | BB+CCB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 2763 | CCB | BB+CCB | D+ACEIs/ARB | D+BB+CCB |
| 2764 | CCB | BB+CCB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 2765 | CCB | BB+CCB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 2766 | CCB | BB+CCB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 2767 | CCB | BB+CCB | BB+ACEI/ARB | D |
| 2768 | CCB | BB+CCB | BB+ACEI/ARB | BB |
| 2769 | CCB | BB+CCB | BB+ACEI/ARB | ACEI/ARB |
| 2770 | CCB | BB+CCB | BB+ACEI/ARB | D+BB |
| 2771 | CCB | BB+CCB | BB+ACEI/ARB | D+CCB |
| 2772 | CCB | BB+CCB | BB+ACEI/ARB | D+ACEI/ARB |
| 2773 | CCB | BB+CCB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 2774 | CCB | BB+CCB | BB+ACEI/ARB | D+BB+CCB |
| 2775 | CCB | BB+CCB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 2776 | CCB | BB+CCB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2777 | CCB | BB+CCB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2778 | CCB | BB+CCB | CCB+ACEI/ARB | D |
| 2779 | CCB | BB+CCB | CCB+ACEI/ARB | BB |
| 2780 | CCB | BB+CCB | CCB+ACEI/ARB | ACEI/ARB |
| 2781 | CCB | BB+CCB | CCB+ACEI/ARB | D+BB |
| 2782 | CCB | BB+CCB | CCB+ACEI/ARB | D+CCB |
| 2783 | CCB | BB+CCB | CCB+ACEI/ARB | D+ACEI/ARB |
| 2784 | CCB | BB+CCB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 2785 | CCB | BB+CCB | CCB+ACEI/ARB | D+BB+CCB |
| 2786 | CCB | BB+CCB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 2787 | CCB | BB+CCB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2788 | CCB | BB+CCB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2789 | CCB | BB+CCB | D+BB+CCB | D |
| 2790 | CCB | BB+CCB | D+BB+CCB | BB |
| 2791 | CCB | BB+CCB | D+BB+CCB | ACEI/ARB |
| 2792 | CCB | BB+CCB | D+BB+CCB | D+BB |
| 2793 | CCB | BB+CCB | D+BB+CCB | D+CCB |
| 2794 | CCB | BB+CCB | D+BB+CCB | D+ACEI/ARB |
| 2795 | CCB | BB+CCB | D+BB+CCB | BB+ACEI/ARB |
| 2796 | CCB | BB+CCB | D+BB+CCB | CCB+ACEI/ARB |
| 2797 | CCB | BB+CCB | D+BB+CCB | D+BB+ACEI/ARB |
| 2798 | CCB | BB+CCB | D+BB+CCB | D+CCB+ACEI/ARB |
| 2799 | CCB | BB+CCB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 2800 | CCB | BB+CCB | D+BB+ACEI/ARB | D |
| 2801 | CCB | BB+CCB | D+BB+ACEI/ARB | BB |
| 2802 | CCB | BB+CCB | D+BB+ACEI/ARB | ACEI/ARB |
| 2803 | CCB | BB+CCB | D+BB+ACEI/ARB | D+BB |
| 2804 | CCB | BB+CCB | D+BB+ACEI/ARB | D+CCB |
| 2805 | CCB | BB+CCB | D+BB+ACEI/ARB | D+ACEI/ARB |
| 2806 | CCB | BB+CCB | D+BB+ACEI/ARB | BB+ACEI/ARB |
| 2807 | CCB | BB+CCB | D+BB+ACEI/ARB | CCB+ACEI/ARB |
| 2808 | CCB | BB+CCB | D+BB+ACEI/ARB | D+BB+CCB |
| 2809 | CCB | BB+CCB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2810 | CCB | BB+CCB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2811 | CCB | BB+CCB | D+CCB+ACEI/ARB | D |
| 2812 | CCB | BB+CCB | D+CCB+ACEI/ARB | BB |
| 2813 | CCB | BB+CCB | D+CCB+ACEI/ARB | ACEI/ARB |
| 2814 | CCB | BB+CCB | D+CCB+ACEI/ARB | D+BB |
| 2815 | CCB | BB+CCB | D+CCB+ACEI/ARB | D+CCB |
| 2816 | CCB | BB+CCB | D+CCB+ACEI/ARB | D+ACEI/ARB |
| 2817 | CCB | BB+CCB | D+CCB+ACEI/ARB | BB+ACEI/ARB |
| 2818 | CCB | BB+CCB | D+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 2819 | CCB | BB+CCB | D+CCB+ACEI/ARB | D+BB+CCB |
| 2820 | CCB | BB+CCB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 2821 | CCB | BB+CCB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2822 | CCB | BB+CCB | BB+CCB+ACEI/ARB | D |
| 2823 | CCB | BB+CCB | BB+CCB+ACEI/ARB | BB |
| 2824 | CCB | BB+CCB | BB+CCB+ACEI/ARB | ACEI/ARB |
| 2825 | CCB | BB+CCB | BB+CCB+ACEI/ARB | D+BB |
| 2826 | CCB | BB+CCB | BB+CCB+ACEI/ARB | D+CCB |
| 2827 | CCB | BB+CCB | BB+CCB+ACEI/ARB | D+ACEI/ARB |
| 2828 | CCB | BB+CCB | BB+CCB+ACEI/ARB | BB+ACEI/ARB |
| 2829 | CCB | BB+CCB | BB+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 2830 | CCB | BB+CCB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 2831 | CCB | BB+CCB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 2832 | CCB | BB+CCB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2833 | CCB | BB+ACEI/ARB | D | BB |
| 2834 | CCB | BB+ACEI/ARB | D | ACEI/ARB |
| 2835 | CCB | BB+ACEI/ARB | D | D+BB |
| 2836 | CCB | BB+ACEI/ARB | D | D+CCB |
| 2837 | CCB | BB+ACEI/ARB | D | D+ACEI/ARB |
| 2838 | CCB | BB+ACEI/ARB | D | BB+CCB |
| 2839 | CCB | BB+ACEI/ARB | D | CCB+ACEI/ARB |
| 2840 | CCB | BB+ACEI/ARB | D | D+BB+CCB |
| 2841 | CCB | BB+ACEI/ARB | D | D+BB+ACEI/ARB |
| 2842 | CCB | BB+ACEI/ARB | D | D+CCB+ACEI/ARB |
| 2843 | CCB | BB+ACEI/ARB | D | BB+CCB+ACEI/ARB |
| 2844 | CCB | BB+ACEI/ARB | BB | D |
| 2845 | CCB | BB+ACEI/ARB | BB | ACEI/ARB |
| 2846 | CCB | BB+ACEI/ARB | BB | D+BB |
| 2847 | CCB | BB+ACEI/ARB | BB | D+CCB |
| 2848 | CCB | BB+ACEI/ARB | BB | D+ACEI/ARB |
| 2849 | CCB | BB+ACEI/ARB | BB | BB+CCB |
| 2850 | CCB | BB+ACEI/ARB | BB | CCB+ACEI/ARB |
| 2851 | CCB | BB+ACEI/ARB | BB | D+BB+CCB |
| 2852 | CCB | BB+ACEI/ARB | BB | D+BB+ACEI/ARB |
| 2853 | CCB | BB+ACEI/ARB | BB | D+CCB+ACEI/ARB |
| 2854 | CCB | BB+ACEI/ARB | BB | BB+CCB+ACEI/ARB |
| 2855 | CCB | BB+ACEI/ARB | ACEI/ARB | D |
| 2856 | CCB | BB+ACEI/ARB | ACEI/ARB | BB |
| 2857 | CCB | BB+ACEI/ARB | ACEI/ARB | D+BB |
| 2858 | CCB | BB+ACEI/ARB | ACEI/ARB | D+CCB |
| 2859 | CCB | BB+ACEI/ARB | ACEI/ARB | D+ACEI/ARB |
| 2860 | CCB | BB+ACEI/ARB | ACEI/ARB | BB+CCB |
| 2861 | CCB | BB+ACEI/ARB | ACEI/ARB | CCB+ACEI/ARB |
| 2862 | CCB | BB+ACEI/ARB | ACEI/ARB | D+BB+CCB |
| 2863 | CCB | BB+ACEI/ARB | ACEI/ARB | D+BB+ACEI/ARB |
| 2864 | CCB | BB+ACEI/ARB | ACEI/ARB | D+CCB+ACEI/ARB |
| 2865 | CCB | BB+ACEI/ARB | ACEI/ARB | BB+CCB+ACEI/ARB |
| 2866 | CCB | BB+ACEI/ARB | D+BB | D |
| 2867 | CCB | BB+ACEI/ARB | D+BB | BB |
| 2868 | CCB | BB+ACEI/ARB | D+BB | ACEI/ARB |
| 2869 | CCB | BB+ACEI/ARB | D+BB | D+CCB |
| 2870 | CCB | BB+ACEI/ARB | D+BB | D+ACEI/ARB |
| 2871 | CCB | BB+ACEI/ARB | D+BB | BB+CCB |
| 2872 | CCB | BB+ACEI/ARB | D+BB | CCB+ACEI/ARB |
| 2873 | CCB | BB+ACEI/ARB | D+BB | D+BB+CCB |
| 2874 | CCB | BB+ACEI/ARB | D+BB | D+BB+ACEI/ARB |
| 2875 | CCB | BB+ACEI/ARB | D+BB | D+CCB+ACEI/ARB |
| 2876 | CCB | BB+ACEI/ARB | D+BB | BB+CCB+ACEI/ARB |
| 2877 | CCB | BB+ACEI/ARB | D+CCB | D |
| 2878 | CCB | BB+ACEI/ARB | D+CCB | BB |
| 2879 | CCB | BB+ACEI/ARB | D+CCB | ACEI/ARB |
| 2880 | CCB | BB+ACEI/ARB | D+CCB | D+BB |
| 2881 | CCB | BB+ACEI/ARB | D+CCB | D+ACEI/ARB |
| 2882 | CCB | BB+ACEI/ARB | D+CCB | BB+CCB |
| 2883 | CCB | BB+ACEI/ARB | D+CCB | CCB+ACEI/ARB |
| 2884 | CCB | BB+ACEI/ARB | D+CCB | D+BB+CCB |
| 2885 | CCB | BB+ACEI/ARB | D+CCB | D+BB+ACEI/ARB |
| 2886 | CCB | BB+ACEI/ARB | D+CCB | D+CCB+ACEI/ARB |
| 2887 | CCB | BB+ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB |
| 2888 | CCB | BB+ACEI/ARB | D+ACEIs/ARB | D |
| 2889 | CCB | BB+ACEI/ARB | D+ACEIs/ARB | BB |
| 2890 | CCB | BB+ACEI/ARB | D+ACEIs/ARB | ACEI/ARB |
| 2891 | CCB | BB+ACEI/ARB | D+ACEIs/ARB | D+BB |
| 2892 | CCB | BB+ACEI/ARB | D+ACEIs/ARB | D+CCB |
| 2893 | CCB | BB+ACEI/ARB | D+ACEIs/ARB | BB+CCB |
| 2894 | CCB | BB+ACEI/ARB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 2895 | CCB | BB+ACEI/ARB | D+ACEIs/ARB | D+BB+CCB |
| 2896 | CCB | BB+ACEI/ARB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 2897 | CCB | BB+ACEI/ARB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 2898 | CCB | BB+ACEI/ARB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 2899 | CCB | BB+ACEI/ARB | BB+CCB | D |
| 2900 | CCB | BB+ACEI/ARB | BB+CCB | BB |
| 2901 | CCB | BB+ACEI/ARB | BB+CCB | ACEI/ARB |
| 2902 | CCB | BB+ACEI/ARB | BB+CCB | D+BB |
| 2903 | CCB | BB+ACEI/ARB | BB+CCB | D+CCB |
| 2904 | CCB | BB+ACEI/ARB | BB+CCB | D+ACEI/ARB |
| 2905 | CCB | BB+ACEI/ARB | BB+CCB | CCB+ACEI/ARB |
| 2906 | CCB | BB+ACEI/ARB | BB+CCB | D+BB+CCB |
| 2907 | CCB | BB+ACEI/ARB | BB+CCB | D+BB+ACEI/ARB |
| 2908 | CCB | BB+ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB |
| 2909 | CCB | BB+ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB |
| 2910 | CCB | BB+ACEI/ARB | CCB+ACEI/ARB | D |
| 2911 | CCB | BB+ACEI/ARB | CCB+ACEI/ARB | BB |
| 2912 | CCB | BB+ACEI/ARB | CCB+ACEI/ARB | ACEI/ARB |
| 2913 | CCB | BB+ACEI/ARB | CCB+ACEI/ARB | D+BB |
| 2914 | CCB | BB+ACEI/ARB | CCB+ACEI/ARB | D+CCB |
| 2915 | CCB | BB+ACEI/ARB | CCB+ACEI/ARB | D+ACEI/ARB |
| 2916 | CCB | BB+ACEI/ARB | CCB+ACEI/ARB | BB+CCB |
| 2917 | CCB | BB+ACEI/ARB | CCB+ACEI/ARB | D+BB+CCB |
| 2918 | CCB | BB+ACEI/ARB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 2919 | CCB | BB+ACEI/ARB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2920 | CCB | BB+ACEI/ARB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2921 | CCB | BB+ACEI/ARB | D+BB+CCB | D |
| 2922 | CCB | BB+ACEI/ARB | D+BB+CCB | BB |
| 2923 | CCB | BB+ACEI/ARB | D+BB+CCB | ACEI/ARB |
| 2924 | CCB | BB+ACEI/ARB | D+BB+CCB | D+BB |
| 2925 | CCB | BB+ACEI/ARB | D+BB+CCB | D+CCB |
| 2926 | CCB | BB+ACEI/ARB | D+BB+CCB | D+ACEI/ARB |
| 2927 | CCB | BB+ACEI/ARB | D+BB+CCB | BB+CCB |
| 2928 | CCB | BB+ACEI/ARB | D+BB+CCB | CCB+ACEI/ARB |
| 2929 | CCB | BB+ACEI/ARB | D+BB+CCB | D+BB+ACEI/ARB |
| 2930 | CCB | BB+ACEI/ARB | D+BB+CCB | D+CCB+ACEI/ARB |
| 2931 | CCB | BB+ACEI/ARB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 2932 | CCB | BB+ACEI/ARB | D+BB+ACEI/ARB | D |
| 2933 | CCB | BB+ACEI/ARB | D+BB+ACEI/ARB | BB |
| 2934 | CCB | BB+ACEI/ARB | D+BB+ACEI/ARB | ACEI/ARB |
| 2935 | CCB | BB+ACEI/ARB | D+BB+ACEI/ARB | D+BB |
| 2936 | CCB | BB+ACEI/ARB | D+BB+ACEI/ARB | D+CCB |
| 2937 | CCB | BB+ACEI/ARB | D+BB+ACEI/ARB | D+ACEI/ARB |
| 2938 | CCB | BB+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB |
| 2939 | CCB | BB+ACEI/ARB | D+BB+ACEI/ARB | CCB+ACEI/ARB |
