Can frailty inform the management of hypertension in older people?

Oliver Marcus Todd

Submitted in accordance with the requirements for the degree of
Doctor of Philosophy

The University of Leeds
School of Medicine

November 2020

Intellectual Property Statement

The candidate confirms that the work submitted is his/her own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Publications

Chapter 2 contains work based on the following publication:

1. Todd OM, Wilkinson C, Hale M, Wong NL, Hall M, Sheppard JP, McManus RJ, Rockwood K, Young J, Gale CP, Clegg A (2019). Is the association between blood pressure and mortality in older adults different with frailty? A systematic review and meta-analysis. *Age and Ageing* 48(5) 627-635.
   Attributable content to Oliver Todd: set the review question and inclusion criteria, performed the search, reviewed the abstracts and selected papers, extracted relevant data, undertook the meta-analysis and wrote the manuscript.
   Contributions of other authors: CW, MH, NLW performed second review of the abstracts and full texts for inclusion. CW also performed second data entry and checked meta-analysis results. All authors contributed to the preparation of the manuscript and approved the final manuscript. Deirdre Andre, research librarian at the University of Leeds helped devise the search strategy. Mark Perry (Bradford Institute of Health Research) assisted with the design of the literature search. Martin J Bland (University of York) helped with statistical methods of data extraction for the meta-analysis.

Chapter 3 contains work based on the following publication:

2. Todd O, Wilkinson C, Hollinghurst J, Sheppard J, Jones D, Akbari A, McManus R, Rockwood K, Lyons R, Harris D, Halcox J, Gilthorpe M, Hall M, Gale C, Clegg A (2019). Frailty as a prognostic factor in older adults with hypertension: protocol for an observational cohort study

using routine data from primary care. British Geriatrics Society Cardiovascular Section: September 6th 2019. Conference Abstract.
Attributable content to Oliver Todd: writing and presentation of the abstract.
Contributions of other authors: All authors contributed to the concept and proof read the abstract.

Chapter 5 contains work based on the following publications:

3. Todd OM, Clegg A, Godfrey M (2019). Am I frail, love? Yes, I suppose I am: what ten older people can tell us about living with frailty. *Innovation in Aging* 3 (Supplement 1): S293-294. Conference Abstract.
4. Todd O, Clegg A, Young J, Godfrey M (2019). Managing hypertension in people with frailty: an exploration of a patient led approach. *Age and Ageing* 48 (Issue supplement 2) ii11-ii12. Conference Abstract.
   Attributable content to Oliver Todd: Developed concept, successfully applied for ethical approval, conducted interviews and analysis, wrote and presented abstract
   Contributions of other authors: MG supervised interview technique and data analysis, MG and AC contributed to concept, interpretation and proof reading of the abstract.

Chapter 6 contains work based on the following publication:

5. Todd OM, Burton JK, Dodds RM, Hollinghurst J, Lyons RA, Quinn TJ, Schneider A, Walesby KE, Wilkinson C, Conroy S, Gale CP, Hall M, Walters K, Clegg AP (2020). New Horizons in the use of routine data for ageing research. *Age and Ageing* 49 (5) 716-722.
   Attributable content to Oliver Todd: Developed the concept, established a collaborative group, organised workshop, writing of the manuscript.
   Contributions of other authors: JKB, RMD, JH, RAL, TJQ, AS, KEW, CW, APC contributed and/or presented at a workshop on this theme at the British Geriatrics Society Spring Conference, May 2019, Cardiff, UK. SC, CPG, MH, KW contributed to the final manuscript.

Dedication

for my wife, Freya, and our family

Acknowledgements

I am tremendously grateful to Andy Clegg, Marlous Hall, Chris Gale, John Young and Mary Godfrey for all you have taught me, for your encouragement, and for sticking with me throughout. I would like to thank the generosity of the Dunhill Medical Trust for this research training fellowship which has been a very rich and wonderful experience.

I would like to thank the ten participants who gave their time and expertise in the narrative interview study, and Dorothy and Janet Jones for their invaluable guidance in designing this study.

I am very grateful to three teams: for their collaboration and support; for their generosity in hosting me at various stages through the fellowship; and, for teaching me new skills and ways of thinking. They are: James Sheppard and Richard McManus at the Nuffield Department of Primary Care Health Sciences, University of Oxford; Joe Hollinghurst, Ashley Akbari, and Ronan Lyons at the SAIL Databank, Swansea University; and Kenneth Rockwood, Sherri Fay and all the Geriatric Medicine Research team at Nova Scotia Health Authority and Dalhousie University.

I am indebted to David Stansfield for his eagle eye in proof-reading this thesis, to Arthur Duncan-Jones at Public Health Wales for his assistance on

statistical comparisons between Wales and England, and Martin J Bland at the University of York for his assistance with the meta-analysis. I have benefited greatly from the generous mentorship of John Gladman, at the University of Nottingham, and Trevor Sheldon at Bradford Institute for Health Research.

I would like to especially thank Chris Wilkinson, Mohammad Yadegarfar, Bernadette Dondo, Theresa Munyombwe, Mark Gilthorpe, Thiago Guimarães, Majid Riaz and Stephen Clark at the Leeds Institute for Data Analytics. I would also like to thank Anne Forster, Farhat Mahmood, Lesley Brown, Saim Mahmood, Deborah King, Chung Fu, Rekesh Corepal, Tom Crocker, Seline Perry, and Elizabeth Teale at the Bradford Institute for Health Research. In particular, I am very grateful to Rebecca Hawkins who stepped in at the last minute to help supervise my qualitative work. I am very grateful for the support and encouragement of clinical colleagues at Bradford Royal Infirmary, especially Eliz Brierley, Alex Brown, Alison McMurtry and Maj Pushpangadan.

Finally, this work was motivated by my grandparents Patricia Todd, Günter Kretzschmar, and Dan O'Driscoll. This thesis is written in the fond memory of Mary Godfrey, who very sadly died in September 2020. Mary's enthusiasm for this enquiry and her strong advocacy for the voice of the older person greatly influenced me, and I hope this work lives up to her high standards.

Abstract

Background

Hypertension increases the risk of cardiovascular disease. Whilst blood pressure (BP) lowering can reduce this risk, it can also cause adverse effects. This PhD study uses mixed methods to explore the utility of frailty to identify older people for whom the association of BP and outcomes is different.

Methods

Meta-analysis summarised observational studies to date. A retrospective cohort study used linked electronic health records from the Welsh Secure Anonymised Information Linkage (SAIL) databank. Frailty was measured using the electronic frailty index. Time to event analysis measured first ever major adverse cardiovascular event (MACE), all-cause mortality and injurious falls. Narrative interviews explored the perspectives of ten older people on the utility of frailty in managing hypertension on their terms.

Results

Meta-analysis identified that all-cause mortality was lower for older people who were not frail with systolic BP < 140 mm Hg compared to > 140 mm Hg, but there was no association in the context of frailty. In a population of 145,598 people with hypertension over the age of 65, compared to participants who were fit, people with frailty were associated with significantly higher MACE events despite adjustment for known cardiovascular risk factors (increased risk of 38% in mild frailty, 84% in moderate frailty, 117% in severe frailty). Frailty did not modify the association of BP and outcomes, but frailty did modify the association of BP-lowering medication and outcomes. Narrative interviews explored ways in which frailty could guide hypertension management towards what matters most to the individual.

Discussion

Findings provide evidence that frailty can usefully identify older people with increased risk of cardiovascular and non-cardiovascular outcomes in the context of hypertension management and suggest that the modifying effect of frailty in this context is in the degree to which someone sustains benefit or suffers adverse effects of BP-lowering treatment.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

@geridata	Ageing Data Research Collaborative
AASK	African American Study of Kidney Disease and Hypertension
ABPM	Ambulatory Blood Pressure monitoring
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	Angiotensin Converting Enzyme
ACh	Acetyl-choline
ACM	All-cause mortality
ADDE	Annual District Death Extract
ADR	Adverse Drug Reaction
AF	Atrial fibrillation
AHA	American Health Association
AI	Artificial intelligence
AIC	Akaike information criterion
AKI	Acute kidney injury
ALF	Anonymised linkage field
ARB	Angiotensin Receptor Blockers
ARR	Absolute risk reduction
AT-1	Angiotensin 1 Receptor
AT-2	Angiotensin 2 Receptors
BGS	British Geriatrics Society
BHS	British Hypertension Society
BIC	Bayesian information criterion
BMI	Body mass index
BNF	British national formulary
BP	Blood Pressure
CALIBER	Cardiovascular disease research using linked bespoke

	studies and electronic health records
Cardio-SIS	Studio Italiano Sugli Effetti CARDIOvascolari del Controllo della Pressione Arteriosa SIStolica
CARE75+	Community Ageing Research
CCF	Congestive cardiac failure
Chol: HDL	Cholesterol to High density lipoprotein ratio
CFAS	Cognitive Function and Ageing Study
CHD	Coronary heart disease
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
COREQ	Consolidated Criteria for Recording of Qualitative Research
CPRD	Clinical Practice Research Database
CRP	C-reactive protein
CTV-2	Read Version 2 codes
CTV-3	Clinical Terms Version 3
CV	Cardiovascular
CVD	Cerebrovascular disease
DB2	Database 2
dBP	diastolic blood pressure, measured in mm Hg
DISCO	Discovery of Symptomatic Cancer Optimally
DM	Diabetes mellitus
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ED	Emergency department
EDDS	Emergency department data set
eFI	electronic Frailty Index
eGFR	electronic Glomerular Filtration Rate