| 2940 | CCB | BB+ACEI/ARB | D+BB+ACEI/ARB | D+BB+CCB |
| 2941 | CCB | BB+ACEI/ARB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2942 | CCB | BB+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2943 | CCB | BB+ACEI/ARB | D+CCB+ACEI/ARB | D |
| 2944 | CCB | BB+ACEI/ARB | D+CCB+ACEI/ARB | BB |
| 2945 | CCB | BB+ACEI/ARB | D+CCB+ACEI/ARB | ACEI/ARB |
| 2946 | CCB | BB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB |
| 2947 | CCB | BB+ACEI/ARB | D+CCB+ACEI/ARB | D+CCB |
| 2948 | CCB | BB+ACEI/ARB | D+CCB+ACEI/ARB | D+ACEI/ARB |
| 2949 | CCB | BB+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB |
| 2950 | CCB | BB+ACEI/ARB | D+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 2951 | CCB | BB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+CCB |
| 2952 | CCB | BB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 2953 | CCB | BB+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 2954 | CCB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D |
| 2955 | CCB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | BB |
| 2956 | CCB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | ACEI/ARB |
| 2957 | CCB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB |
| 2958 | CCB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB |
| 2959 | CCB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+ACEI/ARB |
| 2960 | CCB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | BB+CCB |
| 2961 | CCB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 2962 | CCB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 2963 | CCB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 2964 | CCB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 2965 | CCB | CCB+ACEI/ARB | D | BB |
| 2966 | CCB | CCB+ACEI/ARB | D | ACEI/ARB |
| 2967 | CCB | CCB+ACEI/ARB | D | D+BB |
| 2968 | CCB | CCB+ACEI/ARB | D | D+CCB |
| 2969 | CCB | CCB+ACEI/ARB | D | D+ACEI/ARB |
| 2970 | CCB | CCB+ACEI/ARB | D | BB+CCB |
| 2971 | CCB | CCB+ACEI/ARB | D | BB+ACEI/ARB |
| 2972 | CCB | CCB+ACEI/ARB | D | D+BB+CCB |
| 2973 | CCB | CCB+ACEI/ARB | D | D+BB+ACEI/ARB |
| 2974 | CCB | CCB+ACEI/ARB | D | D+CCB+ACEI/ARB |
| 2975 | CCB | CCB+ACEI/ARB | D | BB+CCB+ACEI/ARB |
| 2976 | CCB | CCB+ACEI/ARB | BB | D |
| 2977 | CCB | CCB+ACEI/ARB | BB | ACEI/ARB |
| 2978 | CCB | CCB+ACEI/ARB | BB | D+BB |
| 2979 | CCB | CCB+ACEI/ARB | BB | D+CCB |
| 2980 | CCB | CCB+ACEI/ARB | BB | D+ACEI/ARB |
| 2981 | CCB | CCB+ACEI/ARB | BB | BB+CCB |
| 2982 | CCB | CCB+ACEI/ARB | BB | BB+ACEI/ARB |
| 2983 | CCB | CCB+ACEI/ARB | BB | D+BB+CCB |
| 2984 | CCB | CCB+ACEI/ARB | BB | D+BB+ACEI/ARB |
| 2985 | CCB | CCB+ACEI/ARB | BB | D+CCB+ACEI/ARB |
| 2986 | CCB | CCB+ACEI/ARB | BB | BB+CCB+ACEI/ARB |
| 2987 | CCB | CCB+ACEI/ARB | ACEI/ARB | D |
| 2988 | CCB | CCB+ACEI/ARB | ACEI/ARB | BB |
| 2989 | CCB | CCB+ACEI/ARB | ACEI/ARB | D+BB |
| 2990 | CCB | CCB+ACEI/ARB | ACEI/ARB | D+CCB |
| 2991 | CCB | CCB+ACEI/ARB | ACEI/ARB | D+ACEI/ARB |
| 2992 | CCB | CCB+ACEI/ARB | ACEI/ARB | BB+CCB |
| 2993 | CCB | CCB+ACEI/ARB | ACEI/ARB | BB+ACEI/ARB |
| 2994 | CCB | CCB+ACEI/ARB | ACEI/ARB | D+BB+CCB |
| 2995 | CCB | CCB+ACEI/ARB | ACEI/ARB | D+BB+ACEI/ARB |
| 2996 | CCB | CCB+ACEI/ARB | ACEI/ARB | D+CCB+ACEI/ARB |
| 2997 | CCB | CCB+ACEI/ARB | ACEI/ARB | BB+CCB+ACEI/ARB |
| 2998 | CCB | CCB+ACEI/ARB | D+BB | D |
| 2999 | CCB | CCB+ACEI/ARB | D+BB | BB |
| 3000 | CCB | CCB+ACEI/ARB | D+BB | ACEI/ARB |
| 3001 | CCB | CCB+ACEI/ARB | D+BB | D+CCB |
| 3002 | CCB | CCB+ACEI/ARB | D+BB | D+ACEI/ARB |
| 3003 | CCB | CCB+ACEI/ARB | D+BB | BB+CCB |
| 3004 | CCB | CCB+ACEI/ARB | D+BB | BB+ACEI/ARB |
| 3005 | CCB | CCB+ACEI/ARB | D+BB | D+BB+CCB |
| 3006 | CCB | CCB+ACEI/ARB | D+BB | D+BB+ACEI/ARB |
| 3007 | CCB | CCB+ACEI/ARB | D+BB | D+CCB+ACEI/ARB |
| 3008 | CCB | CCB+ACEI/ARB | D+BB | BB+CCB+ACEI/ARB |
| 3009 | CCB | CCB+ACEI/ARB | D+CCB | D |
| 3010 | CCB | CCB+ACEI/ARB | D+CCB | BB |
| 3011 | CCB | CCB+ACEI/ARB | D+CCB | ACEI/ARB |
| 3012 | CCB | CCB+ACEI/ARB | D+CCB | D+BB |
| 3013 | CCB | CCB+ACEI/ARB | D+CCB | D+ACEI/ARB |
| 3014 | CCB | CCB+ACEI/ARB | D+CCB | BB+CCB |
| 3015 | CCB | CCB+ACEI/ARB | D+CCB | BB+ACEI/ARB |
| 3016 | CCB | CCB+ACEI/ARB | D+CCB | D+BB+CCB |
| 3017 | CCB | CCB+ACEI/ARB | D+CCB | D+BB+ACEI/ARB |
| 3018 | CCB | CCB+ACEI/ARB | D+CCB | D+CCB+ACEI/ARB |
| 3019 | CCB | CCB+ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB |
| 3020 | CCB | CCB+ACEI/ARB | D+ACEIs/ARB | D |
| 3021 | CCB | CCB+ACEI/ARB | D+ACEIs/ARB | BB |
| 3022 | CCB | CCB+ACEI/ARB | D+ACEIs/ARB | ACEI/ARB |
| 3023 | CCB | CCB+ACEI/ARB | D+ACEIs/ARB | D+BB |
| 3024 | CCB | CCB+ACEI/ARB | D+ACEIs/ARB | D+CCB |
| 3025 | CCB | CCB+ACEI/ARB | D+ACEIs/ARB | BB+CCB |
| 3026 | CCB | CCB+ACEI/ARB | D+ACEIs/ARB | BB+ACEI/ARB |
| 3027 | CCB | CCB+ACEI/ARB | D+ACEIs/ARB | D+BB+CCB |
| 3028 | CCB | CCB+ACEI/ARB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 3029 | CCB | CCB+ACEI/ARB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 3030 | CCB | CCB+ACEI/ARB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 3031 | CCB | CCB+ACEI/ARB | BB+CCB | D |
| 3032 | CCB | CCB+ACEI/ARB | BB+CCB | BB |
| 3033 | CCB | CCB+ACEI/ARB | BB+CCB | ACEI/ARB |
| 3034 | CCB | CCB+ACEI/ARB | BB+CCB | D+BB |
| 3035 | CCB | CCB+ACEI/ARB | BB+CCB | D+CCB |
| 3036 | CCB | CCB+ACEI/ARB | BB+CCB | D+ACEI/ARB |
| 3037 | CCB | CCB+ACEI/ARB | BB+CCB | BB+ACEI/ARB |
| 3038 | CCB | CCB+ACEI/ARB | BB+CCB | D+BB+CCB |
| 3039 | CCB | CCB+ACEI/ARB | BB+CCB | D+BB+ACEI/ARB |
| 3040 | CCB | CCB+ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB |
| 3041 | CCB | CCB+ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB |
| 3042 | CCB | CCB+ACEI/ARB | BB+ACEI/ARB | D |
| 3043 | CCB | CCB+ACEI/ARB | BB+ACEI/ARB | BB |
| 3044 | CCB | CCB+ACEI/ARB | BB+ACEI/ARB | ACEI/ARB |
| 3045 | CCB | CCB+ACEI/ARB | BB+ACEI/ARB | D+BB |
| 3046 | CCB | CCB+ACEI/ARB | BB+ACEI/ARB | D+CCB |
| 3047 | CCB | CCB+ACEI/ARB | BB+ACEI/ARB | D+ACEI/ARB |
| 3048 | CCB | CCB+ACEI/ARB | BB+ACEI/ARB | BB+CCB |
| 3049 | CCB | CCB+ACEI/ARB | BB+ACEI/ARB | D+BB+CCB |
| 3050 | CCB | CCB+ACEI/ARB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 3051 | CCB | CCB+ACEI/ARB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3052 | CCB | CCB+ACEI/ARB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3053 | CCB | CCB+ACEI/ARB | D+BB+CCB | D |
| 3054 | CCB | CCB+ACEI/ARB | D+BB+CCB | BB |
| 3055 | CCB | CCB+ACEI/ARB | D+BB+CCB | ACEI/ARB |
| 3056 | CCB | CCB+ACEI/ARB | D+BB+CCB | D+BB |
| 3057 | CCB | CCB+ACEI/ARB | D+BB+CCB | D+CCB |
| 3058 | CCB | CCB+ACEI/ARB | D+BB+CCB | D+ACEI/ARB |
| 3059 | CCB | CCB+ACEI/ARB | D+BB+CCB | BB+CCB |
| 3060 | CCB | CCB+ACEI/ARB | D+BB+CCB | BB+ACEI/ARB |
| 3061 | CCB | CCB+ACEI/ARB | D+BB+CCB | D+BB+ACEI/ARB |
| 3062 | CCB | CCB+ACEI/ARB | D+BB+CCB | D+CCB+ACEI/ARB |
| 3063 | CCB | CCB+ACEI/ARB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 3064 | CCB | CCB+ACEI/ARB | D+BB+ACEI/ARB | D |
| 3065 | CCB | CCB+ACEI/ARB | D+BB+ACEI/ARB | BB |
| 3066 | CCB | CCB+ACEI/ARB | D+BB+ACEI/ARB | ACEI/ARB |
| 3067 | CCB | CCB+ACEI/ARB | D+BB+ACEI/ARB | D+BB |
| 3068 | CCB | CCB+ACEI/ARB | D+BB+ACEI/ARB | D+CCB |
| 3069 | CCB | CCB+ACEI/ARB | D+BB+ACEI/ARB | D+ACEI/ARB |
| 3070 | CCB | CCB+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB |
| 3071 | CCB | CCB+ACEI/ARB | D+BB+ACEI/ARB | BB+ACEI/ARB |
| 3072 | CCB | CCB+ACEI/ARB | D+BB+ACEI/ARB | D+BB+CCB |
| 3073 | CCB | CCB+ACEI/ARB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3074 | CCB | CCB+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3075 | CCB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | D |
| 3076 | CCB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | BB |
| 3077 | CCB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | ACEI/ARB |
| 3078 | CCB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB |
| 3079 | CCB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | D+CCB |
| 3080 | CCB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | D+ACEI/ARB |
| 3081 | CCB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB |
| 3082 | CCB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | BB+ACEI/ARB |
| 3083 | CCB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+CCB |
| 3084 | CCB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 3085 | CCB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3086 | CCB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D |
| 3087 | CCB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | BB |
| 3088 | CCB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | ACEI/ARB |
| 3089 | CCB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB |
| 3090 | CCB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB |
| 3091 | CCB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+ACEI/ARB |
| 3092 | CCB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | BB+CCB |
| 3093 | CCB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | BB+ACEI/ARB |
| 3094 | CCB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 3095 | CCB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 3096 | CCB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3097 | ACEI/ARB | D | BB | CCB |
| 3098 | ACEI/ARB | D | BB | D+BB |
| 3099 | ACEI/ARB | D | BB | D+CCB |
| 3100 | ACEI/ARB | D | BB | D+ACEI/ARB |
| 3101 | ACEI/ARB | D | BB | BB+CCB |
| 3102 | ACEI/ARB | D | BB | BB+ACEI/ARB |
| 3103 | ACEI/ARB | D | BB | CCB+ACEI/ARB |
| 3104 | ACEI/ARB | D | CCB | BB |
| 3105 | ACEI/ARB | D | CCB | D+BB |
| 3106 | ACEI/ARB | D | CCB | D+CCB |
| 3107 | ACEI/ARB | D | CCB | D+ACEI/ARB |
| 3108 | ACEI/ARB | D | CCB | BB+CCB |
| 3109 | ACEI/ARB | D | CCB | BB+ACEI/ARB |
| 3110 | ACEI/ARB | D | CCB | CCB+ACEI/ARB |
| 3111 | ACEI/ARB | D | D+BB | BB |
| 3112 | ACEI/ARB | D | D+BB | CCB |
| 3113 | ACEI/ARB | D | D+BB | D+CCB |
| 3114 | ACEI/ARB | D | D+BB | D+ACEI/ARB |
| 3115 | ACEI/ARB | D | D+BB | BB+CCB |
| 3116 | ACEI/ARB | D | D+BB | BB+ACEI/ARB |
| 3117 | ACEI/ARB | D | D+BB | CCB+ACEI/ARB |
| 3118 | ACEI/ARB | D | D+BB | D+BB+CCB |
| 3119 | ACEI/ARB | D | D+BB | D+BB+ACEI/ARB |
| 3120 | ACEI/ARB | D | D+BB | D+CCB+ACEI/ARB |
| 3121 | ACEI/ARB | D | D+BB | BB+CCB+ACEI/ARB |
| 3122 | ACEI/ARB | D | D+CCB | BB |
| 3123 | ACEI/ARB | D | D+CCB | CCB |
| 3124 | ACEI/ARB | D | D+CCB | D+BB |
| 3125 | ACEI/ARB | D | D+CCB | D+ACEI/ARB |
| 3126 | ACEI/ARB | D | D+CCB | BB+CCB |
| 3127 | ACEI/ARB | D | D+CCB | BB+ACEI/ARB |
| 3128 | ACEI/ARB | D | D+CCB | CCB+ACEI/ARB |
| 3129 | ACEI/ARB | D | D+CCB | D+BB+CCB |
| 3130 | ACEI/ARB | D | D+CCB | D+BB+ACEI/ARB |
| 3131 | ACEI/ARB | D | D+CCB | D+CCB+ACEI/ARB |
| 3132 | ACEI/ARB | D | D+CCB | BB+CCB+ACEI/ARB |
| 3133 | ACEI/ARB | D | D+ACEIs/ARB | BB |
| 3134 | ACEI/ARB | D | D+ACEIs/ARB | CCB |
| 3135 | ACEI/ARB | D | D+ACEIs/ARB | D+BB |
| 3136 | ACEI/ARB | D | D+ACEIs/ARB | D+CCB |
| 3137 | ACEI/ARB | D | D+ACEIs/ARB | BB+CCB |
| 3138 | ACEI/ARB | D | D+ACEIs/ARB | BB+ACEI/ARB |
| 3139 | ACEI/ARB | D | D+ACEIs/ARB | CCB+ACEI/ARB |
| 3140 | ACEI/ARB | D | D+ACEIs/ARB | D+BB+CCB |
| 3141 | ACEI/ARB | D | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 3142 | ACEI/ARB | D | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 3143 | ACEI/ARB | D | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 3144 | ACEI/ARB | D | BB+CCB | BB |
| 3145 | ACEI/ARB | D | BB+CCB | CCB |
| 3146 | ACEI/ARB | D | BB+CCB | D+BB |
| 3147 | ACEI/ARB | D | BB+CCB | D+CCB |
| 3148 | ACEI/ARB | D | BB+CCB | D+ACEI/ARB |
| 3149 | ACEI/ARB | D | BB+CCB | BB+ACEI/ARB |
| 3150 | ACEI/ARB | D | BB+CCB | CCB+ACEI/ARB |
| 3151 | ACEI/ARB | D | BB+CCB | D+BB+CCB |
| 3152 | ACEI/ARB | D | BB+CCB | D+BB+ACEI/ARB |
| 3153 | ACEI/ARB | D | BB+CCB | D+CCB+ACEI/ARB |
| 3154 | ACEI/ARB | D | BB+CCB | BB+CCB+ACEI/ARB |
| 3155 | ACEI/ARB | D | BB+ACEI/ARB | BB |
| 3156 | ACEI/ARB | D | BB+ACEI/ARB | CCB |
| 3157 | ACEI/ARB | D | BB+ACEI/ARB | D+BB |
| 3158 | ACEI/ARB | D | BB+ACEI/ARB | D+CCB |
| 3159 | ACEI/ARB | D | BB+ACEI/ARB | D+ACEI/ARB |
| 3160 | ACEI/ARB | D | BB+ACEI/ARB | BB+CCB |
| 3161 | ACEI/ARB | D | BB+ACEI/ARB | CCB+ACEI/ARB |
| 3162 | ACEI/ARB | D | BB+ACEI/ARB | D+BB+CCB |
| 3163 | ACEI/ARB | D | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 3164 | ACEI/ARB | D | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3165 | ACEI/ARB | D | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3166 | ACEI/ARB | D | CCB+ACEI/ARB | BB |
| 3167 | ACEI/ARB | D | CCB+ACEI/ARB | CCB |
| 3168 | ACEI/ARB | D | CCB+ACEI/ARB | D+BB |
| 3169 | ACEI/ARB | D | CCB+ACEI/ARB | D+CCB |
| 3170 | ACEI/ARB | D | CCB+ACEI/ARB | D+ACEI/ARB |
| 3171 | ACEI/ARB | D | CCB+ACEI/ARB | BB+CCB |
| 3172 | ACEI/ARB | D | CCB+ACEI/ARB | BB+ACEI/ARB |
| 3173 | ACEI/ARB | D | CCB+ACEI/ARB | D+BB+CCB |
| 3174 | ACEI/ARB | D | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 3175 | ACEI/ARB | D | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3176 | ACEI/ARB | D | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3177 | ACEI/ARB | BB | D | CCB |
| 3178 | ACEI/ARB | BB | D | D+BB |
| 3179 | ACEI/ARB | BB | D | D+CCB |
| 3180 | ACEI/ARB | BB | D | D+ACEI/ARB |
| 3181 | ACEI/ARB | BB | D | BB+CCB |
| 3182 | ACEI/ARB | BB | D | BB+ACEI/ARB |
| 3183 | ACEI/ARB | BB | D | CCB+ACEI/ARB |
| 3184 | ACEI/ARB | BB | CCB | D |
| 3185 | ACEI/ARB | BB | CCB | D+BB |
| 3186 | ACEI/ARB | BB | CCB | D+CCB |
| 3187 | ACEI/ARB | BB | CCB | D+ACEI/ARB |
| 3188 | ACEI/ARB | BB | CCB | BB+CCB |
| 3189 | ACEI/ARB | BB | CCB | BB+ACEI/ARB |
| 3190 | ACEI/ARB | BB | CCB | CCB+ACEI/ARB |
| 3191 | ACEI/ARB | BB | D+BB | D |
| 3192 | ACEI/ARB | BB | D+BB | CCB |
| 3193 | ACEI/ARB | BB | D+BB | D+CCB |
| 3194 | ACEI/ARB | BB | D+BB | D+ACEI/ARB |
| 3195 | ACEI/ARB | BB | D+BB | BB+CCB |
| 3196 | ACEI/ARB | BB | D+BB | BB+ACEI/ARB |
| 3197 | ACEI/ARB | BB | D+BB | CCB+ACEI/ARB |
| 3198 | ACEI/ARB | BB | D+BB | D+BB+CCB |
| 3199 | ACEI/ARB | BB | D+BB | D+BB+ACEI/ARB |
| 3200 | ACEI/ARB | BB | D+BB | D+CCB+ACEI/ARB |
| 3201 | ACEI/ARB | BB | D+BB | BB+CCB+ACEI/ARB |
| 3202 | ACEI/ARB | BB | D+CCB | D |
| 3203 | ACEI/ARB | BB | D+CCB | CCB |
| 3204 | ACEI/ARB | BB | D+CCB | D+BB |
| 3205 | ACEI/ARB | BB | D+CCB | D+ACEI/ARB |
| 3206 | ACEI/ARB | BB | D+CCB | BB+CCB |
| 3207 | ACEI/ARB | BB | D+CCB | BB+ACEI/ARB |
| 3208 | ACEI/ARB | BB | D+CCB | CCB+ACEI/ARB |
| 3209 | ACEI/ARB | BB | D+CCB | D+BB+CCB |
| 3210 | ACEI/ARB | BB | D+CCB | D+BB+ACEI/ARB |
| 3211 | ACEI/ARB | BB | D+CCB | D+CCB+ACEI/ARB |
| 3212 | ACEI/ARB | BB | D+CCB | BB+CCB+ACEI/ARB |
| 3213 | ACEI/ARB | BB | D+ACEIs/ARB | D |
| 3214 | ACEI/ARB | BB | D+ACEIs/ARB | CCB |
| 3215 | ACEI/ARB | BB | D+ACEIs/ARB | D+BB |
| 3216 | ACEI/ARB | BB | D+ACEIs/ARB | D+CCB |
| 3217 | ACEI/ARB | BB | D+ACEIs/ARB | BB+CCB |
| 3218 | ACEI/ARB | BB | D+ACEIs/ARB | BB+ACEI/ARB |
| 3219 | ACEI/ARB | BB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 3220 | ACEI/ARB | BB | D+ACEIs/ARB | D+BB+CCB |
| 3221 | ACEI/ARB | BB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 3222 | ACEI/ARB | BB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 3223 | ACEI/ARB | BB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 3224 | ACEI/ARB | BB | BB+CCB | D |
| 3225 | ACEI/ARB | BB | BB+CCB | CCB |
| 3226 | ACEI/ARB | BB | BB+CCB | D+BB |
| 3227 | ACEI/ARB | BB | BB+CCB | D+CCB |
| 3228 | ACEI/ARB | BB | BB+CCB | D+ACEI/ARB |
| 3229 | ACEI/ARB | BB | BB+CCB | BB+ACEI/ARB |
| 3230 | ACEI/ARB | BB | BB+CCB | CCB+ACEI/ARB |
| 3231 | ACEI/ARB | BB | BB+CCB | D+BB+CCB |
| 3232 | ACEI/ARB | BB | BB+CCB | D+BB+ACEI/ARB |
| 3233 | ACEI/ARB | BB | BB+CCB | D+CCB+ACEI/ARB |
| 3234 | ACEI/ARB | BB | BB+CCB | BB+CCB+ACEI/ARB |
| 3235 | ACEI/ARB | BB | BB+ACEI/ARB | D |
| 3236 | ACEI/ARB | BB | BB+ACEI/ARB | CCB |
| 3237 | ACEI/ARB | BB | BB+ACEI/ARB | D+BB |
| 3238 | ACEI/ARB | BB | BB+ACEI/ARB | D+CCB |
| 3239 | ACEI/ARB | BB | BB+ACEI/ARB | D+ACEI/ARB |
| 3240 | ACEI/ARB | BB | BB+ACEI/ARB | BB+CCB |
| 3241 | ACEI/ARB | BB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 3242 | ACEI/ARB | BB | BB+ACEI/ARB | D+BB+CCB |
| 3243 | ACEI/ARB | BB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 3244 | ACEI/ARB | BB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3245 | ACEI/ARB | BB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3246 | ACEI/ARB | BB | CCB+ACEI/ARB | D |
| 3247 | ACEI/ARB | BB | CCB+ACEI/ARB | CCB |
| 3248 | ACEI/ARB | BB | CCB+ACEI/ARB | D+BB |
| 3249 | ACEI/ARB | BB | CCB+ACEI/ARB | D+CCB |
| 3250 | ACEI/ARB | BB | CCB+ACEI/ARB | D+ACEI/ARB |
| 3251 | ACEI/ARB | BB | CCB+ACEI/ARB | BB+CCB |
| 3252 | ACEI/ARB | BB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 3253 | ACEI/ARB | BB | CCB+ACEI/ARB | D+BB+CCB |
| 3254 | ACEI/ARB | BB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 3255 | ACEI/ARB | BB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3256 | ACEI/ARB | BB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3257 | ACEI/ARB | CCB | D | BB |
| 3258 | ACEI/ARB | CCB | D | D+BB |
| 3259 | ACEI/ARB | CCB | D | D+CCB |
| 3260 | ACEI/ARB | CCB | D | D+ACEI/ARB |
| 3261 | ACEI/ARB | CCB | D | BB+CCB |
| 3262 | ACEI/ARB | CCB | D | BB+ACEI/ARB |
| 3263 | ACEI/ARB | CCB | D | CCB+ACEI/ARB |
| 3264 | ACEI/ARB | CCB | BB | D |
| 3265 | ACEI/ARB | CCB | BB | D+BB |
| 3266 | ACEI/ARB | CCB | BB | D+CCB |
| 3267 | ACEI/ARB | CCB | BB | D+ACEI/ARB |
| 3268 | ACEI/ARB | CCB | BB | BB+CCB |
| 3269 | ACEI/ARB | CCB | BB | BB+ACEI/ARB |
| 3270 | ACEI/ARB | CCB | BB | CCB+ACEI/ARB |
| 3271 | ACEI/ARB | CCB | D+BB | D |
| 3272 | ACEI/ARB | CCB | D+BB | BB |
| 3273 | ACEI/ARB | CCB | D+BB | D+CCB |
| 3274 | ACEI/ARB | CCB | D+BB | D+ACEI/ARB |
| 3275 | ACEI/ARB | CCB | D+BB | BB+CCB |
| 3276 | ACEI/ARB | CCB | D+BB | BB+ACEI/ARB |
| 3277 | ACEI/ARB | CCB | D+BB | CCB+ACEI/ARB |
| 3278 | ACEI/ARB | CCB | D+BB | D+BB+CCB |
| 3279 | ACEI/ARB | CCB | D+BB | D+BB+ACEI/ARB |
| 3280 | ACEI/ARB | CCB | D+BB | D+CCB+ACEI/ARB |
| 3281 | ACEI/ARB | CCB | D+BB | BB+CCB+ACEI/ARB |
| 3282 | ACEI/ARB | CCB | D+CCB | D |
| 3283 | ACEI/ARB | CCB | D+CCB | BB |
| 3284 | ACEI/ARB | CCB | D+CCB | D+BB |
| 3285 | ACEI/ARB | CCB | D+CCB | D+ACEI/ARB |
| 3286 | ACEI/ARB | CCB | D+CCB | BB+CCB |
| 3287 | ACEI/ARB | CCB | D+CCB | BB+ACEI/ARB |
| 3288 | ACEI/ARB | CCB | D+CCB | CCB+ACEI/ARB |
| 3289 | ACEI/ARB | CCB | D+CCB | D+BB+CCB |
| 3290 | ACEI/ARB | CCB | D+CCB | D+BB+ACEI/ARB |
| 3291 | ACEI/ARB | CCB | D+CCB | D+CCB+ACEI/ARB |
| 3292 | ACEI/ARB | CCB | D+CCB | BB+CCB+ACEI/ARB |
| 3293 | ACEI/ARB | CCB | D+ACEIs/ARB | D |
| 3294 | ACEI/ARB | CCB | D+ACEIs/ARB | BB |
| 3295 | ACEI/ARB | CCB | D+ACEIs/ARB | D+BB |
| 3296 | ACEI/ARB | CCB | D+ACEIs/ARB | D+CCB |
| 3297 | ACEI/ARB | CCB | D+ACEIs/ARB | BB+CCB |
| 3298 | ACEI/ARB | CCB | D+ACEIs/ARB | BB+ACEI/ARB |
| 3299 | ACEI/ARB | CCB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 3300 | ACEI/ARB | CCB | D+ACEIs/ARB | D+BB+CCB |
| 3301 | ACEI/ARB | CCB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 3302 | ACEI/ARB | CCB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 3303 | ACEI/ARB | CCB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 3304 | ACEI/ARB | CCB | BB+CCB | D |