EHR	Electronic health records
EMBASE	Excerpta Medica dataBASE
EMIS	Egton Medical Information Systems
eNOS	endothelial Nitric Oxide Synthase
ESC	European society for cardiology
ESRD	End stage renal disease
ET	Endothelin
EWHPE	European Working Party for Hypertension in Elderly
F	Female
FCE	Finished consultant episodes
FI	frailty index
GDPR	European Union General Data Protection Regulation
GFI	Groeningen frailty index
GFR	Glomerular Filtration Rate
GP	General practitioner
GS	Gait speed
HbA1c	Glycated haemoglobin
HDL	High density lipoprotein
HES	Hospital Episode Statistics
HF	Heart failure
HFS	Hospital frailty score
HIRU	Health Information Research Unit
HOPE-3	Heart Outcomes Prevention Evaluation-3
HOT	Hypertension Optimal Treatment
HR	Hazard ratio
HYVET	Hypertension in the Very Elderly Trial
IBM	International Business Machines
ICD-9	International Classification of Disease manual, 9th edition
IGRP	Independent governance review panel

IHD	Ischaemic heart disease
IL	Interleukin
IMD	Index of Multiple Deprivation
IPD	individual patient data
IQR	Inter-quartile range
IV	Inverse Variance
JAMA	Journal of the American Medical Association
JATOS	Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients;
JNC	Joint National Committee
kg	kilograms
kg/m^2	kilograms per metre squared
LAPAQ	Longitudinal aging study Amsterdam (LASA) physical activity questionnaire
LSOA	Lower super output area
LVH	Left ventricular hypertrophy
M	Male
M	Metres
m/s	metres per second
MACE	Major adverse cardiovascular event
MACRAL	Matching algorithm for consistent results in anonymised linkage
mAP	Mean arterial pressure
MCCD	Medical certificate of cause of death
MCP-1	Monocyte chemoattractant protein-1
MEDLINE	Medical literature analysis and retrieval system online
mg/dL	milligrams per decilitre
MI	Myocardial infarction
MI	Multiple imputation
MICE	Multiple imputation by chained equations

mids	Multiply imputed data set
MINAP	Myocardial ischaemia national audit project
mira	Multiply imputed repeated analysis
mm Hg	millimetres of mercury
MMSE	Mini-mental status exam
mmol/l	millimoles per litre
MOOSE	Meta-analysis of observational studies in epidemiology
MPP	Massively parallel processing architecture
MRC	Medical Research Council (UK)
N	Sample size
Na	Sodium
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NO	Nitric Oxide
NOS	Not otherwise specified
NTS	Nucleus Tractus Solitarii
NWIS	NHS Wales Informatics Service
OFI	Osteoporotic fracture index
OH	Orthostatic hypotension
ONS	Office for National Statistics
OPCS-4	Office of population censuses and surveys classification of surgical operations and procedures, 4th revision
OPTIMISE	OPtimising Treatment for Mild Systolic hypertension in the Elderly
P	p-value
PARTAGE	Predictive Values of BP and Arterial Stiffness in Institutionalised Very Aged Population
PAS	Central patient administrative system
PEDW	Patient episode data Wales
PH	Proportional Hazards

PP	Pulse Pressure
PPP	Public Private Partnership
Pre-DIVA	Prevention of Dementia – Intensive Vascular care
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROGRESS	PROGnosis RESearch Strategy
PROSPERO	International database of prospectively registered systematic reviews in health and social care
PSC	Prospective study collaboration
QOF	Quality outcomes framework
RAAS	Renin Angiotensin Aldosterone System
RALF_PE	Regional Anonymised Linkage Field per person
RCT	Randomised Controlled Trials
REC	Research ethics committee
RECORD	REporting of studies Conducted using Observational Routinely-collected Data guideline
RoBANS	Risk of bias assessment tool for non-randomized studies
ROS	Reactive Oxygen Species
RR	Relative Risk
SAE	Significant adverse events
SAIL	Secure Anonymised Information Linkage
SANS	sympathetic autonomic nervous system
SASP	Senescence Associated Secretory Phenotype
sBP	systolic blood pressure
SE	Standard error
SHEP	Systolic Hypertension in the Elderly Program
SI	Standard International units
SLE	Systemic lupus erythematosus
SNOMED-CT	Systemised Nomenclature of Medicine-Clinical Terms

SPRINT	SPRINT = Systolic Blood Pressure Intervention Trial
SPS3	SPS3 = Secondary Prevention of Small Subcortical Strokes
SQL	Structure query language
STOP	Swedish trial in old patients with hypertension
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SWaLLow	Study of blood pressure: What matters in Later Life?
Syst-China	Systolic Hypertension in China
Syst-Eur	Systolic Hypertension in Europe trial
THIN	The Health Improvement Network
TNF-alpha	Tumour Necrosis Factor-alpha
TRUD	Technology Reference data Update Distribution
TTP	Trusted third party
UK	United Kingdom
UKPDS	UK prospective diabetes study group
UKSeRP	UK Secure Research Platform
USA	United States of America
VALISH	Valsartan in Elderly Isolated Systolic Hypertension Study
VPN	Virtual private network
WDSD	Welsh Demographic Service data set
WHO	World Health Organisation
WLGP	Welsh Longitudinal General Practice
WW1	World war 1
WW2	World war 2
Yrs	Years

Preface

Chapter 1 will review the current understanding of the pathophysiology of hypertension in the context of ageing. In Chapter 2, the available evidence will be critically appraised in a systematic review and meta-analysis. The methodology for the routine data study will be outlined in Chapter 3, and main findings in Chapter 4. In Chapter 5, I will present the methods and findings from a series of narrative interviews undertaken to explore a patient's perspective on the utility of frailty in hypertension management. The findings of the review, quantitative and qualitative studies will be presented and analysed in the context of current literature in Chapter 6, identifying implications for future research, policy and clinical practice.

Chapter 1 – Introduction

1.1 Summary

The understanding of hypertension as a disease of vascular ageing is new and evolving. In this chapter, recent advances are outlined in the understanding of vascular ageing as central to the aetiology of hypertension. I will consider each of the major pathological risk factors for hypertension in the context of vascular ageing. The role of treatment for hypertension is explored, both in terms of the benefits and the harms of BP-lowering medication. Following on from this, I outline grounds to consider the role of frailty in hypertension management from each perspective, with respect to the underlying biology and the challenges of identifying when and how to treat hypertension.

1.2 Definition of hypertension

Hypertension describes persistently raised arterial blood pressure (1). Hypertension may be best defined as the level at which the benefits of treatment exceed those of withholding treatment (2). International guidelines differ in their diagnostic criteria for hypertension, in the UK the National Institute for Health and Care Excellence (NICE) guidelines define hypertension as blood pressure > 140 / 90 millimetres of mercury (mm Hg). It is the most common preventable risk factor for mortality worldwide, and it is also a leading cause of global disparity in life years (3), disability (4), and, cardiovascular disease (5). Ranked by risk associated disability-adjusted life year, hypertension is the

leading cause of death overall, accountable for an estimated 10.4 million deaths (6) out of a total of 54.6 million deaths worldwide in 2017 (7).

1.3 Epidemiology

The prevalence of hypertension in the adult population in England is 30% among men, and 26% among women (8) making it the most common long-term condition nationally (9). In the context of the UK, approximately 19 million people are estimated to have hypertension. Second only to upper respiratory tract infections, hypertension is the most common reason to attend primary care (10). In people older than 45 years hypertension is the most prevalent long-term condition (11). In the UK, the cost of hypertension management was estimated at £2.1 billion of the £120 billion NHS budget in 2014 (12).

Worldwide, the number of people with hypertension has increased with population growth since 1975 (13) when it affected 594 million (15%) of the world's population. Over the next ten years the proportion of the population who have hypertension is anticipated to increase significantly from 1.13 billion (15%) in 2015 to 1.56 billion (19%) in 2025 (14). Whilst prevalence in high income countries is stable or in decline (15), the prevalence in low and middle income countries is on the rise (16).

The rise in hypertension prevalence is understood to relate to population ageing, increasingly sedentary lifestyles and a global shift towards urbanisation. Hypertension rises in a community or society where there is also a fall in

calorific energy expenditure and consequent change in body composition – for example, before and after the mechanisation of sleds in the Inuit community in Canada (17).

There is marked variation of blood pressure between individuals some of which depends on characteristics of the population studied, for example, ethnicity and age. Hypertension, in the USA varies significantly by ethnicity: prevalence is 42% among African Americans, and 26% among Hispanic Americans, 28% among White, and 25% Asian Americans (18). Hypertension in African Americans is also associated with a higher mortality than hypertension in White Americans (19, 20). In England, there is also variation in the prevalence of hypertension among those of the same age and ethnic group – with 3 fold variation in prevalence among middle aged men (21). Deprivation is also associated with disproportionately poor outcomes in hypertension (22).

1.4 Changes over the life-course

The systolic blood pressure trajectory across a life course has been described as having four distinct stages (23). During childhood and adolescence rising blood pressure follows rapid growth in a regular manner, with an interval delay of 1-2 years (24). Longitudinal studies demonstrate that blood pressure then increases further through middle age and into older age, characterised by systolic and diastolic hypertension (23, 25). After the age of 50 years, the diastolic component seems to plateau before tending to decline thereafter (26). Hence there is an increase in pulse pressure (the difference between systolic

and diastolic blood pressures), described as isolated systolic hypertension. In the majority of these patients, hypertension develops ‘de novo’. For example, in the Framingham cohort, in the absence of high blood pressures earlier in life (27), people aged between 55 and 65 years had a remaining lifetime risk of developing hypertension of 93% in men and 91% in women (28).

More than two thirds of men and three quarters of women in the USA who are over the age of 75 years have a diagnosis of hypertension (29). Over the age of 70 years, the blood pressure of some people continues to increase, whereas for others blood pressure is in decline up to 15 to 18 years prior to death (30-32). Life course trajectories of systolic blood pressure demonstrate deceleration and eventual decline in later life (1).

These age related changes are not necessarily inevitable as there is evidence they are not present in certain populations. This difference has been attributed to more active lifestyles, leaner physique and diets containing less sugar and salt (33).

1.5 Hypertension pathogenesis

Whilst the majority of hypertension (90-95%) is referred to as primary hypertension – it is highly heterogeneous and multi-factorial. The remainder constitutes secondary hypertension (5-10%), i.e. secondary to another disorder. This thesis will focus on primary hypertension.

Hypertension represents an extreme of the normal spectrum of physiology that identifies a state of heightened risk resulting from multiple interacting pathophysiological mechanisms (34). In his highly cited paper in JAMA in 1949, Irvine Page, having himself investigated renal, hormonal and neural mechanisms underlying hypertension, concluded that “even the simplest hypertension is a mosaic in which many mechanisms are to a greater or lesser extent involved” (35). This theory, known as the mosaic theory of hypertension (36), has withstood much scrutiny, and the molecular and cellular interactions are now better delineated (36). (**Figure 1-1**). However, ageing has not been considered among these factors, other than as a measure of greater exposure over time to interacting environmental and genetic risk factors.

Figure 1-1 Representation of the Mosaic theory of hypertension

Mosaic Theory adapted from Page (35), and Harrison (36): RAAS = Renin Angiotensin Aldosterone System; SANS = sympathetic autonomic nervous system.

The understanding of hypertension as a disease of vascular ageing is new and evolving. I will now outline recent advances in the understanding of vascular ageing, as central to the aetiology of hypertension and consider each of the mosaic factors with respect to vascular ageing.

1.5.1 Blood pressure control

Blood pressure varies constantly - across the cardiac cycle and in response to highly tuned physiological regulation. Typically blood pressure is characterised by its highest and lowest levels, namely systolic pressure at the point of maximum pressure exerted on the arterial wall when the heart contracts, and diastolic pressure, the pressure exerted when the ventricle is maximally relaxed (37). Blood pressure (BP) has both steady state and dynamic components, relating to separate functions.

The function of the steady BP component is to deliver blood to capillary beds throughout the body. The steady state, defined as the average of the systolic and diastolic pressures (mean arterial pressure(mAP)) is important for the first of BP's functions, to enable conduit (38), to deliver blood to capillary beds through the body. Steady state BP is determined by Darcy's law – the level of volume (cardiac output) and the level of resistance (systemic vascular resistance) (see **Equation 1-1**). This replicates Ohm's law for electrical current (39). Mean arterial pressure is maintained throughout the arterial tree (40).

Equation 1-1Darcy's Law (39):
Mean Arterial Blood Pressure = Systemic Vascular Resistance x Cardiac Output

The function of the dynamic BP component is to cushion the oscillatory function of the heart through the coupling of the heart and vasculature (41). The dynamic component is represented by pulse pressure (PP), that is the difference between the systolic and diastolic blood pressure, and is measured by the pulse wave (42). The power generating the pulse wave is determined by the left ventricle, while the form of the wave is determined by the central arteries where it is first received (43).

1.5.2 Vascular architecture

In cross-section, the blood vessel wall consists three structural layers (40):

- Tunica Intima – innermost is the thin layer closest to the lumen containing a single cell layer of endothelium on a basement membrane with a scaffold of thin extracellular matrix composed of elastin and collagen (44).
- Tunica Media – organised by longitudinal vascular smooth muscle cells interwoven in elastic lamellae and a collagenous ground substance (45). This structure is regulated by a slow, stable but dynamic cycling of production and degradation of crosslinking with a scaffold of proteins, collagen and elastin. The matrix is influenced by levels of sodium, aldosterone, and collagen accumulation stimulated by angiotensin II.

Thickening of the intima and media may occur at places of vascular curvature.

- Tunica Adventitia – collagen containing connective tissue with the proportion of collagen higher at sites of bifurcations contributing to stiffness at these points (45).

Arterial architecture also varies axially, along the length of the arterial tree (42). Arteries may be broadly distinguished as proximal and distal according to differences in function (40).

Proximal arteries constitute the aorta and its main branches. Proximal arteries evolve from the embryological neural crest (46) and contain high proportions of elastic laminae. Vascular smooth muscle cells in proximal arteries tend to be proliferative in phenotype. Proximal arteries are distinguished by being highly sensitive to changes in blood pressure, with high levels of elastic recoil particularly in the levels of the tunica media and adventitia (47). The architecture is dynamic in response to the level of blood pressure: engaging elastin at a lower pressure and collagen at a higher pressure (42).

In contrast, distal arteries evolve from the embryological mesoderm (46). Collagen is better represented in the medial wall and vascular smooth muscle cells tend to have a contractile or synthetic phenotype (45). The vascular smooth muscle cells phenotype is closely allied to their active mechanical properties in distal arteries which tend to be stiffer. Distal arteries are distinguished by their sensitivity and responsiveness to vasoactive mediators,

particularly those emanating from the vascular endothelium (nitric oxide, angiotensin, noradrenaline and endothelin) (48).

Anatomically the distinction between proximal and distal exists somewhere at the level of the diaphragm, but in reality there is a gradual change across the length of the arterial tree which is dynamic in response to location, local pathogenic environment and the process of ageing (40).

In summary, proximal vessels have high recoil, being adapted to their role of cushioning to dampen central artery pulsations. Distal arteries are adapted to maintain constant pressure with higher resistance and falling compliance (49). These design features enable mean arterial pressure to be maintained at the same level throughout the arterial tree (86). The cross-sectional area of blood vessels reduces with increasing distance from the heart, the vascular wall becomes more rigid and pulse pressure increases because of increasing wave reflection (40). In health, there is a significant difference in pulse pressure between the proximal and distal arteries (50).

1.5.2.1 Ageing

Ageing induces intrinsic changes to the vascular wall. These changes play a dominant role in affecting vascular change, potentially affecting BP (51). Arterial wall thickens particularly at the levels of the tunica intima and media (52-54), causing a doubling to tripling of vessel wall thickness between the ages of 20 and 90 years.

Elastin has a long half-life counting as one of the most inert constituents of mammals (55). However, elastin still fatigues as a result of accumulated sheer stress (42). Increasing pressure load over time increases elastin stretch, elastin fractures and extra-cellular matrix changes, stimulating a proliferation of collagen, fibrosis and the deposition of calcium (arterial calcification) (56). The elastin/ collagen ratio in the media of the arterial wall changes with age therefore. This is the process of arteriosclerosis.

Arteriosclerosis is distinct from atherosclerosis, which in contrast, is primarily an inflammatory process associated with plaque formation (57). However, arteriosclerosis can accelerate and reduce the threshold for atherosclerosis in the context of risk factors such as a high-lipid diet (58). Arteriosclerosis involves collagen cross-linking, matrix metalloproteinases (MMPs), and the deposition of other substances including chondroitin which act to stiffen the extra-cellular matrix (59-63). The resultant disruption of the extra-cellular matrix leads to a pro-inflammatory environment which can progress the atherosclerotic process and plaque formation (64). Indeed arteriosclerosis is likely to be a dominant cause underlying atherosclerosis as evidenced by the examination of Egyptian mummies which demonstrate atherosclerotic change in association with age, despite the lack of modern dietary risk factors in the society in which they lived (65).

As a result of arteriosclerosis arterial compliance of the blood vessel falls (66). In rigid vessels, a relatively slight increase/ decrease in intra-vascular volume

will greatly increase/ decrease intra-vascular pressure (67). Functional stiffness increases with higher pressures and loss of arterial compliance leads to increasing pulsatile load. With decreasing compliance, the left ventricle must work much harder to propel the blood forward without the aid of elastic recoil.

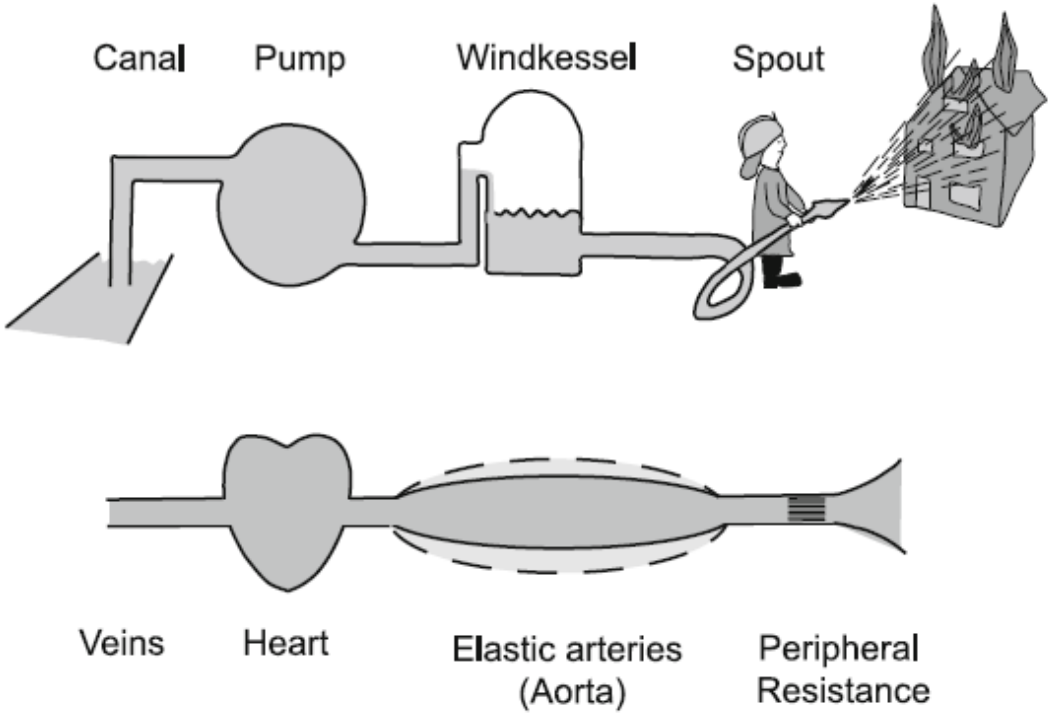
1.5.3 Pulse wave

The pulse wave, like any pressure wave, can be characterised by its amplitude and frequency.