| 3305 | ACEI/ARB | CCB | BB+CCB | BB |
| 3306 | ACEI/ARB | CCB | BB+CCB | D+BB |
| 3307 | ACEI/ARB | CCB | BB+CCB | D+CCB |
| 3308 | ACEI/ARB | CCB | BB+CCB | D+ACEI/ARB |
| 3309 | ACEI/ARB | CCB | BB+CCB | BB+ACEI/ARB |
| 3310 | ACEI/ARB | CCB | BB+CCB | CCB+ACEI/ARB |
| 3311 | ACEI/ARB | CCB | BB+CCB | D+BB+CCB |
| 3312 | ACEI/ARB | CCB | BB+CCB | D+BB+ACEI/ARB |
| 3313 | ACEI/ARB | CCB | BB+CCB | D+CCB+ACEI/ARB |
| 3314 | ACEI/ARB | CCB | BB+CCB | BB+CCB+ACEI/ARB |
| 3315 | ACEI/ARB | CCB | BB+ACEI/ARB | D |
| 3316 | ACEI/ARB | CCB | BB+ACEI/ARB | BB |
| 3317 | ACEI/ARB | CCB | BB+ACEI/ARB | D+BB |
| 3318 | ACEI/ARB | CCB | BB+ACEI/ARB | D+CCB |
| 3319 | ACEI/ARB | CCB | BB+ACEI/ARB | D+ACEI/ARB |
| 3320 | ACEI/ARB | CCB | BB+ACEI/ARB | BB+CCB |
| 3321 | ACEI/ARB | CCB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 3322 | ACEI/ARB | CCB | BB+ACEI/ARB | D+BB+CCB |
| 3323 | ACEI/ARB | CCB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 3324 | ACEI/ARB | CCB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3325 | ACEI/ARB | CCB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3326 | ACEI/ARB | CCB | CCB+ACEI/ARB | D |
| 3327 | ACEI/ARB | CCB | CCB+ACEI/ARB | BB |
| 3328 | ACEI/ARB | CCB | CCB+ACEI/ARB | D+BB |
| 3329 | ACEI/ARB | CCB | CCB+ACEI/ARB | D+CCB |
| 3330 | ACEI/ARB | CCB | CCB+ACEI/ARB | D+ACEI/ARB |
| 3331 | ACEI/ARB | CCB | CCB+ACEI/ARB | BB+CCB |
| 3332 | ACEI/ARB | CCB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 3333 | ACEI/ARB | CCB | CCB+ACEI/ARB | D+BB+CCB |
| 3334 | ACEI/ARB | CCB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 3335 | ACEI/ARB | CCB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3336 | ACEI/ARB | CCB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3337 | ACEI/ARB | D+BB | D | BB |
| 3338 | ACEI/ARB | D+BB | D | CCB |
| 3339 | ACEI/ARB | D+BB | D | D+CCB |
| 3340 | ACEI/ARB | D+BB | D | D+ACEI/ARB |
| 3341 | ACEI/ARB | D+BB | D | BB+CCB |
| 3342 | ACEI/ARB | D+BB | D | BB+ACEI/ARB |
| 3343 | ACEI/ARB | D+BB | D | CCB+ACEI/ARB |
| 3344 | ACEI/ARB | D+BB | D | D+BB+CCB |
| 3345 | ACEI/ARB | D+BB | D | D+BB+ACEI/ARB |
| 3346 | ACEI/ARB | D+BB | D | D+CCB+ACEI/ARB |
| 3347 | ACEI/ARB | D+BB | D | BB+CCB+ACEI/ARB |
| 3348 | ACEI/ARB | D+BB | BB | D |
| 3349 | ACEI/ARB | D+BB | BB | CCB |
| 3350 | ACEI/ARB | D+BB | BB | D+CCB |
| 3351 | ACEI/ARB | D+BB | BB | D+ACEI/ARB |
| 3352 | ACEI/ARB | D+BB | BB | BB+CCB |
| 3353 | ACEI/ARB | D+BB | BB | BB+ACEI/ARB |
| 3354 | ACEI/ARB | D+BB | BB | CCB+ACEI/ARB |
| 3355 | ACEI/ARB | D+BB | BB | D+BB+CCB |
| 3356 | ACEI/ARB | D+BB | BB | D+BB+ACEI/ARB |
| 3357 | ACEI/ARB | D+BB | BB | D+CCB+ACEI/ARB |
| 3358 | ACEI/ARB | D+BB | BB | BB+CCB+ACEI/ARB |
| 3359 | ACEI/ARB | D+BB | CCB | D |
| 3360 | ACEI/ARB | D+BB | CCB | BB |
| 3361 | ACEI/ARB | D+BB | CCB | D+CCB |
| 3362 | ACEI/ARB | D+BB | CCB | D+ACEI/ARB |
| 3363 | ACEI/ARB | D+BB | CCB | BB+CCB |
| 3364 | ACEI/ARB | D+BB | CCB | BB+ACEI/ARB |
| 3365 | ACEI/ARB | D+BB | CCB | CCB+ACEI/ARB |
| 3366 | ACEI/ARB | D+BB | CCB | D+BB+CCB |
| 3367 | ACEI/ARB | D+BB | CCB | D+BB+ACEI/ARB |
| 3368 | ACEI/ARB | D+BB | CCB | D+CCB+ACEI/ARB |
| 3369 | ACEI/ARB | D+BB | CCB | BB+CCB+ACEI/ARB |
| 3370 | ACEI/ARB | D+BB | D+CCB | D |
| 3371 | ACEI/ARB | D+BB | D+CCB | BB |
| 3372 | ACEI/ARB | D+BB | D+CCB | CCB |
| 3373 | ACEI/ARB | D+BB | D+CCB | D+ACEI/ARB |
| 3374 | ACEI/ARB | D+BB | D+CCB | BB+CCB |
| 3375 | ACEI/ARB | D+BB | D+CCB | BB+ACEI/ARB |
| 3376 | ACEI/ARB | D+BB | D+CCB | CCB+ACEI/ARB |
| 3377 | ACEI/ARB | D+BB | D+CCB | D+BB+CCB |
| 3378 | ACEI/ARB | D+BB | D+CCB | D+BB+ACEI/ARB |
| 3379 | ACEI/ARB | D+BB | D+CCB | D+CCB+ACEI/ARB |
| 3380 | ACEI/ARB | D+BB | D+CCB | BB+CCB+ACEI/ARB |
| 3381 | ACEI/ARB | D+BB | D+ACEIs/ARB | D |
| 3382 | ACEI/ARB | D+BB | D+ACEIs/ARB | BB |
| 3383 | ACEI/ARB | D+BB | D+ACEIs/ARB | CCB |
| 3384 | ACEI/ARB | D+BB | D+ACEIs/ARB | D+CCB |
| 3385 | ACEI/ARB | D+BB | D+ACEIs/ARB | BB+CCB |
| 3386 | ACEI/ARB | D+BB | D+ACEIs/ARB | BB+ACEI/ARB |
| 3387 | ACEI/ARB | D+BB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 3388 | ACEI/ARB | D+BB | D+ACEIs/ARB | D+BB+CCB |
| 3389 | ACEI/ARB | D+BB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 3390 | ACEI/ARB | D+BB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 3391 | ACEI/ARB | D+BB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 3392 | ACEI/ARB | D+BB | BB+CCB | D |
| 3393 | ACEI/ARB | D+BB | BB+CCB | BB |
| 3394 | ACEI/ARB | D+BB | BB+CCB | CCB |
| 3395 | ACEI/ARB | D+BB | BB+CCB | D+CCB |
| 3396 | ACEI/ARB | D+BB | BB+CCB | D+ACEI/ARB |
| 3397 | ACEI/ARB | D+BB | BB+CCB | BB+ACEI/ARB |
| 3398 | ACEI/ARB | D+BB | BB+CCB | CCB+ACEI/ARB |
| 3399 | ACEI/ARB | D+BB | BB+CCB | D+BB+CCB |
| 3400 | ACEI/ARB | D+BB | BB+CCB | D+BB+ACEI/ARB |
| 3401 | ACEI/ARB | D+BB | BB+CCB | D+CCB+ACEI/ARB |
| 3402 | ACEI/ARB | D+BB | BB+CCB | BB+CCB+ACEI/ARB |
| 3403 | ACEI/ARB | D+BB | BB+ACEI/ARB | D |
| 3404 | ACEI/ARB | D+BB | BB+ACEI/ARB | BB |
| 3405 | ACEI/ARB | D+BB | BB+ACEI/ARB | CCB |
| 3406 | ACEI/ARB | D+BB | BB+ACEI/ARB | D+CCB |
| 3407 | ACEI/ARB | D+BB | BB+ACEI/ARB | D+ACEI/ARB |
| 3408 | ACEI/ARB | D+BB | BB+ACEI/ARB | BB+CCB |
| 3409 | ACEI/ARB | D+BB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 3410 | ACEI/ARB | D+BB | BB+ACEI/ARB | D+BB+CCB |
| 3411 | ACEI/ARB | D+BB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 3412 | ACEI/ARB | D+BB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3413 | ACEI/ARB | D+BB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3414 | ACEI/ARB | D+BB | CCB+ACEI/ARB | D |
| 3415 | ACEI/ARB | D+BB | CCB+ACEI/ARB | BB |
| 3416 | ACEI/ARB | D+BB | CCB+ACEI/ARB | CCB |
| 3417 | ACEI/ARB | D+BB | CCB+ACEI/ARB | D+CCB |
| 3418 | ACEI/ARB | D+BB | CCB+ACEI/ARB | D+ACEI/ARB |
| 3419 | ACEI/ARB | D+BB | CCB+ACEI/ARB | BB+CCB |
| 3420 | ACEI/ARB | D+BB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 3421 | ACEI/ARB | D+BB | CCB+ACEI/ARB | D+BB+CCB |
| 3422 | ACEI/ARB | D+BB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 3423 | ACEI/ARB | D+BB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3424 | ACEI/ARB | D+BB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3425 | ACEI/ARB | D+BB | D+BB+CCB | D |
| 3426 | ACEI/ARB | D+BB | D+BB+CCB | BB |
| 3427 | ACEI/ARB | D+BB | D+BB+CCB | CCB |
| 3428 | ACEI/ARB | D+BB | D+BB+CCB | D+CCB |
| 3429 | ACEI/ARB | D+BB | D+BB+CCB | D+ACEI/ARB |
| 3430 | ACEI/ARB | D+BB | D+BB+CCB | BB+CCB |
| 3431 | ACEI/ARB | D+BB | D+BB+CCB | BB+ACEI/ARB |
| 3432 | ACEI/ARB | D+BB | D+BB+CCB | CCB+ACEI/ARB |
| 3433 | ACEI/ARB | D+BB | D+BB+CCB | D+BB+ACEI/ARB |
| 3434 | ACEI/ARB | D+BB | D+BB+CCB | D+CCB+ACEI/ARB |
| 3435 | ACEI/ARB | D+BB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 3436 | ACEI/ARB | D+BB | D+BB+ACEI/ARB | D |
| 3437 | ACEI/ARB | D+BB | D+BB+ACEI/ARB | BB |
| 3438 | ACEI/ARB | D+BB | D+BB+ACEI/ARB | CCB |
| 3439 | ACEI/ARB | D+BB | D+BB+ACEI/ARB | D+CCB |
| 3440 | ACEI/ARB | D+BB | D+BB+ACEI/ARB | D+ACEI/ARB |
| 3441 | ACEI/ARB | D+BB | D+BB+ACEI/ARB | BB+CCB |
| 3442 | ACEI/ARB | D+BB | D+BB+ACEI/ARB | BB+ACEI/ARB |
| 3443 | ACEI/ARB | D+BB | D+BB+ACEI/ARB | CCB+ACEI/ARB |
| 3444 | ACEI/ARB | D+BB | D+BB+ACEI/ARB | D+BB+CCB |
| 3445 | ACEI/ARB | D+BB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3446 | ACEI/ARB | D+BB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3447 | ACEI/ARB | D+BB | D+CCB+ACEI/ARB | D |
| 3448 | ACEI/ARB | D+BB | D+CCB+ACEI/ARB | BB |
| 3449 | ACEI/ARB | D+BB | D+CCB+ACEI/ARB | CCB |
| 3450 | ACEI/ARB | D+BB | D+CCB+ACEI/ARB | D+CCB |
| 3451 | ACEI/ARB | D+BB | D+CCB+ACEI/ARB | D+ACEI/ARB |
| 3452 | ACEI/ARB | D+BB | D+CCB+ACEI/ARB | BB+CCB |
| 3453 | ACEI/ARB | D+BB | D+CCB+ACEI/ARB | BB+ACEI/ARB |
| 3454 | ACEI/ARB | D+BB | D+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 3455 | ACEI/ARB | D+BB | D+CCB+ACEI/ARB | D+BB+CCB |
| 3456 | ACEI/ARB | D+BB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 3457 | ACEI/ARB | D+BB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3458 | ACEI/ARB | D+BB | BB+CCB+ACEI/ARB | D |
| 3459 | ACEI/ARB | D+BB | BB+CCB+ACEI/ARB | BB |
| 3460 | ACEI/ARB | D+BB | BB+CCB+ACEI/ARB | CCB |
| 3461 | ACEI/ARB | D+BB | BB+CCB+ACEI/ARB | D+CCB |
| 3462 | ACEI/ARB | D+BB | BB+CCB+ACEI/ARB | D+ACEI/ARB |
| 3463 | ACEI/ARB | D+BB | BB+CCB+ACEI/ARB | BB+CCB |
| 3464 | ACEI/ARB | D+BB | BB+CCB+ACEI/ARB | BB+ACEI/ARB |
| 3465 | ACEI/ARB | D+BB | BB+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 3466 | ACEI/ARB | D+BB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 3467 | ACEI/ARB | D+BB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 3468 | ACEI/ARB | D+BB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3469 | ACEI/ARB | D+CCB | D | BB |
| 3470 | ACEI/ARB | D+CCB | D | CCB |
| 3471 | ACEI/ARB | D+CCB | D | D+BB |
| 3472 | ACEI/ARB | D+CCB | D | D+ACEI/ARB |
| 3473 | ACEI/ARB | D+CCB | D | BB+CCB |
| 3474 | ACEI/ARB | D+CCB | D | BB+ACEI/ARB |
| 3475 | ACEI/ARB | D+CCB | D | CCB+ACEI/ARB |
| 3476 | ACEI/ARB | D+CCB | D | D+BB+CCB |
| 3477 | ACEI/ARB | D+CCB | D | D+BB+ACEI/ARB |
| 3478 | ACEI/ARB | D+CCB | D | D+CCB+ACEI/ARB |
| 3479 | ACEI/ARB | D+CCB | D | BB+CCB+ACEI/ARB |
| 3480 | ACEI/ARB | D+CCB | BB | D |
| 3481 | ACEI/ARB | D+CCB | BB | CCB |
| 3482 | ACEI/ARB | D+CCB | BB | D+BB |
| 3483 | ACEI/ARB | D+CCB | BB | D+ACEI/ARB |
| 3484 | ACEI/ARB | D+CCB | BB | BB+CCB |
| 3485 | ACEI/ARB | D+CCB | BB | BB+ACEI/ARB |