1.5.3.1 Pulse wave amplitude

Amplitude is determined by vessel wall compliance and elasticity. Compliance is defined as the ability of a vessel to expand with an increased volume of blood (68). When the rate of blood entering these vessels exceeds that leaving them (equal to the net discharge of blood in systole and that discharged during diastole), the arterial wall acts as the mechanical equivalent of an electrical capacitor (69). Approximately half the contractile force of the heart is driven into capillary forward flow and approximately half is converted into elastic recoil in the vessel wall (70). In this way, energy is stored in the walls, and then during recoil, energy is restored to further propulsive action during diastole (Windkessel effect (**Figure 1-2**)) (71). This enables large vessels such as the aorta to convert the intermittent output of the heart to a steady outflow at the distal high resistance terminals of arterioles, thereby acting as a shock absorber.

Figure 1-2 An explanation of the 'Windkessel' effect



Windkessel effect or elastic reservoir, taken from Otto Frank's use of the term in German meaning 'air chamber' as used by a fire engine in the 18th century. Figure taken from paper by Westerhof, Lankhaar & Westerhof 2008 (72), reproduced under the terms of the Creative Commons Attribution Noncommercial License (https://creativecommons.org/licenses/by-nc/2.0).

1.5.3.2 Pulse wave frequency

The normal pulse waveform constitutes a forward travelling wave following the cardiac contraction and a backward travelling wave due to reflection from peripheral arteries (42).

The frequency of the wave is determined by reflections which occur at bifurcations of vessels and at the transition points where elastic arteries become resistance vessels (73). Wave reflections start distally at arterioles, and are affected by arteriolar constriction. There is evidence that reflections occur more

quickly when the cross-sectional area of distal circulation is reduced (i.e. through vascular remodelling and wall hypertrophy) (74), rarefaction of branching arterioles and networks (75) and that these factors may be influenced by genetics, and early growth of the vascular architecture (40), as well as the 'length' of the arterial tree, which tends to be shorter in women (76). The distal microvasculature therefore plays an important role in determining peripheral vascular resistance.

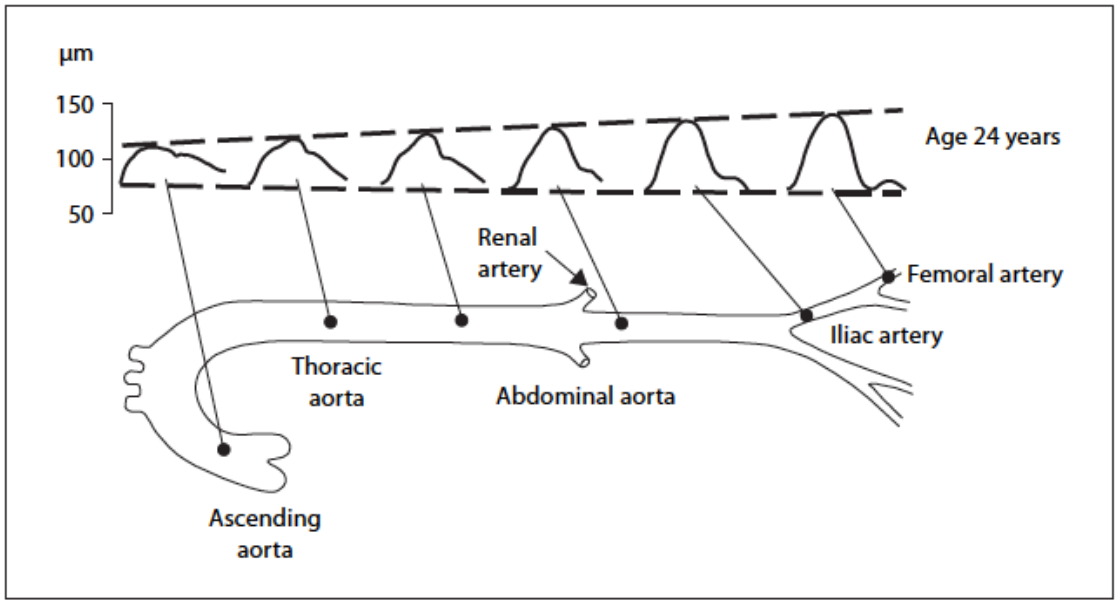
Figure 1-3 The concept of laminar flow

Reflections are minimised by laminar flow (**Figure 1-3**), so called because flow is ordered in layers, with each layer of blood remaining at the same distance from the vessel wall (77). The centremost layer stays central, the layers are in parallel, and there is no interaction between layers (39). Fluid molecules touching the wall move more slowly because of adherence to the vessel wall; so the next layer slips over these molecules; the middle layer can move rapidly because of the lesser friction (68). This enables the flow at the centre of the vessel to be far greater than in those layers towards the edge with a parabolic profile for velocity of blood flow (77). Where laminar flow is disrupted it leads to reflections – thereby affecting the frequency of the pulse waveform.

Arterial pressure waves become distorted as they are transmitted down the arterial system, changing their configuration (**Figure 1-4**). As a result of amplification, as blood travels further from the heart, the systolic blood pressure

and pulse wave pressure increase to reach a higher level at the distal artery than proximally (78). Amplification develops along the length of the aorta so that the mean arterial pressure stays the same throughout.

Figure 1-4 Amplification of the pulse wave across the length of the arterial tree



As blood travels further from the heart, pulse pressure amplifies as it is a sum of both the forward pressure from the heart and the backward pressure from reflections of the forward waves as the pulse travels more distally The notch at the end of ventricular contraction soon disappears while the systolic portions become narrow and elevated and a hump appears on the diastolic portion. Such wave characteristics are pronounced in the young (79). Reproduced with permission from Karger (79).

1.5.3.3 Ageing

First, there is a reduction in the maximum cardiac output achieved by the heart with advancing age (80). The acceleration of heart rate in response to exercise decreases, the left ventricle becomes stiffer and increasingly fails to relax sufficiently, leading to reduced exercise capacity (80, 81). As the power of the

left ventricle ejection wanes with age, the role of the central artery wall becomes more important, in terms of both affecting amplitude and frequency of the pressure wave.

Second, arteriosclerosis predominantly affects the central arteries. Central arterial stiffening reduces the cushioning function of these vessels (49). Central artery stiffening disrupts the variation of wall function along the length of the arterial tree. A defining efficiency of blood pressure physiology in youth is the timing of reflective waves in diastole, described as pressure wave amplification (40). Central arterial stiffening acts to lessen the difference in pulse pressure between proximal and distal arteries, and therefore cause a loss of the amplification seen in youth.

Third, the point of reflection becomes more proximal with age. Therefore, a reflected wave reaches the aortic valve before valve closure leading to increases in systolic pressure and reductions in diastolic pressure. Instead of dampening high initial pressures, these altered vessel walls now reflect back, causing an early return of the pulsatile wave. This reduces the period of systole (82, 83), augments the aortic systolic pressure wave, and reduces the diastolic pressure, thereby increasing pulse pressure (84, 85). Wide pulse pressure, characterises the ‘de novo’ hypertension diagnosed most often in old age (86). Both changes in amplitude (as measured by pulse wave velocity) and in frequency (as measured by reflected waves) are themselves associated with increased cardiovascular risk (87, 88).

Fourth, higher central pulsatility is associated with damage when transmitted to target organs. High pulsatile pressures, turbulent flow, and the intensification of blood flow during systole lead to cyclical stress or shearing forces on the arterial wall (89, 90). Shear stress causes vascular remodelling through processes of inflammation, endothelial damage, oxidative stress and vasoconstriction, activating the growth of additional smooth muscle cells. Vascular luminal enlargement can be seen as a compensating phenomenon to normalise circumferential wall stress, enabling the maintenance of compliance, in spite of aortic stiffening and increasing intra-mural thickness.

Finally, the change in the timing of the loading sequence on vessels alters the ventricular-vascular coupling. End-systolic wall stretch must contend not only with the afterload of systemic vascular resistance, but also the afterload of wave reflection. This causes an increased cardiac afterload, leading to left ventricular hypertrophy (91) and decreasing coronary perfusion during diastole. As a consequence, diastolic cardiac relaxation is incomplete, manifesting functionally as decreased early diastolic filling rate and volume, characterising diastolic dysfunction of the heart.

1.5.4 Endothelium

The endothelium provides an important barrier function between blood and tissues, while also impacting on lamellar flow and selective permeability (92). Molecules released from the endothelium affect vasomotor tone, coagulation, proliferation and inflammation (93).

The endothelium produces an array of vasoactive substances. Chief amongst these is nitric oxide (NO) which plays a pivotal role in controlling vascular tone. This is in addition to its role in salt sensitivity (discussed further in **Section 1.5.6**). Shear stress triggers the production of endothelial nitric oxide synthetase (eNOS) (94), converting L-arginine into NO in the presence of tetrahydrobiopterin (BH4) (44). NO causes relaxation of the vascular smooth muscle cells via the release of cyclic guanosine monophosphate (cGMP) (95). Several other vasodilatory substances produced by the endothelium include adrenomedullin (96), prostacyclin and endothelium derived hyperpolarising factors (37). At the same time, shear stress causes a concomitant endothelial release of opposing superoxide anions (97). These are free radicals that bind to NO to inactivate it.

To counter the vasodilatory substances, the endothelium also produces several vasoconstrictors. Predominant among them is endothelin I, which activates ET-1 receptors in the vascular smooth muscle to cause them to contract (98). Other vasoconstrictors include prostanoids (thromboxane A2 and prostaglandin A2) and local angiotensin II (37).

1.5.4.1 Ageing

The increasing pulse pressure that results from the arteriosclerosis and changes in pulse wave pressure, causes sheer stress and ensuing damage to the endothelium. Endothelial dysfunction is evident in those without clinical

hypertension but with a family history of hypertension, indicating it is a pathway to developing hypertension. Ageing is associated with changes in the primary endothelial wall functions that are protective and anti-atherosclerotic, causing it to become pro-sclerotic (99).

Endothelial wall function is normally characterised by a constant secretion of nitric oxide in response to sheer stress, but this lessens with age. The release of free radicals in response to sheer stress increase and become dominant in the absence of NO (100). Several factors contribute to this loss of NO including the reduced production of eNOS species (101). As with somatic cells, endothelial cells are limited in their ability to divide (102), and so enter a senescent state associated with reduced eNOS activity (103). eNOS is modulated by oestrogen and growth hormone (104) both of which reduce with age. Indeed oestrogen therapy has been shown to preserve endothelial function in post-menopausal women. With age eNOS uncoupling reduces (105); BH4 falls; and Arginine competition with eNOS to bind with L-Arginine increases (106).

Simultaneously, a state of oxidative stress evolves in the endothelium where oxidative stress is defined as an imbalance of production and removal of reactive oxygen species. Superoxide ions are increasingly available and bind to NO to inactivate it. Endothelin I increases in potency as Endothelin type 1 receptors become more sensitive with age (107). There is evidence that ET-1 receptor antagonists are effective in reducing blood pressure in older but not younger men (108).

This creates an imbalance, leading to dysfunctional endothelium throughout the vascular architecture (109), resulting in greater vasoconstriction and peripheral vascular resistance (110). Therefore, flow mediated dilation is reduced with age. In a study of 238 people aged 15-74, dilation in response to reactive hyperaemia was reduced by 0.21% per year in men from the age of 40, and 0.49% per year in women from the age of 50, whilst the vasodilatory response to glyceryl tri-nitrate was unchanged (111). In older people, there were higher levels of pro-inflammatory nuclear factor κB (NFκB), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-alpha) and monocyte chemoattractant protein-1 (MCP-1) (112) associated with a lower endothelium dilator response.

The inflammatory state of the dysfunctional endothelium has been implicated in some of the complications of hypertension in old age (113, 114). The loss of endothelium mediated dilation makes the endothelium more sensitive to the stress of increased blood volume, exacerbates the effects of shear stress and leads to pressure induced injury to the vascular wall, contributing to the potential for plaque deposition and atherosclerosis (115).

Newly dominant reactive oxygen species (ROS) lead to DNA damage (116), while signalling pathways lead to a remodelling of the tunica media. This causes an increase in medial thickness and a decrease in luminal diameter (117). Released vascular mediators include the matrix metalloproteinases involved in the degradation of extra-cellular matrix, which enables the diapedis of inflammatory cells through the junctional connections between endothelial cells.

There is a failure to repair this damage with age because the endothelial progenitor cells lose their capacity to migrate and repair (118). Senescence Associated Secretory Phenotype (SASP) cells promote the degeneration of endothelium to engender a state of chronic endothelial stress (119).

1.5.5 Regulatory systems

The regulation of arterial blood pressure varies across a time course (68). Immediately (over seconds to minutes), BP is controlled by the central and autonomic nervous systems. In the short to medium term (over minutes to hours), BP is regulated by volume status (intravascular volume) and it's renal and endocrine control (the renin angiotensin aldosterone system). In the long term (over days to months), BP level is influenced by changes in the vascular environment (the endothelium) (37). The role of each of these will now be considered, not in temporal order, but in order of the magnitude of their contribution to hypertension. The context of ageing will be evaluated for each in turn.

1.5.6 Intravascular volume

Sodium is the principal cation in the extracellular fluid compartment. Therefore regulation of total body sodium plays a central role in long term blood pressure control (68). Raised sodium stimulates water retention, increasing blood volume which raises blood pressure. The process of auto-regulation (120) means that an increased blood volume leads to increased systemic vascular resistance

(121). When BP rises, renal excretion of sodium and water increase and mechanisms act to reduce peripheral and renal blood pressure to reduce vascular resistance (122). The pressure-natriuesis curve is central to normal blood pressure control. Whichever the causal pathway of hypertension, for high blood pressure to be maintained, the set-point of the pressure-natriuesis curve must be increased (123). This describes the volume dependent mechanisms of hypertension.

The role of salt in association with high BP is long established (124). A Western diet typically includes 150 mmol / day of salt. In contrast, populations with intake <50 mmol/ day have substantially lower blood pressure (125). Evidence of a linear dose response relationship between salt and BP had been demonstrated in a meta-analysis of intervention trials (126), studies of human and animal physiology (127) and public health interventions at the population level (128).

Nitric oxide released from the endothelium plays a central role in the pressure-natriuesis compensatory mechanism (37). In the event NO is not released, the regulatory mechanism fails and hypertension persists. This describes a state of ‘salt sensitivity’, a phenotype that can be triggered by genetic and environmental factors. Salt sensitivity is operationally defined as an increase in mean arterial blood pressure (5 mm Hg) or more during a high compared to a low dietary sodium intake (110). In a ‘salt sensitive’ state, small increments or normal intake of salt can alone trigger hypertension. Chronic salt ingestion (129) can itself cause salt sensitivity by causing endothelial dysfunction resulting in a failure of NO release (130).

1.5.6.1 Ageing

Within the kidney, sodium reabsorption occurs predominantly in the ascending loop of Henle which is located in the renal medulla (131). Sodium transporters are highly energy dependent and therefore vulnerable to ischaemic insult at low pressure. Ageing kidneys receive less cortical blood flow (10% reduction per decade), leading to an impaired ability of the kidney to excrete sodium (132). Age-related progressive deterioration in the ability to excrete salt efficiently leads to higher blood pressure (133).

The majority of older individuals have salt sensitivity (134). Endothelial dysfunction is a key characteristic of vascular ageing, meaning more people are salt sensitive with salt intakes that would not ordinarily have been problematic. Loss of compensatory mechanisms (via NO) mean older individuals are far more susceptible to the BP effects of changing sodium intake, having not been sensitive during their earlier life.

Premature vascular ageing may be precipitated by predisposing genetic and early environmental exposures, which can make an individual more susceptible to sodium retention, particularly if there are factors predisposing to endothelial dysfunction. One factor for example, is oligo-nephropathy in people who are born with low birth weight (132). A compression of the period of active growth until puberty leads to a mismatch of the growth related renal function to meet metabolic demands (135). This perinatal programming results in the under-

development of the medullary micro-circulation and cortical afferent arterioles that are so important in managing sodium levels throughout life (136).

1.5.7 Renin Angiotensin Aldosterone System

Renin, angiotensin and aldosterone have central roles in regulating sodium, affecting the pressure-natriuesis relationship and therefore blood pressure. The Renin Angiotensin Aldosterone System (RAAS) is stimulated in the context of volume depletion, and inhibited in fluid overload (137). The RAAS is present throughout all tissues of the body, although its role in systemic blood pressure control lies predominantly in the kidney.

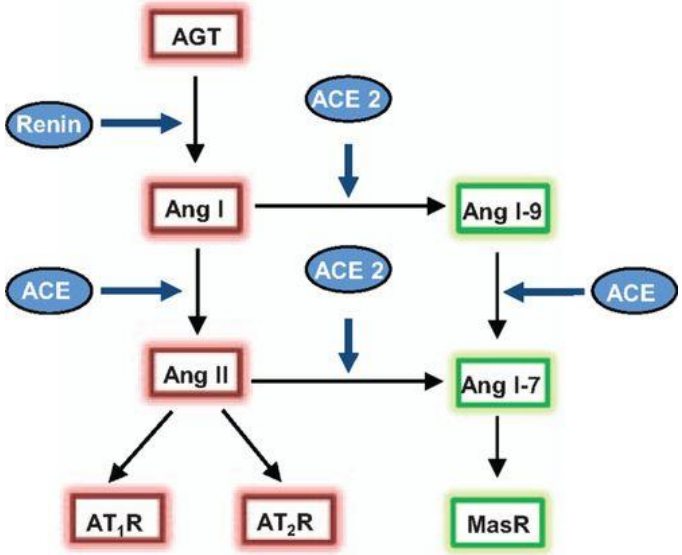
Renin is an enzyme cleaved from its precursor, prorenin in smooth muscle cells of the afferent arteriole of the juxta-glomerular apparatus (39). This process is triggered by a fall in sodium levels, a fall in renal artery perfusion pressures, or an increased sympathetic activity in response to a fall in arterial blood pressure (37). Renin enables the conversion of Angiotensinogen to Angiotensin I. Angiotensin I is converted by Angiotensin Converting Enzyme (ACE) to form Angiotensin II (**Figure 1-5**).