| 3486 | ACEI/ARB | D+CCB | BB | CCB+ACEI/ARB |
| 3487 | ACEI/ARB | D+CCB | BB | D+BB+CCB |
| 3488 | ACEI/ARB | D+CCB | BB | D+BB+ACEI/ARB |
| 3489 | ACEI/ARB | D+CCB | BB | D+CCB+ACEI/ARB |
| 3490 | ACEI/ARB | D+CCB | BB | BB+CCB+ACEI/ARB |
| 3491 | ACEI/ARB | D+CCB | CCB | D |
| 3492 | ACEI/ARB | D+CCB | CCB | BB |
| 3493 | ACEI/ARB | D+CCB | CCB | D+BB |
| 3494 | ACEI/ARB | D+CCB | CCB | D+ACEI/ARB |
| 3495 | ACEI/ARB | D+CCB | CCB | BB+CCB |
| 3496 | ACEI/ARB | D+CCB | CCB | BB+ACEI/ARB |
| 3497 | ACEI/ARB | D+CCB | CCB | CCB+ACEI/ARB |
| 3498 | ACEI/ARB | D+CCB | CCB | D+BB+CCB |
| 3499 | ACEI/ARB | D+CCB | CCB | D+BB+ACEI/ARB |
| 3500 | ACEI/ARB | D+CCB | CCB | D+CCB+ACEI/ARB |
| 3501 | ACEI/ARB | D+CCB | CCB | BB+CCB+ACEI/ARB |
| 3502 | ACEI/ARB | D+CCB | D+BB | D |
| 3503 | ACEI/ARB | D+CCB | D+BB | BB |
| 3504 | ACEI/ARB | D+CCB | D+BB | CCB |
| 3505 | ACEI/ARB | D+CCB | D+BB | D+ACEI/ARB |
| 3506 | ACEI/ARB | D+CCB | D+BB | BB+CCB |
| 3507 | ACEI/ARB | D+CCB | D+BB | BB+ACEI/ARB |
| 3508 | ACEI/ARB | D+CCB | D+BB | CCB+ACEI/ARB |
| 3509 | ACEI/ARB | D+CCB | D+BB | D+BB+CCB |
| 3510 | ACEI/ARB | D+CCB | D+BB | D+BB+ACEI/ARB |
| 3511 | ACEI/ARB | D+CCB | D+BB | D+CCB+ACEI/ARB |
| 3512 | ACEI/ARB | D+CCB | D+BB | BB+CCB+ACEI/ARB |
| 3513 | ACEI/ARB | D+CCB | D+ACEIs/ARB | D |
| 3514 | ACEI/ARB | D+CCB | D+ACEIs/ARB | BB |
| 3515 | ACEI/ARB | D+CCB | D+ACEIs/ARB | CCB |
| 3516 | ACEI/ARB | D+CCB | D+ACEIs/ARB | D+BB |
| 3517 | ACEI/ARB | D+CCB | D+ACEIs/ARB | BB+CCB |
| 3518 | ACEI/ARB | D+CCB | D+ACEIs/ARB | BB+ACEI/ARB |
| 3519 | ACEI/ARB | D+CCB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 3520 | ACEI/ARB | D+CCB | D+ACEIs/ARB | D+BB+CCB |
| 3521 | ACEI/ARB | D+CCB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 3522 | ACEI/ARB | D+CCB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 3523 | ACEI/ARB | D+CCB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 3524 | ACEI/ARB | D+CCB | BB+CCB | D |
| 3525 | ACEI/ARB | D+CCB | BB+CCB | BB |
| 3526 | ACEI/ARB | D+CCB | BB+CCB | CCB |
| 3527 | ACEI/ARB | D+CCB | BB+CCB | D+BB |
| 3528 | ACEI/ARB | D+CCB | BB+CCB | D+ACEI/ARB |
| 3529 | ACEI/ARB | D+CCB | BB+CCB | BB+ACEI/ARB |
| 3530 | ACEI/ARB | D+CCB | BB+CCB | CCB+ACEI/ARB |
| 3531 | ACEI/ARB | D+CCB | BB+CCB | D+BB+CCB |
| 3532 | ACEI/ARB | D+CCB | BB+CCB | D+BB+ACEI/ARB |
| 3533 | ACEI/ARB | D+CCB | BB+CCB | D+CCB+ACEI/ARB |
| 3534 | ACEI/ARB | D+CCB | BB+CCB | BB+CCB+ACEI/ARB |
| 3535 | ACEI/ARB | D+CCB | BB+ACEI/ARB | D |
| 3536 | ACEI/ARB | D+CCB | BB+ACEI/ARB | BB |
| 3537 | ACEI/ARB | D+CCB | BB+ACEI/ARB | CCB |
| 3538 | ACEI/ARB | D+CCB | BB+ACEI/ARB | D+BB |
| 3539 | ACEI/ARB | D+CCB | BB+ACEI/ARB | D+ACEI/ARB |
| 3540 | ACEI/ARB | D+CCB | BB+ACEI/ARB | BB+CCB |
| 3541 | ACEI/ARB | D+CCB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 3542 | ACEI/ARB | D+CCB | BB+ACEI/ARB | D+BB+CCB |
| 3543 | ACEI/ARB | D+CCB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 3544 | ACEI/ARB | D+CCB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3545 | ACEI/ARB | D+CCB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3546 | ACEI/ARB | D+CCB | CCB+ACEI/ARB | D |
| 3547 | ACEI/ARB | D+CCB | CCB+ACEI/ARB | BB |
| 3548 | ACEI/ARB | D+CCB | CCB+ACEI/ARB | CCB |
| 3549 | ACEI/ARB | D+CCB | CCB+ACEI/ARB | D+BB |
| 3550 | ACEI/ARB | D+CCB | CCB+ACEI/ARB | D+ACEI/ARB |
| 3551 | ACEI/ARB | D+CCB | CCB+ACEI/ARB | BB+CCB |
| 3552 | ACEI/ARB | D+CCB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 3553 | ACEI/ARB | D+CCB | CCB+ACEI/ARB | D+BB+CCB |
| 3554 | ACEI/ARB | D+CCB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 3555 | ACEI/ARB | D+CCB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3556 | ACEI/ARB | D+CCB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3557 | ACEI/ARB | D+CCB | D+BB+CCB | D |
| 3558 | ACEI/ARB | D+CCB | D+BB+CCB | BB |
| 3559 | ACEI/ARB | D+CCB | D+BB+CCB | CCB |
| 3560 | ACEI/ARB | D+CCB | D+BB+CCB | D+BB |
| 3561 | ACEI/ARB | D+CCB | D+BB+CCB | D+ACEI/ARB |
| 3562 | ACEI/ARB | D+CCB | D+BB+CCB | BB+CCB |
| 3563 | ACEI/ARB | D+CCB | D+BB+CCB | BB+ACEI/ARB |
| 3564 | ACEI/ARB | D+CCB | D+BB+CCB | CCB+ACEI/ARB |
| 3565 | ACEI/ARB | D+CCB | D+BB+CCB | D+BB+ACEI/ARB |
| 3566 | ACEI/ARB | D+CCB | D+BB+CCB | D+CCB+ACEI/ARB |
| 3567 | ACEI/ARB | D+CCB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 3568 | ACEI/ARB | D+CCB | D+BB+ACEI/ARB | D |
| 3569 | ACEI/ARB | D+CCB | D+BB+ACEI/ARB | BB |
| 3570 | ACEI/ARB | D+CCB | D+BB+ACEI/ARB | CCB |
| 3571 | ACEI/ARB | D+CCB | D+BB+ACEI/ARB | D+BB |
| 3572 | ACEI/ARB | D+CCB | D+BB+ACEI/ARB | D+ACEI/ARB |
| 3573 | ACEI/ARB | D+CCB | D+BB+ACEI/ARB | BB+CCB |
| 3574 | ACEI/ARB | D+CCB | D+BB+ACEI/ARB | BB+ACEI/ARB |
| 3575 | ACEI/ARB | D+CCB | D+BB+ACEI/ARB | CCB+ACEI/ARB |
| 3576 | ACEI/ARB | D+CCB | D+BB+ACEI/ARB | D+BB+CCB |
| 3577 | ACEI/ARB | D+CCB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3578 | ACEI/ARB | D+CCB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3579 | ACEI/ARB | D+CCB | D+CCB+ACEI/ARB | D |
| 3580 | ACEI/ARB | D+CCB | D+CCB+ACEI/ARB | BB |
| 3581 | ACEI/ARB | D+CCB | D+CCB+ACEI/ARB | CCB |
| 3582 | ACEI/ARB | D+CCB | D+CCB+ACEI/ARB | D+BB |
| 3583 | ACEI/ARB | D+CCB | D+CCB+ACEI/ARB | D+ACEI/ARB |
| 3584 | ACEI/ARB | D+CCB | D+CCB+ACEI/ARB | BB+CCB |
| 3585 | ACEI/ARB | D+CCB | D+CCB+ACEI/ARB | BB+ACEI/ARB |
| 3586 | ACEI/ARB | D+CCB | D+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 3587 | ACEI/ARB | D+CCB | D+CCB+ACEI/ARB | D+BB+CCB |
| 3588 | ACEI/ARB | D+CCB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 3589 | ACEI/ARB | D+CCB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3590 | ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB | D |
| 3591 | ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB | BB |
| 3592 | ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB | CCB |
| 3593 | ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB | D+BB |
| 3594 | ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB | D+ACEI/ARB |
| 3595 | ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB | BB+CCB |
| 3596 | ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB | BB+ACEI/ARB |
| 3597 | ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 3598 | ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 3599 | ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 3600 | ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3601 | ACEI/ARB | D+ACEI/ARB | D | BB |
| 3602 | ACEI/ARB | D+ACEI/ARB | D | CCB |
| 3603 | ACEI/ARB | D+ACEI/ARB | D | D+BB |
| 3604 | ACEI/ARB | D+ACEI/ARB | D | D+CCB |
| 3605 | ACEI/ARB | D+ACEI/ARB | D | BB+CCB |
| 3606 | ACEI/ARB | D+ACEI/ARB | D | BB+ACEI/ARB |
| 3607 | ACEI/ARB | D+ACEI/ARB | D | CCB+ACEI/ARB |
| 3608 | ACEI/ARB | D+ACEI/ARB | D | D+BB+CCB |
| 3609 | ACEI/ARB | D+ACEI/ARB | D | D+BB+ACEI/ARB |
| 3610 | ACEI/ARB | D+ACEI/ARB | D | D+CCB+ACEI/ARB |
| 3611 | ACEI/ARB | D+ACEI/ARB | D | BB+CCB+ACEI/ARB |
| 3612 | ACEI/ARB | D+ACEI/ARB | BB | D |
| 3613 | ACEI/ARB | D+ACEI/ARB | BB | CCB |
| 3614 | ACEI/ARB | D+ACEI/ARB | BB | D+BB |
| 3615 | ACEI/ARB | D+ACEI/ARB | BB | D+CCB |
| 3616 | ACEI/ARB | D+ACEI/ARB | BB | BB+CCB |
| 3617 | ACEI/ARB | D+ACEI/ARB | BB | BB+ACEI/ARB |
| 3618 | ACEI/ARB | D+ACEI/ARB | BB | CCB+ACEI/ARB |
| 3619 | ACEI/ARB | D+ACEI/ARB | BB | D+BB+CCB |
| 3620 | ACEI/ARB | D+ACEI/ARB | BB | D+BB+ACEI/ARB |
| 3621 | ACEI/ARB | D+ACEI/ARB | BB | D+CCB+ACEI/ARB |
| 3622 | ACEI/ARB | D+ACEI/ARB | BB | BB+CCB+ACEI/ARB |
| 3623 | ACEI/ARB | D+ACEI/ARB | CCB | D |
| 3624 | ACEI/ARB | D+ACEI/ARB | CCB | BB |
| 3625 | ACEI/ARB | D+ACEI/ARB | CCB | D+BB |
| 3626 | ACEI/ARB | D+ACEI/ARB | CCB | D+CCB |
| 3627 | ACEI/ARB | D+ACEI/ARB | CCB | BB+CCB |
| 3628 | ACEI/ARB | D+ACEI/ARB | CCB | BB+ACEI/ARB |
| 3629 | ACEI/ARB | D+ACEI/ARB | CCB | CCB+ACEI/ARB |
| 3630 | ACEI/ARB | D+ACEI/ARB | CCB | D+BB+CCB |
| 3631 | ACEI/ARB | D+ACEI/ARB | CCB | D+BB+ACEI/ARB |
| 3632 | ACEI/ARB | D+ACEI/ARB | CCB | D+CCB+ACEI/ARB |
| 3633 | ACEI/ARB | D+ACEI/ARB | CCB | BB+CCB+ACEI/ARB |
| 3634 | ACEI/ARB | D+ACEI/ARB | D+BB | D |
| 3635 | ACEI/ARB | D+ACEI/ARB | D+BB | BB |
| 3636 | ACEI/ARB | D+ACEI/ARB | D+BB | CCB |
| 3637 | ACEI/ARB | D+ACEI/ARB | D+BB | D+CCB |
| 3638 | ACEI/ARB | D+ACEI/ARB | D+BB | BB+CCB |
| 3639 | ACEI/ARB | D+ACEI/ARB | D+BB | BB+ACEI/ARB |
| 3640 | ACEI/ARB | D+ACEI/ARB | D+BB | CCB+ACEI/ARB |
| 3641 | ACEI/ARB | D+ACEI/ARB | D+BB | D+BB+CCB |
| 3642 | ACEI/ARB | D+ACEI/ARB | D+BB | D+BB+ACEI/ARB |
| 3643 | ACEI/ARB | D+ACEI/ARB | D+BB | D+CCB+ACEI/ARB |
| 3644 | ACEI/ARB | D+ACEI/ARB | D+BB | BB+CCB+ACEI/ARB |
| 3645 | ACEI/ARB | D+ACEI/ARB | D+CCB | D |
| 3646 | ACEI/ARB | D+ACEI/ARB | D+CCB | BB |
| 3647 | ACEI/ARB | D+ACEI/ARB | D+CCB | CCB |
| 3648 | ACEI/ARB | D+ACEI/ARB | D+CCB | D+BB |
| 3649 | ACEI/ARB | D+ACEI/ARB | D+CCB | BB+CCB |
| 3650 | ACEI/ARB | D+ACEI/ARB | D+CCB | BB+ACEI/ARB |
| 3651 | ACEI/ARB | D+ACEI/ARB | D+CCB | CCB+ACEI/ARB |
| 3652 | ACEI/ARB | D+ACEI/ARB | D+CCB | D+BB+CCB |
| 3653 | ACEI/ARB | D+ACEI/ARB | D+CCB | D+BB+ACEI/ARB |
| 3654 | ACEI/ARB | D+ACEI/ARB | D+CCB | D+CCB+ACEI/ARB |
| 3655 | ACEI/ARB | D+ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB |
| 3656 | ACEI/ARB | D+ACEI/ARB | BB+CCB | D |
| 3657 | ACEI/ARB | D+ACEI/ARB | BB+CCB | BB |
| 3658 | ACEI/ARB | D+ACEI/ARB | BB+CCB | CCB |
| 3659 | ACEI/ARB | D+ACEI/ARB | BB+CCB | D+BB |
| 3660 | ACEI/ARB | D+ACEI/ARB | BB+CCB | D+CCB |
| 3661 | ACEI/ARB | D+ACEI/ARB | BB+CCB | BB+ACEI/ARB |
| 3662 | ACEI/ARB | D+ACEI/ARB | BB+CCB | CCB+ACEI/ARB |