Angiotensin II has a crucial role in hypertension (138), with differential effects on AT-1 receptors, where it acts to raise blood pressure, and on AT-2 receptors, where it acts to reduce blood pressure. Key mechanisms of the AT-1 receptor are the stimulation of sodium absorption and the inhibition of sodium excretion, part of which is achieved through its stimulation of aldosterone release from the

adrenal glomerulosa. Aldosterone binds to the mineralocorticoid receptor, and activates sodium reabsorption at the level of the collecting duct (139), as well as in the colon. Aldosterone has broad effects on endothelial function, vascular wall architecture and as a vasoconstrictor. Also aldosterone stimulates sodium resorption in the collecting duct (139).

Renin is higher in those with a family member who has hypertension, and among Africans compared to Europeans for whom the same salt intake is associated with a greater rise in blood pressure (140). Differences in the sexes are observed too. Increasing hypertension in women post-menopause correlates with the loss of oestrogen which is a modulator of the Renin Angiotensin Aldosterone System (141).

Figure 1-5 A schematic of the Renin Angiotensin Aldosterone System



Angiotensin converting enzyme (ACE); Angiotensin type I receptor (AT1 R); angiotensin type II receptor (AT2 R). Reproduced with permission from Wolters Kluwer, licence number 5085291207131 (142).

Angiotensin II causes smooth muscle cell contraction, vasoconstriction at the level of arterioles, and activation of the Na^+-K^+ ATPase, Na^+/H^+ exchanger III and NaHCO3 cotransporter 1 to enable active transport of Na^+ at the proximal tubule, enabling sodium re-absorption, and reducing medullary blood flow. Better understanding is currently emerging of the protective effects of ACE II, and the conversion of Angiotensin II to Angiotensin 1-7, which have opposing and vasodilatory effects (143).

1.5.7.1 Ageing

From the age of 30 years upward, glomeruli become replaced by fibrous tissue, glomerular capillaries are pruned, to be replaced with mesangium, and the basement membrane thickens (144). These changes are associated with increased release of Angiotensin II, tied in with an increasing glomerular filtration fraction and increasing sodium reabsorption at the proximal tubule. Normally, Angiotensin II has the potential for causing oxidative stress only in specific and regulated scenarios (142). The chronic activation of Angiotensin II leads to Angiotensin II dependent production of Reactive Oxygen Species (ROS) (145), thereby driving a persistent pro-inflammatory state of oxidative stress. This promotes senescence, reducing the availability of NO thereby impacting salt sensitivity driven hypertension.

With age, the production of ACE in endothelial cells and vascular smooth muscle cells increases (146-148). As a result, Angiotensin II rises markedly with age and in association with the rise in ACE. The production of renin (149) and

aldosterone also fall with age. Overall the modulating dynamic of the renin-angiotensin system wanes (150). The chronic activation in old age of ACE and angiotensin II may underlie the increased effectiveness of their inhibition by ACE-inhibitors and angiotensin receptor blockers to prevent end-organ damage associated with hypertension in later life (142, 151). The decline of Aldosterone is associated with a fall in sodium reabsorption at the cortical collecting duct – normally responsible for the fine tuning of Na^+ levels alongside K^+ and other protons. With age therefore, urinary Na^+ excretion increases and it is for that reason the risks of hyponatraemia and hypovolaemia become increased in the context of reduced salt diets or on prescription with potent diuretics (152).

1.5.8 Sympathetic Autonomic Nervous System

Neural control has a short term effect on blood pressure through total peripheral vascular resistance and capacitance as well as cardiac pumping activity (68). Neural control is predominantly operated through the Sympathetic Autonomic Nervous System via the control of venous capacitance. Neural innervation of both arteries and veins can exploit differences between them in the volume – pressure relationships to shift blood volume from one part of the circulation (e.g. systemic) to central (e.g. heart). Nearly one third of the blood volume of a tissue can be mobilised by stimulating sympathetic nerves at physiologic frequencies. This can be highly effective, for example, in the context of haemorrhage (153).

Arterial afferent receptors stimulate negative feedback via the brain to engage the autonomic nervous system (39). Afferent receptors take various forms:

- High pressure (arterial) baroreceptors involve spray like sensory nerve endings in the vessel walls (68). These detect vessel wall distension of major vessels in the neck and thoracic cavity, particularly at the carotid sinus and the aortic arch (132). Low pressure baroreceptors are located in the atria, ventricles and the pulmonary arteries, and are activated by increases in volume and filling. When stretched by elevated BP, these receptors reduce nerve firing, inhibiting sympathetic activity.
- Peripheral chemoreceptors also lie in the aortic arch and carotid and are stimulated by hypoxia, hypercapnoea and acidosis. They trigger vasoconstriction at resistance and capacitance vessels (154). Central chemoreceptors in the medulla are excited by cerebral ischaemia and elevate arterial pressure causing sudden and absolute peripheral vasoconstriction.
- Sensory afferents in the kidneys trigger the Nucleus Tractus Solitarii (NTS) to stimulate reflex sympathetic activation in the presence of ischaemic metabolites (adenosine or urea). In the skin and viscera, painful stimuli evoke a pressor response, while distention of the viscera can evoke a depressor response. In the lungs, pulmonary reflexes relating to inflation cause systemic vasodilation and a decrease in arterial BP.

Afferents (via the vagus (X) and glossopharyngeal (IX) nerves) are received at the vasomotor centre in the medulla oblongata, to trigger a negative feedback loop. Signals are relayed to the NTS and transmitted to the vasomotor centre, specifically to the vasoconstrictor centre (rostral ventro-lateral nuclei) and the vasodilator centre in the nucleus ambiguous and dorsal vagal nucleus (68).

The efferent vasoconstrictor pathways exit via the spinal cord along the paravertebral sympathetic chain or the prevertebral ganglion in the abdomen. Triggered by low blood pressure, sympathetic activation increases the contractility of the heart (via adrenaline binding to beta-receptors), and causes vasoconstriction of the arterioles and venous circulation (via noradrenaline binding to alpha-receptors to cause smooth muscle contraction) (153). Sympathetic activation thereby increases stroke volume. The major efferent vasodilator pathway is parasympathetic, via the vagus nerve which innervates the heart to release acetyl-choline (ACh). ACh binds to cholinergic receptors at the sino-atrial and atrio-ventricular nodes to slow conduction, reducing heart rate and contractility. Parasympathetic activation also inhibits sympathetic activation at the vasomotor centre (5).

An imbalance of sympathetic over parasympathetic activation is associated with hypertension (155), with obesity (156), and with renal failure (157). Over time chronic sympathetic over-activity is associated with a tendency for greater sodium reabsorption. High chronic levels of catecholamines are associated with renal injury which predispose a long term salt sensitivity that persists long after the sympathetic over-activity has normalised (37, 130). Chronic activation of alpha adreno-receptor in the endothelium is also known to pre-dispose to proliferation of vascular smooth muscle cells and endothelial dysfunction (158).

Stimulation of multiple regions of the cerebral cortex control the vasomotor centre (68). There is evidence that central nervous system control has input

from multiple BP regulating systems. Animal studies demonstrate feedback of serum levels of sodium and angiotensin II at the sub-fornical organ and the organum vasculosum of the lamina terminalis (159). These nuclei are remarkable for their poorly formed blood brain barrier. As such they are very sensitive to levels of Angiotensin II and sodium levels in the peripheral circulation. Their higher firing activates, via the hypothalamus, the vasoconstrictor centre in the rostral ventrolateral medulla. In hypertension, high levels of Angiotensin II have been described, and systemic blood pressure has been reduced using lesions or angiotensin receptor blockers (ARB) at this level (160).

1.5.8.1 Ageing

There is evidence of age related decline in the sensitivity of the arterial baroreceptor, affecting the regulation of peripheral vascular resistance in two important ways (110). Firstly, a larger change in blood pressure is required to stimulate the baroreceptors to invoke the appropriate compensatory response (161). Baroreceptors become less responsive to high blood pressure (162, 163) low blood pressure (164), following exercise (165), a meal (166), or, a change in posture (167). Secondly, a loss of the night time fall in blood pressure and a rise of the early morning surge is seen with increasing age that suggests diminishing circadian control of baroreceptor function (168). This is consistent with the increasing vascular wall stiffness which may mean that higher pressures are required to cause wall stretch (169).

As a consequence of being less inhibited by the baroreceptor negative feedback, there is a chronic over-activation of the sympathetic nervous system outflow for any given level of blood pressure. Noradrenaline release in tracer kinetic studies are higher and there is evidence of higher levels of sympathetic nerve activity (170). In older adults with hypertension, arterial alpha adreno-receptor responsiveness is also increased. With age, noradrenaline production is increased (171), and there are decreases in its clearance (172) contributing to an amplified response in terms of both degree and duration to hypotensive stimuli (171).

End-organ responsiveness is unequally reduced with age, with a shift of balance between alpha versus beta receptor responsiveness that favours vasoconstriction. The ability of a vessel to dilate, mediated by beta-2 adrenergic receptors is impaired with age. The number of receptors is unchanged, for example on rat myocytes (173), or human lymphocytes (174) but the beta receptor response is blunted (175, 176) and on human lymphocytes their affinity for agonists reduce with age (177). In contrast, the vasoconstrictor ability that is mediated via alpha adrenergic receptors is preserved with age (176). Overall this leads to a greater predilection for vasoconstriction with age, contributing to higher systemic vascular resistance.

1.5.9 Summary of biology

Primary hypertension is a mosaic of multiple causes (35). Until recently, the widely accepted theory was that the growing risk of hypertension associated

with age was related primarily to prolonged exposure to the environment, for example, through greater opportunity to develop obesity and therefore hypertension.

The influence of ageing on the development of hypertension has been described in two respects:

1. Firstly in respect of ageing vasculature: recent advances in the understanding of genetic and molecular vascular physiology have supported vascular ageing as central to the aetiology of hypertension. Vascular ageing is understood as the common pathway on which various agents of the mosaic act. It is a process that is not inevitable, but is accelerated by various pathologies which trigger the development of hypertension in early or mid-life.
2. Secondly in respect of the dysregulation associated with ageing of normal homeostatic mechanisms of fluid balance, sympathetic negative feedback and modulation by RAAS. The loss of these regulatory mechanisms make it more difficult to maintain stable blood pressure and the individual more vulnerable to perturbations of blood pressure in the context of stressor events, including salt and water loss or physiological challenge.

The available evidence indicates that ageing frames the context of hypertension, in each of the major pathways of pathogenesis. Until this point, this chapter has focused on biology and the relevance of ageing. However,

considering ageing as a framework is also justifiable when one considers its application to patient care, as discussed below.

1.6 Hypertension disease status

From a clinical perspective, the concept of hypertension is defined primarily by its relation to future cardiovascular end-organ disease. Hypertension has been associated with poor prognosis for more than four thousand years (178), and associated with end-organ damage, specifically renal disease since as early as the 6th century (179). However, it was not until the development of microscopy and more liberal attitudes to autopsy in Europe, that renal and cardiac end organ damage became measurable (179-181). With evidence that persistent high blood pressure preceded the development of associated renal disease, Dr Frederick Akbar Mahomed defined hypertension as a disease in 1874 (182).

Hypertension remained an academic interest and only became clinically relevant once BP was measurable. In 1760, Stephen Hales recorded the first measurement of BP by attaching the windpipe of a goose to the carotid of a horse, itself tied to a fallen gate, to measure a column of eight feet of blood whose pressure proceeded to decline until the horse died (179, 183). Non-invasive, more practical means soon developed, with the use of mercury whose greater atomic weight enabled pressure differences to be measured on a shorter distance (184), a float to ascertain a level (185), and the inflatable rubber balloon to tourniquet the arm (186). It was Kortokoff, a Russian army general who developed the method of measuring BP in 1901 by auscultating for

the obliteration of the pulse, with increasing pressure applied using the tourniquet to discern systolic and diastolic pressures by using the stethoscope (187).

In the 1960's there was significant controversy about the disease status of hypertension. Weitz, Platt, Morrison and Morris were impressed by the Mendelian dominant behaviour of hypertension with clear dichotomies of blood pressure defining hypertension. By contrast, Pickering and Oldham advanced the case of hypertension, by contrast representing a quantitative not a qualitative deviation from the norm, with no natural dividing line between normal and abnormal, but a state of continued or reducing risk across a spectrum (188).

Although they have limitations, thresholds still have utility in clinical practice in guiding treatment. However, as will be discussed, the linearity of the association of BP with risk remains an area of significant uncertainty that this thesis hopes to address.

1.6.1 Blood pressure measurement

The measurement of BP is influenced by the environment the patient is in, when they have their BP measured. Discrepancies between home or ambulatory readings and BP readings in the clinic are common. Clinic readings can over-estimate a person's true BP, for example because of the anxiety of a patient in a clinical setting – often called the 'white coat effect' (189). This may lead to a

false positive diagnosis of hypertension and over-treatment in a person with already normal BP. Clinic readings can also under-estimate a person's true BP, leading to a missed diagnosis of hypertension, so called masked hypertension. Masked hypertension is associated with increased cardiovascular risk. Both white coat and masked hypertension are more common with ageing (190).

A further challenge to the accurate measurement of BP is its variability across time. BP variability which increases with age. Short term variability is understood to relate to a person's behaviour, emotion, postural change and circadian rhythm (191). Long term variability may relate to the type and dose of prescribed medications, degree of adherence, and other factors which are not well understood. Long-term BP variability is itself a risk factor for the development of future cardiovascular disease, and the inclusion of BP variability improves the prognostic ability of cardiovascular risk models (192).

1.6.2 Cardiovascular risk

There are a wider set of mediating factors involved in the causal pathway from hypertension to cardiovascular disease. Hence hypertension is often characterised as part of a wider cardiovascular risk profile involving a number of interacting factors in a multiplicative way (193). The concurrence of cardiovascular risk factors has collectively been termed the metabolic syndrome. Cardiovascular risk factors cannot therefore be considered in isolation and a comprehensive approach is required to ameliorate cardiovascular risk across all factors(194). Key related cardiovascular risk factors are summarised here.

1.6.2.1 Obesity

Obesity is defined as a body mass index of 30 kg/m^2 or more. After adjusting for age, the increased prevalence in hypertension in men and women worldwide (**Section 1.3**) can be attributed to the rising prevalence of obesity (195). Obesity represents a salt-sensitive state(196), as a consequence of the activation of the RAAS (197) and the SANS systems (198). In a meta-analysis of 18 trials, overall weight loss between 3 – 9% of body weight reduced BP by 3 mm Hg (199). The average age of trial participants was 55 years (range 18 to 80 years). In observational studies of older people, the association of obesity and hypertension is less clear. In the INVEST study which included a well-treated cohort: higher Body Mass Index (BMI) was associated with decreased mortality(200).

1.6.2.2 Dyslipidaemia

Hyperlipidaemia is defined as a total cholesterol of 240 mg/dl or higher. Increase in lipid levels and BP are closely related: between one third and two thirds of people with hypertension also have hyperlipidaemia (201). Compared to patients with hypertension or hyperlipidaemia only, those with both had a two to three times higher risk of atherosclerotic disease and three to four times higher risk of myocardial infarction (202). Total cholesterol increases with age, and associated with an increased risk in men (203), but this risk attenuates with age (204), and the role of dyslipidaemia in cardiovascular risk is less well established over the age of 80 year old (205).

1.6.2.3 Diabetes mellitus

Hypertension is associated with insulin resistance, and the co-pathology of hypertension has an amplifying effect on microvascular and macrovascular diabetic end-organ damage (206). Diabetes nearly doubles the risk of cardiovascular death, hospitalisation for myocardial infarction and stroke compared to people without diabetes (207). Diabetes mellitus is the leading cause of end-stage renal disease in high, middle and many low-income countries(208), and hypertension accelerates the progression of diabetic kidney disease. Higher mean arterial pressure is associated with increased annual decline in glomerular filtration rate (209). Therefore the prevalence of hypertension in people with diabetes is closely related to markers of diabetic nephropathy: in those with microalbuminuria, prevalence of hypertension is 40-83%; in those with macroalbuminuria, hypertension prevalence is 78 – 96% (210).

1.6.2.4 Smoking

Smoking tobacco causes damage to the vascular endothelium through increased platelet aggregability and reactivity as well as free radical production (211). Smoking is associated with increased systolic blood pressure, particularly over the age of 60 years old (212). Smoking cessation reduces blood pressure (213) and is associated with a reduction in cardiovascular risk (214) and these benefits of quitting do not attenuate with age (215).

1.6.2.5 Diet

Of the environmental factors influencing BP, diet is predominant. Evidence exists for the benefit associated specifically with sodium, potassium, and alcohol intake as well as particular dietary patterns (216).

- Sodium intake: an increase in daily sodium intake is associated with an increase in BP. In adults with treated hypertension a reduction of 4.5g salt per day in the diet was associated with a reduction in BP of 22.7 / 9.1 mm Hg (217).
- Potassium intake: increasing potassium intake is associated with a reduction in BP. Fruit and vegetables are rich in potassium. Increasing potassium intake by 50 mmol/day was associated with a reduction in BP in people with hypertension of 4.4 / 2.5 mm Hg (218).
- Alcohol intake above two drinks per day is associated with increased BP, and decreased consumption by a median of 76% lowered BP by 3.3 / 2.0 mm Hg(219).
- Diets associated with lower BP include the vegetarian diet (220). The Mediterranean diet has been associated with a reduction in cardiovascular disease but modest reductions in BP (221). The Dietary Approaches to Stop Hypertension (DASH) emphasizes the intake of fruit vegetables, low fat dairy and reduced saturated and total fats. The trial reduced blood pressure and is recommended to reduce cardiovascular disease (222).

1.6.2.6 Exercise

Broadly, exercise has been associated with BP reduction and reduction in CV risk (223). The effective of exercise in reducing BP depends on the type of BP :

1. Dynamic aerobic exercise defined as repetitive movement to increase cardiovascular workload. Within 8-12 weeks meta-analysis of 105 trials have demonstrated that aerobic exercise can reduced BP by 3.5 / 2.5 mm Hg in those without hypertension, and by 8.3 / 6.8 mm Hg in those with hypertension(224). There is some evidence that aerobic interval training is superior to continuous training in reducing BP(225), and that the effectiveness of aerobic versus resistance training may vary depending on sex(226). The optimal intensity and ideal duration remains uncertain, but AHA guidelines recommend 30 minutes per day of aerobic exercise to reduced BP(227).
2. Dynamic resistance training represents for example weight lifting or stretching bands. There is an association of this form of exercise modestly reducing BP - -1.8/ - 3.2 mm Hg but the mechanism is not understood, and the quality of evidence inferior to that for aerobic exercise. AHA guidelines recommend 2-3 times per week added to aerobic exercise but recognise that the quality of evidence is inferior (Class II)
3. Isometric resistance training represents muscles contracted at increased tension but without shortening for example using a handgrip dynamometer. A meta-analysis of 11 trials in only 302 participants recently demonstrated highly effective reduction of BP – 5.2 / 3.9 mm Hg with greater effect in those with established hypertension. AHA guidelines recommend undertaking this for 12 – 15 minutes 3 – 5 times

per week but that the evidence quality to support this recommendation is less good (IIB).