| 3663 | ACEI/ARB | D+ACEI/ARB | BB+CCB | D+BB+CCB |
| 3664 | ACEI/ARB | D+ACEI/ARB | BB+CCB | D+BB+ACEI/ARB |
| 3665 | ACEI/ARB | D+ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB |
| 3666 | ACEI/ARB | D+ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB |
| 3667 | ACEI/ARB | D+ACEI/ARB | BB+ACEI/ARB | D |
| 3668 | ACEI/ARB | D+ACEI/ARB | BB+ACEI/ARB | BB |
| 3669 | ACEI/ARB | D+ACEI/ARB | BB+ACEI/ARB | CCB |
| 3670 | ACEI/ARB | D+ACEI/ARB | BB+ACEI/ARB | D+BB |
| 3671 | ACEI/ARB | D+ACEI/ARB | BB+ACEI/ARB | D+CCB |
| 3672 | ACEI/ARB | D+ACEI/ARB | BB+ACEI/ARB | BB+CCB |
| 3673 | ACEI/ARB | D+ACEI/ARB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 3674 | ACEI/ARB | D+ACEI/ARB | BB+ACEI/ARB | D+BB+CCB |
| 3675 | ACEI/ARB | D+ACEI/ARB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 3676 | ACEI/ARB | D+ACEI/ARB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3677 | ACEI/ARB | D+ACEI/ARB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3678 | ACEI/ARB | D+ACEI/ARB | CCB+ACEI/ARB | D |
| 3679 | ACEI/ARB | D+ACEI/ARB | CCB+ACEI/ARB | BB |
| 3680 | ACEI/ARB | D+ACEI/ARB | CCB+ACEI/ARB | CCB |
| 3681 | ACEI/ARB | D+ACEI/ARB | CCB+ACEI/ARB | D+BB |
| 3682 | ACEI/ARB | D+ACEI/ARB | CCB+ACEI/ARB | D+CCB |
| 3683 | ACEI/ARB | D+ACEI/ARB | CCB+ACEI/ARB | BB+CCB |
| 3684 | ACEI/ARB | D+ACEI/ARB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 3685 | ACEI/ARB | D+ACEI/ARB | CCB+ACEI/ARB | D+BB+CCB |
| 3686 | ACEI/ARB | D+ACEI/ARB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 3687 | ACEI/ARB | D+ACEI/ARB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3688 | ACEI/ARB | D+ACEI/ARB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3689 | ACEI/ARB | D+ACEI/ARB | D+BB+CCB | D |
| 3690 | ACEI/ARB | D+ACEI/ARB | D+BB+CCB | BB |
| 3691 | ACEI/ARB | D+ACEI/ARB | D+BB+CCB | CCB |
| 3692 | ACEI/ARB | D+ACEI/ARB | D+BB+CCB | D+BB |
| 3693 | ACEI/ARB | D+ACEI/ARB | D+BB+CCB | D+CCB |
| 3694 | ACEI/ARB | D+ACEI/ARB | D+BB+CCB | BB+CCB |
| 3695 | ACEI/ARB | D+ACEI/ARB | D+BB+CCB | BB+ACEI/ARB |
| 3696 | ACEI/ARB | D+ACEI/ARB | D+BB+CCB | CCB+ACEI/ARB |
| 3697 | ACEI/ARB | D+ACEI/ARB | D+BB+CCB | D+BB+ACEI/ARB |
| 3698 | ACEI/ARB | D+ACEI/ARB | D+BB+CCB | D+CCB+ACEI/ARB |
| 3699 | ACEI/ARB | D+ACEI/ARB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 3700 | ACEI/ARB | D+ACEI/ARB | D+BB+ACEI/ARB | D |
| 3701 | ACEI/ARB | D+ACEI/ARB | D+BB+ACEI/ARB | BB |
| 3702 | ACEI/ARB | D+ACEI/ARB | D+BB+ACEI/ARB | CCB |
| 3703 | ACEI/ARB | D+ACEI/ARB | D+BB+ACEI/ARB | D+BB |
| 3704 | ACEI/ARB | D+ACEI/ARB | D+BB+ACEI/ARB | D+CCB |
| 3705 | ACEI/ARB | D+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB |
| 3706 | ACEI/ARB | D+ACEI/ARB | D+BB+ACEI/ARB | BB+ACEI/ARB |
| 3707 | ACEI/ARB | D+ACEI/ARB | D+BB+ACEI/ARB | CCB+ACEI/ARB |
| 3708 | ACEI/ARB | D+ACEI/ARB | D+BB+ACEI/ARB | D+BB+CCB |
| 3709 | ACEI/ARB | D+ACEI/ARB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3710 | ACEI/ARB | D+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3711 | ACEI/ARB | D+ACEI/ARB | D+CCB+ACEI/ARB | D |
| 3712 | ACEI/ARB | D+ACEI/ARB | D+CCB+ACEI/ARB | BB |
| 3713 | ACEI/ARB | D+ACEI/ARB | D+CCB+ACEI/ARB | CCB |
| 3714 | ACEI/ARB | D+ACEI/ARB | D+CCB+ACEI/ARB | D+BB |
| 3715 | ACEI/ARB | D+ACEI/ARB | D+CCB+ACEI/ARB | D+CCB |
| 3716 | ACEI/ARB | D+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB |
| 3717 | ACEI/ARB | D+ACEI/ARB | D+CCB+ACEI/ARB | BB+ACEI/ARB |
| 3718 | ACEI/ARB | D+ACEI/ARB | D+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 3719 | ACEI/ARB | D+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+CCB |
| 3720 | ACEI/ARB | D+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 3721 | ACEI/ARB | D+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3722 | ACEI/ARB | D+ACEI/ARB | BB+CCB+ACEI/ARB | D |
| 3723 | ACEI/ARB | D+ACEI/ARB | BB+CCB+ACEI/ARB | BB |
| 3724 | ACEI/ARB | D+ACEI/ARB | BB+CCB+ACEI/ARB | CCB |
| 3725 | ACEI/ARB | D+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB |
| 3726 | ACEI/ARB | D+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB |
| 3727 | ACEI/ARB | D+ACEI/ARB | BB+CCB+ACEI/ARB | BB+CCB |
| 3728 | ACEI/ARB | D+ACEI/ARB | BB+CCB+ACEI/ARB | BB+ACEI/ARB |
| 3729 | ACEI/ARB | D+ACEI/ARB | BB+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 3730 | ACEI/ARB | D+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 3731 | ACEI/ARB | D+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 3732 | ACEI/ARB | D+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3733 | ACEI/ARB | BB+CCB | D | BB |
| 3734 | ACEI/ARB | BB+CCB | D | CCB |
| 3735 | ACEI/ARB | BB+CCB | D | D+BB |
| 3736 | ACEI/ARB | BB+CCB | D | D+CCB |
| 3737 | ACEI/ARB | BB+CCB | D | D+ACEI/ARB |
| 3738 | ACEI/ARB | BB+CCB | D | BB+ACEI/ARB |
| 3739 | ACEI/ARB | BB+CCB | D | CCB+ACEI/ARB |
| 3740 | ACEI/ARB | BB+CCB | D | D+BB+CCB |
| 3741 | ACEI/ARB | BB+CCB | D | D+BB+ACEI/ARB |
| 3742 | ACEI/ARB | BB+CCB | D | D+CCB+ACEI/ARB |
| 3743 | ACEI/ARB | BB+CCB | D | BB+CCB+ACEI/ARB |
| 3744 | ACEI/ARB | BB+CCB | BB | D |
| 3745 | ACEI/ARB | BB+CCB | BB | CCB |
| 3746 | ACEI/ARB | BB+CCB | BB | D+BB |
| 3747 | ACEI/ARB | BB+CCB | BB | D+CCB |
| 3748 | ACEI/ARB | BB+CCB | BB | D+ACEI/ARB |
| 3749 | ACEI/ARB | BB+CCB | BB | BB+ACEI/ARB |
| 3750 | ACEI/ARB | BB+CCB | BB | CCB+ACEI/ARB |
| 3751 | ACEI/ARB | BB+CCB | BB | D+BB+CCB |
| 3752 | ACEI/ARB | BB+CCB | BB | D+BB+ACEI/ARB |
| 3753 | ACEI/ARB | BB+CCB | BB | D+CCB+ACEI/ARB |
| 3754 | ACEI/ARB | BB+CCB | BB | BB+CCB+ACEI/ARB |
| 3755 | ACEI/ARB | BB+CCB | CCB | D |
| 3756 | ACEI/ARB | BB+CCB | CCB | BB |
| 3757 | ACEI/ARB | BB+CCB | CCB | D+BB |
| 3758 | ACEI/ARB | BB+CCB | CCB | D+CCB |
| 3759 | ACEI/ARB | BB+CCB | CCB | D+ACEI/ARB |
| 3760 | ACEI/ARB | BB+CCB | CCB | BB+ACEI/ARB |
| 3761 | ACEI/ARB | BB+CCB | CCB | CCB+ACEI/ARB |
| 3762 | ACEI/ARB | BB+CCB | CCB | D+BB+CCB |
| 3763 | ACEI/ARB | BB+CCB | CCB | D+BB+ACEI/ARB |
| 3764 | ACEI/ARB | BB+CCB | CCB | D+CCB+ACEI/ARB |
| 3765 | ACEI/ARB | BB+CCB | CCB | BB+CCB+ACEI/ARB |
| 3766 | ACEI/ARB | BB+CCB | D+BB | D |
| 3767 | ACEI/ARB | BB+CCB | D+BB | BB |
| 3768 | ACEI/ARB | BB+CCB | D+BB | CCB |
| 3769 | ACEI/ARB | BB+CCB | D+BB | D+CCB |
| 3770 | ACEI/ARB | BB+CCB | D+BB | D+ACEI/ARB |
| 3771 | ACEI/ARB | BB+CCB | D+BB | BB+ACEI/ARB |
| 3772 | ACEI/ARB | BB+CCB | D+BB | CCB+ACEI/ARB |
| 3773 | ACEI/ARB | BB+CCB | D+BB | D+BB+CCB |
| 3774 | ACEI/ARB | BB+CCB | D+BB | D+BB+ACEI/ARB |
| 3775 | ACEI/ARB | BB+CCB | D+BB | D+CCB+ACEI/ARB |
| 3776 | ACEI/ARB | BB+CCB | D+BB | BB+CCB+ACEI/ARB |
| 3777 | ACEI/ARB | BB+CCB | D+CCB | D |
| 3778 | ACEI/ARB | BB+CCB | D+CCB | BB |
| 3779 | ACEI/ARB | BB+CCB | D+CCB | CCB |
| 3780 | ACEI/ARB | BB+CCB | D+CCB | D+BB |
| 3781 | ACEI/ARB | BB+CCB | D+CCB | D+ACEI/ARB |
| 3782 | ACEI/ARB | BB+CCB | D+CCB | BB+ACEI/ARB |
| 3783 | ACEI/ARB | BB+CCB | D+CCB | CCB+ACEI/ARB |
| 3784 | ACEI/ARB | BB+CCB | D+CCB | D+BB+CCB |
| 3785 | ACEI/ARB | BB+CCB | D+CCB | D+BB+ACEI/ARB |
| 3786 | ACEI/ARB | BB+CCB | D+CCB | D+CCB+ACEI/ARB |
| 3787 | ACEI/ARB | BB+CCB | D+CCB | BB+CCB+ACEI/ARB |
| 3788 | ACEI/ARB | BB+CCB | D+ACEIs/ARB | D |
| 3789 | ACEI/ARB | BB+CCB | D+ACEIs/ARB | BB |
| 3790 | ACEI/ARB | BB+CCB | D+ACEIs/ARB | CCB |
| 3791 | ACEI/ARB | BB+CCB | D+ACEIs/ARB | D+BB |
| 3792 | ACEI/ARB | BB+CCB | D+ACEIs/ARB | D+CCB |
| 3793 | ACEI/ARB | BB+CCB | D+ACEIs/ARB | BB+ACEI/ARB |
| 3794 | ACEI/ARB | BB+CCB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 3795 | ACEI/ARB | BB+CCB | D+ACEIs/ARB | D+BB+CCB |
| 3796 | ACEI/ARB | BB+CCB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 3797 | ACEI/ARB | BB+CCB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 3798 | ACEI/ARB | BB+CCB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 3799 | ACEI/ARB | BB+CCB | BB+ACEI/ARB | D |
| 3800 | ACEI/ARB | BB+CCB | BB+ACEI/ARB | BB |
| 3801 | ACEI/ARB | BB+CCB | BB+ACEI/ARB | CCB |
| 3802 | ACEI/ARB | BB+CCB | BB+ACEI/ARB | D+BB |
| 3803 | ACEI/ARB | BB+CCB | BB+ACEI/ARB | D+CCB |
| 3804 | ACEI/ARB | BB+CCB | BB+ACEI/ARB | D+ACEI/ARB |
| 3805 | ACEI/ARB | BB+CCB | BB+ACEI/ARB | CCB+ACEI/ARB |
| 3806 | ACEI/ARB | BB+CCB | BB+ACEI/ARB | D+BB+CCB |
| 3807 | ACEI/ARB | BB+CCB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 3808 | ACEI/ARB | BB+CCB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3809 | ACEI/ARB | BB+CCB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3810 | ACEI/ARB | BB+CCB | CCB+ACEI/ARB | D |
| 3811 | ACEI/ARB | BB+CCB | CCB+ACEI/ARB | BB |
| 3812 | ACEI/ARB | BB+CCB | CCB+ACEI/ARB | CCB |
| 3813 | ACEI/ARB | BB+CCB | CCB+ACEI/ARB | D+BB |
| 3814 | ACEI/ARB | BB+CCB | CCB+ACEI/ARB | D+CCB |
| 3815 | ACEI/ARB | BB+CCB | CCB+ACEI/ARB | D+ACEI/ARB |
| 3816 | ACEI/ARB | BB+CCB | CCB+ACEI/ARB | BB+ACEI/ARB |
| 3817 | ACEI/ARB | BB+CCB | CCB+ACEI/ARB | D+BB+CCB |
| 3818 | ACEI/ARB | BB+CCB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 3819 | ACEI/ARB | BB+CCB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3820 | ACEI/ARB | BB+CCB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3821 | ACEI/ARB | BB+CCB | D+BB+CCB | D |
| 3822 | ACEI/ARB | BB+CCB | D+BB+CCB | BB |
| 3823 | ACEI/ARB | BB+CCB | D+BB+CCB | CCB |
| 3824 | ACEI/ARB | BB+CCB | D+BB+CCB | D+BB |
| 3825 | ACEI/ARB | BB+CCB | D+BB+CCB | D+CCB |
| 3826 | ACEI/ARB | BB+CCB | D+BB+CCB | D+ACEI/ARB |
| 3827 | ACEI/ARB | BB+CCB | D+BB+CCB | BB+ACEI/ARB |
| 3828 | ACEI/ARB | BB+CCB | D+BB+CCB | CCB+ACEI/ARB |
| 3829 | ACEI/ARB | BB+CCB | D+BB+CCB | D+BB+ACEI/ARB |
| 3830 | ACEI/ARB | BB+CCB | D+BB+CCB | D+CCB+ACEI/ARB |
| 3831 | ACEI/ARB | BB+CCB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 3832 | ACEI/ARB | BB+CCB | D+BB+ACEI/ARB | D |
| 3833 | ACEI/ARB | BB+CCB | D+BB+ACEI/ARB | BB |
| 3834 | ACEI/ARB | BB+CCB | D+BB+ACEI/ARB | CCB |
| 3835 | ACEI/ARB | BB+CCB | D+BB+ACEI/ARB | D+BB |
| 3836 | ACEI/ARB | BB+CCB | D+BB+ACEI/ARB | D+CCB |
| 3837 | ACEI/ARB | BB+CCB | D+BB+ACEI/ARB | D+ACEI/ARB |
| 3838 | ACEI/ARB | BB+CCB | D+BB+ACEI/ARB | BB+ACEI/ARB |
| 3839 | ACEI/ARB | BB+CCB | D+BB+ACEI/ARB | CCB+ACEI/ARB |
| 3840 | ACEI/ARB | BB+CCB | D+BB+ACEI/ARB | D+BB+CCB |
| 3841 | ACEI/ARB | BB+CCB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3842 | ACEI/ARB | BB+CCB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3843 | ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB | D |
| 3844 | ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB | BB |
| 3845 | ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB | CCB |
| 3846 | ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB | D+BB |
| 3847 | ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB | D+CCB |
| 3848 | ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB | D+ACEI/ARB |
| 3849 | ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB | BB+ACEI/ARB |
| 3850 | ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 3851 | ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB | D+BB+CCB |
| 3852 | ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 3853 | ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3854 | ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB | D |
| 3855 | ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB | BB |
| 3856 | ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB | CCB |
| 3857 | ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB | D+BB |
| 3858 | ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB | D+CCB |
| 3859 | ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB | D+ACEI/ARB |
| 3860 | ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB | BB+ACEI/ARB |
| 3861 | ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 3862 | ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 3863 | ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 3864 | ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3865 | ACEI/ARB | BB+ACEI/ARB | D | BB |
| 3866 | ACEI/ARB | BB+ACEI/ARB | D | CCB |
| 3867 | ACEI/ARB | BB+ACEI/ARB | D | D+BB |
| 3868 | ACEI/ARB | BB+ACEI/ARB | D | D+CCB |
| 3869 | ACEI/ARB | BB+ACEI/ARB | D | D+ACEI/ARB |
| 3870 | ACEI/ARB | BB+ACEI/ARB | D | BB+CCB |
| 3871 | ACEI/ARB | BB+ACEI/ARB | D | CCB+ACEI/ARB |
| 3872 | ACEI/ARB | BB+ACEI/ARB | D | D+BB+CCB |
| 3873 | ACEI/ARB | BB+ACEI/ARB | D | D+BB+ACEI/ARB |
| 3874 | ACEI/ARB | BB+ACEI/ARB | D | D+CCB+ACEI/ARB |
| 3875 | ACEI/ARB | BB+ACEI/ARB | D | BB+CCB+ACEI/ARB |
| 3876 | ACEI/ARB | BB+ACEI/ARB | BB | D |
| 3877 | ACEI/ARB | BB+ACEI/ARB | BB | CCB |
| 3878 | ACEI/ARB | BB+ACEI/ARB | BB | D+BB |
| 3879 | ACEI/ARB | BB+ACEI/ARB | BB | D+CCB |
| 3880 | ACEI/ARB | BB+ACEI/ARB | BB | D+ACEI/ARB |
| 3881 | ACEI/ARB | BB+ACEI/ARB | BB | BB+CCB |
| 3882 | ACEI/ARB | BB+ACEI/ARB | BB | CCB+ACEI/ARB |
| 3883 | ACEI/ARB | BB+ACEI/ARB | BB | D+BB+CCB |
| 3884 | ACEI/ARB | BB+ACEI/ARB | BB | D+BB+ACEI/ARB |
| 3885 | ACEI/ARB | BB+ACEI/ARB | BB | D+CCB+ACEI/ARB |
| 3886 | ACEI/ARB | BB+ACEI/ARB | BB | BB+CCB+ACEI/ARB |
| 3887 | ACEI/ARB | BB+ACEI/ARB | CCB | D |
| 3888 | ACEI/ARB | BB+ACEI/ARB | CCB | BB |
| 3889 | ACEI/ARB | BB+ACEI/ARB | CCB | D+BB |
| 3890 | ACEI/ARB | BB+ACEI/ARB | CCB | D+CCB |
| 3891 | ACEI/ARB | BB+ACEI/ARB | CCB | D+ACEI/ARB |
| 3892 | ACEI/ARB | BB+ACEI/ARB | CCB | BB+CCB |
| 3893 | ACEI/ARB | BB+ACEI/ARB | CCB | CCB+ACEI/ARB |
| 3894 | ACEI/ARB | BB+ACEI/ARB | CCB | D+BB+CCB |
| 3895 | ACEI/ARB | BB+ACEI/ARB | CCB | D+BB+ACEI/ARB |
| 3896 | ACEI/ARB | BB+ACEI/ARB | CCB | D+CCB+ACEI/ARB |
| 3897 | ACEI/ARB | BB+ACEI/ARB | CCB | BB+CCB+ACEI/ARB |
| 3898 | ACEI/ARB | BB+ACEI/ARB | D+BB | D |
| 3899 | ACEI/ARB | BB+ACEI/ARB | D+BB | BB |
| 3900 | ACEI/ARB | BB+ACEI/ARB | D+BB | CCB |
| 3901 | ACEI/ARB | BB+ACEI/ARB | D+BB | D+CCB |
| 3902 | ACEI/ARB | BB+ACEI/ARB | D+BB | D+ACEI/ARB |
| 3903 | ACEI/ARB | BB+ACEI/ARB | D+BB | BB+CCB |
| 3904 | ACEI/ARB | BB+ACEI/ARB | D+BB | CCB+ACEI/ARB |
| 3905 | ACEI/ARB | BB+ACEI/ARB | D+BB | D+BB+CCB |
| 3906 | ACEI/ARB | BB+ACEI/ARB | D+BB | D+BB+ACEI/ARB |
| 3907 | ACEI/ARB | BB+ACEI/ARB | D+BB | D+CCB+ACEI/ARB |
| 3908 | ACEI/ARB | BB+ACEI/ARB | D+BB | BB+CCB+ACEI/ARB |
| 3909 | ACEI/ARB | BB+ACEI/ARB | D+CCB | D |
| 3910 | ACEI/ARB | BB+ACEI/ARB | D+CCB | BB |
| 3911 | ACEI/ARB | BB+ACEI/ARB | D+CCB | CCB |
| 3912 | ACEI/ARB | BB+ACEI/ARB | D+CCB | D+BB |
| 3913 | ACEI/ARB | BB+ACEI/ARB | D+CCB | D+ACEI/ARB |
| 3914 | ACEI/ARB | BB+ACEI/ARB | D+CCB | BB+CCB |
| 3915 | ACEI/ARB | BB+ACEI/ARB | D+CCB | CCB+ACEI/ARB |
| 3916 | ACEI/ARB | BB+ACEI/ARB | D+CCB | D+BB+CCB |
| 3917 | ACEI/ARB | BB+ACEI/ARB | D+CCB | D+BB+ACEI/ARB |
| 3918 | ACEI/ARB | BB+ACEI/ARB | D+CCB | D+CCB+ACEI/ARB |
| 3919 | ACEI/ARB | BB+ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB |
| 3920 | ACEI/ARB | BB+ACEI/ARB | D+ACEIs/ARB | D |
| 3921 | ACEI/ARB | BB+ACEI/ARB | D+ACEIs/ARB | BB |
| 3922 | ACEI/ARB | BB+ACEI/ARB | D+ACEIs/ARB | CCB |
| 3923 | ACEI/ARB | BB+ACEI/ARB | D+ACEIs/ARB | D+BB |
| 3924 | ACEI/ARB | BB+ACEI/ARB | D+ACEIs/ARB | D+CCB |
| 3925 | ACEI/ARB | BB+ACEI/ARB | D+ACEIs/ARB | BB+CCB |
| 3926 | ACEI/ARB | BB+ACEI/ARB | D+ACEIs/ARB | CCB+ACEI/ARB |
| 3927 | ACEI/ARB | BB+ACEI/ARB | D+ACEIs/ARB | D+BB+CCB |
| 3928 | ACEI/ARB | BB+ACEI/ARB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 3929 | ACEI/ARB | BB+ACEI/ARB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 3930 | ACEI/ARB | BB+ACEI/ARB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 3931 | ACEI/ARB | BB+ACEI/ARB | BB+CCB | D |
| 3932 | ACEI/ARB | BB+ACEI/ARB | BB+CCB | BB |
| 3933 | ACEI/ARB | BB+ACEI/ARB | BB+CCB | CCB |
| 3934 | ACEI/ARB | BB+ACEI/ARB | BB+CCB | D+BB |
| 3935 | ACEI/ARB | BB+ACEI/ARB | BB+CCB | D+CCB |
| 3936 | ACEI/ARB | BB+ACEI/ARB | BB+CCB | D+ACEI/ARB |
| 3937 | ACEI/ARB | BB+ACEI/ARB | BB+CCB | CCB+ACEI/ARB |
| 3938 | ACEI/ARB | BB+ACEI/ARB | BB+CCB | D+BB+CCB |
| 3939 | ACEI/ARB | BB+ACEI/ARB | BB+CCB | D+BB+ACEI/ARB |
| 3940 | ACEI/ARB | BB+ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB |
| 3941 | ACEI/ARB | BB+ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB |
| 3942 | ACEI/ARB | BB+ACEI/ARB | CCB+ACEI/ARB | D |
| 3943 | ACEI/ARB | BB+ACEI/ARB | CCB+ACEI/ARB | BB |
| 3944 | ACEI/ARB | BB+ACEI/ARB | CCB+ACEI/ARB | CCB |
| 3945 | ACEI/ARB | BB+ACEI/ARB | CCB+ACEI/ARB | D+BB |
| 3946 | ACEI/ARB | BB+ACEI/ARB | CCB+ACEI/ARB | D+CCB |
| 3947 | ACEI/ARB | BB+ACEI/ARB | CCB+ACEI/ARB | D+ACEI/ARB |
| 3948 | ACEI/ARB | BB+ACEI/ARB | CCB+ACEI/ARB | BB+CCB |
| 3949 | ACEI/ARB | BB+ACEI/ARB | CCB+ACEI/ARB | D+BB+CCB |
| 3950 | ACEI/ARB | BB+ACEI/ARB | CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 3951 | ACEI/ARB | BB+ACEI/ARB | CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3952 | ACEI/ARB | BB+ACEI/ARB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3953 | ACEI/ARB | BB+ACEI/ARB | D+BB+CCB | D |
| 3954 | ACEI/ARB | BB+ACEI/ARB | D+BB+CCB | BB |
| 3955 | ACEI/ARB | BB+ACEI/ARB | D+BB+CCB | CCB |
| 3956 | ACEI/ARB | BB+ACEI/ARB | D+BB+CCB | D+BB |
| 3957 | ACEI/ARB | BB+ACEI/ARB | D+BB+CCB | D+CCB |
| 3958 | ACEI/ARB | BB+ACEI/ARB | D+BB+CCB | D+ACEI/ARB |
| 3959 | ACEI/ARB | BB+ACEI/ARB | D+BB+CCB | BB+CCB |
| 3960 | ACEI/ARB | BB+ACEI/ARB | D+BB+CCB | CCB+ACEI/ARB |
| 3961 | ACEI/ARB | BB+ACEI/ARB | D+BB+CCB | D+BB+ACEI/ARB |
| 3962 | ACEI/ARB | BB+ACEI/ARB | D+BB+CCB | D+CCB+ACEI/ARB |
| 3963 | ACEI/ARB | BB+ACEI/ARB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 3964 | ACEI/ARB | BB+ACEI/ARB | D+BB+ACEI/ARB | D |
| 3965 | ACEI/ARB | BB+ACEI/ARB | D+BB+ACEI/ARB | BB |
| 3966 | ACEI/ARB | BB+ACEI/ARB | D+BB+ACEI/ARB | CCB |
| 3967 | ACEI/ARB | BB+ACEI/ARB | D+BB+ACEI/ARB | D+BB |
| 3968 | ACEI/ARB | BB+ACEI/ARB | D+BB+ACEI/ARB | D+CCB |
| 3969 | ACEI/ARB | BB+ACEI/ARB | D+BB+ACEI/ARB | D+ACEI/ARB |
| 3970 | ACEI/ARB | BB+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB |
| 3971 | ACEI/ARB | BB+ACEI/ARB | D+BB+ACEI/ARB | CCB+ACEI/ARB |
| 3972 | ACEI/ARB | BB+ACEI/ARB | D+BB+ACEI/ARB | D+BB+CCB |
| 3973 | ACEI/ARB | BB+ACEI/ARB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3974 | ACEI/ARB | BB+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3975 | ACEI/ARB | BB+ACEI/ARB | D+CCB+ACEI/ARB | D |
| 3976 | ACEI/ARB | BB+ACEI/ARB | D+CCB+ACEI/ARB | BB |
| 3977 | ACEI/ARB | BB+ACEI/ARB | D+CCB+ACEI/ARB | CCB |
| 3978 | ACEI/ARB | BB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB |
| 3979 | ACEI/ARB | BB+ACEI/ARB | D+CCB+ACEI/ARB | D+CCB |
| 3980 | ACEI/ARB | BB+ACEI/ARB | D+CCB+ACEI/ARB | D+ACEI/ARB |
| 3981 | ACEI/ARB | BB+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB |
| 3982 | ACEI/ARB | BB+ACEI/ARB | D+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 3983 | ACEI/ARB | BB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+CCB |
| 3984 | ACEI/ARB | BB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 3985 | ACEI/ARB | BB+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 3986 | ACEI/ARB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D |
| 3987 | ACEI/ARB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | BB |
| 3988 | ACEI/ARB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | CCB |
| 3989 | ACEI/ARB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB |
| 3990 | ACEI/ARB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB |
| 3991 | ACEI/ARB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+ACEI/ARB |
| 3992 | ACEI/ARB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | BB+CCB |
| 3993 | ACEI/ARB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | CCB+ACEI/ARB |
| 3994 | ACEI/ARB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 3995 | ACEI/ARB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 3996 | ACEI/ARB | BB+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |
| 3997 | ACEI/ARB | CCB+ACEI/ARB | D | BB |
| 3998 | ACEI/ARB | CCB+ACEI/ARB | D | CCB |
| 3999 | ACEI/ARB | CCB+ACEI/ARB | D | D+BB |
| 4000 | ACEI/ARB | CCB+ACEI/ARB | D | D+CCB |
| 4001 | ACEI/ARB | CCB+ACEI/ARB | D | D+ACEI/ARB |
| 4002 | ACEI/ARB | CCB+ACEI/ARB | D | BB+CCB |
| 4003 | ACEI/ARB | CCB+ACEI/ARB | D | BB+ACEI/ARB |
| 4004 | ACEI/ARB | CCB+ACEI/ARB | D | D+BB+CCB |
| 4005 | ACEI/ARB | CCB+ACEI/ARB | D | D+BB+ACEI/ARB |
| 4006 | ACEI/ARB | CCB+ACEI/ARB | D | D+CCB+ACEI/ARB |
| 4007 | ACEI/ARB | CCB+ACEI/ARB | D | BB+CCB+ACEI/ARB |
| 4008 | ACEI/ARB | CCB+ACEI/ARB | BB | D |
| 4009 | ACEI/ARB | CCB+ACEI/ARB | BB | CCB |
| 4010 | ACEI/ARB | CCB+ACEI/ARB | BB | D+BB |
| 4011 | ACEI/ARB | CCB+ACEI/ARB | BB | D+CCB |
| 4012 | ACEI/ARB | CCB+ACEI/ARB | BB | D+ACEI/ARB |
| 4013 | ACEI/ARB | CCB+ACEI/ARB | BB | BB+CCB |
| 4014 | ACEI/ARB | CCB+ACEI/ARB | BB | BB+ACEI/ARB |
| 4015 | ACEI/ARB | CCB+ACEI/ARB | BB | D+BB+CCB |
| 4016 | ACEI/ARB | CCB+ACEI/ARB | BB | D+BB+ACEI/ARB |
| 4017 | ACEI/ARB | CCB+ACEI/ARB | BB | D+CCB+ACEI/ARB |
| 4018 | ACEI/ARB | CCB+ACEI/ARB | BB | BB+CCB+ACEI/ARB |
| 4019 | ACEI/ARB | CCB+ACEI/ARB | CCB | D |
| 4020 | ACEI/ARB | CCB+ACEI/ARB | CCB | BB |
| 4021 | ACEI/ARB | CCB+ACEI/ARB | CCB | D+BB |
| 4022 | ACEI/ARB | CCB+ACEI/ARB | CCB | D+CCB |
| 4023 | ACEI/ARB | CCB+ACEI/ARB | CCB | D+ACEI/ARB |
| 4024 | ACEI/ARB | CCB+ACEI/ARB | CCB | BB+CCB |
| 4025 | ACEI/ARB | CCB+ACEI/ARB | CCB | BB+ACEI/ARB |
| 4026 | ACEI/ARB | CCB+ACEI/ARB | CCB | D+BB+CCB |
| 4027 | ACEI/ARB | CCB+ACEI/ARB | CCB | D+BB+ACEI/ARB |
| 4028 | ACEI/ARB | CCB+ACEI/ARB | CCB | D+CCB+ACEI/ARB |
| 4029 | ACEI/ARB | CCB+ACEI/ARB | CCB | BB+CCB+ACEI/ARB |
| 4030 | ACEI/ARB | CCB+ACEI/ARB | D+BB | D |
| 4031 | ACEI/ARB | CCB+ACEI/ARB | D+BB | BB |
| 4032 | ACEI/ARB | CCB+ACEI/ARB | D+BB | CCB |
| 4033 | ACEI/ARB | CCB+ACEI/ARB | D+BB | D+CCB |
| 4034 | ACEI/ARB | CCB+ACEI/ARB | D+BB | D+ACEI/ARB |
| 4035 | ACEI/ARB | CCB+ACEI/ARB | D+BB | BB+CCB |
| 4036 | ACEI/ARB | CCB+ACEI/ARB | D+BB | BB+ACEI/ARB |
| 4037 | ACEI/ARB | CCB+ACEI/ARB | D+BB | D+BB+CCB |
| 4038 | ACEI/ARB | CCB+ACEI/ARB | D+BB | D+BB+ACEI/ARB |
| 4039 | ACEI/ARB | CCB+ACEI/ARB | D+BB | D+CCB+ACEI/ARB |
| 4040 | ACEI/ARB | CCB+ACEI/ARB | D+BB | BB+CCB+ACEI/ARB |
| 4041 | ACEI/ARB | CCB+ACEI/ARB | D+CCB | D |
| 4042 | ACEI/ARB | CCB+ACEI/ARB | D+CCB | BB |
| 4043 | ACEI/ARB | CCB+ACEI/ARB | D+CCB | CCB |
| 4044 | ACEI/ARB | CCB+ACEI/ARB | D+CCB | D+BB |
| 4045 | ACEI/ARB | CCB+ACEI/ARB | D+CCB | D+ACEI/ARB |
| 4046 | ACEI/ARB | CCB+ACEI/ARB | D+CCB | BB+CCB |
| 4047 | ACEI/ARB | CCB+ACEI/ARB | D+CCB | BB+ACEI/ARB |
| 4048 | ACEI/ARB | CCB+ACEI/ARB | D+CCB | D+BB+CCB |
| 4049 | ACEI/ARB | CCB+ACEI/ARB | D+CCB | D+BB+ACEI/ARB |
| 4050 | ACEI/ARB | CCB+ACEI/ARB | D+CCB | D+CCB+ACEI/ARB |
| 4051 | ACEI/ARB | CCB+ACEI/ARB | D+CCB | BB+CCB+ACEI/ARB |
| 4052 | ACEI/ARB | CCB+ACEI/ARB | D+ACEIs/ARB | D |
| 4053 | ACEI/ARB | CCB+ACEI/ARB | D+ACEIs/ARB | BB |
| 4054 | ACEI/ARB | CCB+ACEI/ARB | D+ACEIs/ARB | CCB |
| 4055 | ACEI/ARB | CCB+ACEI/ARB | D+ACEIs/ARB | D+BB |
| 4056 | ACEI/ARB | CCB+ACEI/ARB | D+ACEIs/ARB | D+CCB |
| 4057 | ACEI/ARB | CCB+ACEI/ARB | D+ACEIs/ARB | BB+CCB |
| 4058 | ACEI/ARB | CCB+ACEI/ARB | D+ACEIs/ARB | BB+ACEI/ARB |
| 4059 | ACEI/ARB | CCB+ACEI/ARB | D+ACEIs/ARB | D+BB+CCB |
| 4060 | ACEI/ARB | CCB+ACEI/ARB | D+ACEIs/ARB | D+BB+ACEI/ARB |
| 4061 | ACEI/ARB | CCB+ACEI/ARB | D+ACEIs/ARB | D+CCB+ACEI/ARB |
| 4062 | ACEI/ARB | CCB+ACEI/ARB | D+ACEIs/ARB | BB+CCB+ACEI/ARB |
| 4063 | ACEI/ARB | CCB+ACEI/ARB | BB+CCB | D |
| 4064 | ACEI/ARB | CCB+ACEI/ARB | BB+CCB | BB |
| 4065 | ACEI/ARB | CCB+ACEI/ARB | BB+CCB | CCB |
| 4066 | ACEI/ARB | CCB+ACEI/ARB | BB+CCB | D+BB |
| 4067 | ACEI/ARB | CCB+ACEI/ARB | BB+CCB | D+CCB |
| 4068 | ACEI/ARB | CCB+ACEI/ARB | BB+CCB | D+ACEI/ARB |
| 4069 | ACEI/ARB | CCB+ACEI/ARB | BB+CCB | BB+ACEI/ARB |
| 4070 | ACEI/ARB | CCB+ACEI/ARB | BB+CCB | D+BB+CCB |
| 4071 | ACEI/ARB | CCB+ACEI/ARB | BB+CCB | D+BB+ACEI/ARB |
| 4072 | ACEI/ARB | CCB+ACEI/ARB | BB+CCB | D+CCB+ACEI/ARB |
| 4073 | ACEI/ARB | CCB+ACEI/ARB | BB+CCB | BB+CCB+ACEI/ARB |
| 4074 | ACEI/ARB | CCB+ACEI/ARB | BB+ACEI/ARB | D |
| 4075 | ACEI/ARB | CCB+ACEI/ARB | BB+ACEI/ARB | BB |
| 4076 | ACEI/ARB | CCB+ACEI/ARB | BB+ACEI/ARB | CCB |
| 4077 | ACEI/ARB | CCB+ACEI/ARB | BB+ACEI/ARB | D+BB |
| 4078 | ACEI/ARB | CCB+ACEI/ARB | BB+ACEI/ARB | D+CCB |
| 4079 | ACEI/ARB | CCB+ACEI/ARB | BB+ACEI/ARB | D+ACEI/ARB |
| 4080 | ACEI/ARB | CCB+ACEI/ARB | BB+ACEI/ARB | BB+CCB |
| 4081 | ACEI/ARB | CCB+ACEI/ARB | BB+ACEI/ARB | D+BB+CCB |
| 4082 | ACEI/ARB | CCB+ACEI/ARB | BB+ACEI/ARB | D+BB+ACEI/ARB |
| 4083 | ACEI/ARB | CCB+ACEI/ARB | BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 4084 | ACEI/ARB | CCB+ACEI/ARB | BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 4085 | ACEI/ARB | CCB+ACEI/ARB | D+BB+CCB | D |
| 4086 | ACEI/ARB | CCB+ACEI/ARB | D+BB+CCB | BB |
| 4087 | ACEI/ARB | CCB+ACEI/ARB | D+BB+CCB | CCB |
| 4088 | ACEI/ARB | CCB+ACEI/ARB | D+BB+CCB | D+BB |
| 4089 | ACEI/ARB | CCB+ACEI/ARB | D+BB+CCB | D+CCB |
| 4090 | ACEI/ARB | CCB+ACEI/ARB | D+BB+CCB | D+ACEI/ARB |
| 4091 | ACEI/ARB | CCB+ACEI/ARB | D+BB+CCB | BB+CCB |
| 4092 | ACEI/ARB | CCB+ACEI/ARB | D+BB+CCB | BB+ACEI/ARB |
| 4093 | ACEI/ARB | CCB+ACEI/ARB | D+BB+CCB | D+BB+ACEI/ARB |
| 4094 | ACEI/ARB | CCB+ACEI/ARB | D+BB+CCB | D+CCB+ACEI/ARB |
| 4095 | ACEI/ARB | CCB+ACEI/ARB | D+BB+CCB | BB+CCB+ACEI/ARB |
| 4096 | ACEI/ARB | CCB+ACEI/ARB | D+BB+ACEI/ARB | D |
| 4097 | ACEI/ARB | CCB+ACEI/ARB | D+BB+ACEI/ARB | BB |
| 4098 | ACEI/ARB | CCB+ACEI/ARB | D+BB+ACEI/ARB | CCB |
| 4099 | ACEI/ARB | CCB+ACEI/ARB | D+BB+ACEI/ARB | D+BB |
| 4100 | ACEI/ARB | CCB+ACEI/ARB | D+BB+ACEI/ARB | D+CCB |
| 4101 | ACEI/ARB | CCB+ACEI/ARB | D+BB+ACEI/ARB | D+ACEI/ARB |
| 4102 | ACEI/ARB | CCB+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB |
| 4103 | ACEI/ARB | CCB+ACEI/ARB | D+BB+ACEI/ARB | BB+ACEI/ARB |
| 4104 | ACEI/ARB | CCB+ACEI/ARB | D+BB+ACEI/ARB | D+BB+CCB |
| 4105 | ACEI/ARB | CCB+ACEI/ARB | D+BB+ACEI/ARB | D+CCB+ACEI/ARB |
| 4106 | ACEI/ARB | CCB+ACEI/ARB | D+BB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 4107 | ACEI/ARB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | D |
| 4108 | ACEI/ARB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | BB |
| 4109 | ACEI/ARB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | CCB |
| 4110 | ACEI/ARB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB |
| 4111 | ACEI/ARB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | D+CCB |
| 4112 | ACEI/ARB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | D+ACEI/ARB |
| 4113 | ACEI/ARB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB |
| 4114 | ACEI/ARB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | BB+ACEI/ARB |
| 4115 | ACEI/ARB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+CCB |
| 4116 | ACEI/ARB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 4117 | ACEI/ARB | CCB+ACEI/ARB | D+CCB+ACEI/ARB | BB+CCB+ACEI/ARB |
| 4118 | ACEI/ARB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D |
| 4119 | ACEI/ARB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | BB |
| 4120 | ACEI/ARB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | CCB |
| 4121 | ACEI/ARB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB |
| 4122 | ACEI/ARB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB |
| 4123 | ACEI/ARB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+ACEI/ARB |
| 4124 | ACEI/ARB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | BB+CCB |
| 4125 | ACEI/ARB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | BB+ACEI/ARB |
| 4126 | ACEI/ARB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+CCB |
| 4127 | ACEI/ARB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+BB+ACEI/ARB |
| 4128 | ACEI/ARB | CCB+ACEI/ARB | BB+CCB+ACEI/ARB | D+CCB+ACEI/ARB |

# Appendix 8. Simulated annealing results depending on the size of the neighbourhood

Table A8.1. Computational results from SA depending on the definition of the neighbourhood

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Definition of the neighbourhood | Size of the neighbourhood | Total iteration number | Time (h) | Time per iteration (s) | Optimal policy number | Total net benefit of the solution | Search rate |
| 25 | 50 | 2,400 | 6.59 | 9.88 | 625\* | 330,150 | 19.58 |
| 50 | 100 | 1,600 | 4.45 | 10.02 | 3721\* | 330,090 | 24.99 |
| 100 | 200 | 2,350 | 6.62 | 10.14 | 3721\* | 330,100 | 30.12 |

1) It was assumed that the initial temperature is 1 and the cooling rate is 0.7.

2) The solution numbers with \* are included in the top eight policies identified from the enumeration in Table ‎7.6.

Figure A8.1. Convergence depending on the definition of the neighbourhood

1. Most of the description in this section is based on Current Medical Diagnosis and Treatment[228] and Applied Therapeutics: The Clinical Use of Drugs[229]. [↑](#footnote-ref-1)