1.7 Hypertension treatment

With notable exceptions (alpha-blockers, beta-blockers, renin inhibitors) (228), the choice of which BP-lowering treatment prescribed to reduce cardiovascular risk is understood to be less important to the level of BP (229-231). In older people, calcium antagonists and diuretics tend to represent treatments of first choice (232). A clinician's choice of agent may be informed by various factors including the target for secondary prevention, a patients' comorbidities, ethnicity and potential for suffering side effects (233). There remains uncertainty whether the effect of reducing cardiovascular mortality can be attributed solely to lowering blood pressure, as many BP-lowering medications have multiple effects which may be cardio-protective. The focus of this PhD is on BP lowering and not on the merits/ harms of particular BP-lowering agents. There are benefits and harms to BP lowering, which will be considered in turn.

1.7.1 Treatment benefits

Hypertension is estimated to be a key contributing factor in up to half of myocardial infarctions, heart failure and strokes (234):

- Stroke: levels of high blood pressure have been correlated with both ischaemic and haemorrhagic stroke. A reduction of diastolic blood

pressure by 5 mm Hg reduces the risk of stroke by one third (235). The association with BP declines with increasing age, despite stroke disease becoming more common.

- Myocardial infarction: blood pressure is positively and continuously associated with the risk of death due to coronary artery disease or non-fatal myocardial infarction (235). This association is smaller than that with stroke. A 5 mm Hg reduction in diastolic blood pressure was associated with a one fifth reduction in the risk of coronary disease events (235).
- Heart failure: in the Framingham cohort, hypertension was associated with a 2 to 6 fold increase in the risk of developing heart failure (236).
- Renal failure: whilst renal failure is not often the outcome of hypertension, renal failure increases with degree of hypertension and hypertension appears to exacerbate and cause a more rapid progression of renal damage, regardless of aetiology (237).
- High blood pressure has been implicated in the development of vascular dementia (the second commonest form of dementia) (238) and increasingly also in levels of Alzheimer's pathology in the brain (239-241).
- Higher than average blood pressure in mid to late life is associated in longitudinal studies with mild intellectual dysfunction, particularly executive function, as demonstrated by impairments in word fluency and delayed word recall, as well as poor visuo-motor skills (242-244). However, other studies into advanced old age have demonstrated that these findings are inconsistent and some studies have failed to demonstrate the association of BP and cognitive outcomes persisting in those aged 75 years and older (245-247). The Hypertension in the Very

Elderly Trial (HYVET) demonstrated no statically significant benefit from BP-lowering therapy on the development of dementia in those over the age of 80 years, while a meta-analysis demonstrated therapy had a favourable effect of borderline significance HR 0.87 CI 0.76 to 1.00] (248-250). Nevertheless, there is evidence of some association with hypertension and overall physical and cognitive decline – particularly in executive function, with rising blood pressure (251, 252).

1.7.1.1 Ageing

A previous school of clinical thought considered hypertension an adaptive response, whose treatment may cause more harm (179, 253). This was disproved by the first intervention trial published in 1970 which demonstrated that hypertension was indeed reversible. Since this, hypertension management has been led by randomised control trial evidence. Clinical practice continued to be more conservative in older adults, until, more recently, trials have demonstrated reversibility extending into advanced old age. **Table 1-1** and **Table 1-2** compare the effects of BP-lowering medication on outcomes found by large scale interventional trials. The median follow up time, population characteristics, and BP targets are compared with evidence of treatment benefit and harm. Whereas trials targeting systolic blood pressure to a level of less than 150 mm Hg (listed in **Table 1-1**) (254) show benefit in cardiovascular risk prevention; the findings of trials targeting systolic BP to less than 140 mm Hg are more mixed in their findings (**Table 1-1** & **Table 1-2**). It is also evident from the summary of trials that adverse effects, especially in early trials were not

reported. More recent trials do report adverse effects but without the same robustness or granularity afforded cardiovascular outcomes.

Table 1-1 Summary of RCTs with sBP targets over 140 mm Hg

Trial	Population/design	Design	Baseline BP & achieved BP	Effect of treatment	Harms of treatment
Veterans (255, 256) 1970	Mean 51y (30-73y) USA all male	n= 143 F/u: 1.1y	B/L: dBP (mean) 115-129 Achieved: ↓sBP 43; sBP 30	↓ Stroke/ MI/ ↑death	Drop-out rate = 8.4% equal between groups.
Australian (257)1980	Mean 50y (30-69y) Australia	n= 3,427 F/u: 4y	B/L: sBP 200 / dBP 95 Achieved: dBP: 88 vs 94	↓mortality ↓CVD↓IHD	Not reported
EWHPE (258) 1985	Mean 72y Europe	n= 840 F/u 5y	B/L: sBP 183/ dBP 101 Achieved 150/85 (5y)	= mortality ↓ CV mortality	Not reported
MRC (259) 1985	Mean 52y (35-64y) UK	n= 17,354 F/u 5.5y	B/L (m) 158/98 (f) 165/99 Target dBP <90	= mortality = coronary events ↓ stroke	↑Glucose intolerance, impotence gout, lethargy nausea, dyspnoea
Primary care trial (260) 1986	Mean 68y (60-79y) UK	n= 884 F/u 4.4y	B/L BP 196/99 Achieved BP 180/89	↓ stroke = MI = mortality	↑ Glucose, Urea, Creatinine, Urate = adverse symptoms
SHEP(261, 262) 1991	Mean 72y USA	n= 4,736 F/u: 14.3y	B/L (Av.) sBP 170/77 Achieved sBP143	↓ stroke ↓MI↓MACE	↑Electrolyte abnormalities; = dementia/ depression
STOP (263) 1991	Mean 76y (70-84y) Sweden	n= 1,627 F/u: 2.1y	B/L BP: 195/102 Achieved BP: 167/87	↓stroke ↓mortality	= withdrawals because of side effects
MRC (264) 1992	Mean 70y (65-74y) UK	n= 4,396 F/u 5.8y	B/L185/91 Achieved 150/77	↓ stroke ↓coronary↓ CV events	↑withdrawals
Syst-Eur (265) 1997	Mean 70y Europe (23)	n= 4,695 F/u: 2y	B/L BP:174/86 Achieved BP: 151/79	↓ stroke ↓ mortality ↓heart failure	= hospital admissions = withdrawals
HOT (266) 1998	Mean 62y (50-80) Europe, America, Asia	n= 19,193 F/u 3.8y	B/L170/105 Achieved: (3 arms) 144/85; 141/83; 140/81	= MACE	2% had adverse events. Difference between groups not reported.
Syst-China	Mean 66y China	n= 2,394 F/u: 3y	B/L BP 170/86 Target sBP <150	↓stroke ↓cv mortality ↓mortality	= non-cardiovascular and cancer mortality
HYVET (267)	Mean 84y Europe, China,	n= 3,845 F/u: 1.8y	B/L 173/91 Achieved: 144/78	↓stroke ↓cv death ↓ mortality	↓ adverse effects in active treatment group

2008	Australia, Tunisia			↓heart failure	

Trials: EWPHE = European Working Party for Hypertension in Elderly; HOT = Hypertension Optimal Treatment; HYVET = Hypertension in the Very Elderly Trial; MRC = Medical Research Council (UK); SHEP = Systolic Hypertension in the Elderly Program; STOP = Swedish trial in old patients with hypertension; Syst-China 1998(268) = Systolic Hypertension in China; Syst-Eur = Systolic Hypertension in Europe trial;

All blood pressure recordings are in mm Hg; B/L = baseline; cv = cardiovascular; CVD = cerebrovascular disease; CV mortality = cardiovascular mortality; IHD = ischaemic heart disease ;MI = myocardial infarction ; RCT = Randomised controlled trials; sBP = systolic blood pressure

Table 1-2 Summary of RCTs with sBP targets under 140 mm Hg

Trial	Population/design	Design	Baseline BP & achieved BP	Effect of treatment	Harms of treatment
AASK 2002(269)	Mean 55y (18-70) USA	n= 1,094 F/u: 4y	B/L (I)152/96 (U) 149/95 Achieved: (I) 128/78 (U) 141/85	= GFR /Death	= adverse effects
JATOS 2008(270)	65-85y Japan	n= 4,418 F/u: 2y	B/L BP: 172/89 Achieved BP: 136/75	= CV disease &renal failure = mortality	= adverse effects
Cardio-SIS 2009 (271)	Mean 67y Italy	n=1,111 F/u: 2y	B/L: sBP 163/90 Achieved:136/80 vs 139/81	↓LVH (ECG) ↓composite of 13 CV outcomes	= adverse effects
ACCORD 2010(272)	Mean 62y USA/ Canada	n= 4,733 F/u 4.7y (DM II)	B/L: 139/76 Achieved: sBP 119	= MI, stroke CV death ↓ stroke	↑ low BP ↑ low K+ \ ↑ AKI
SPS3 Trial 2013(273)	Mean 63y North and South Americas, Spain	n= 3,020 F/u 3.7y Post-stroke	B/L: 143/79 Achieved: sBP 127	= MI = stroke = mortality	= dizziness/ unsteady on standing
VALISH 2013(274)	Mean 76y (70-84y) Japan	n= 3,079 F/u: 2.85y	B/L: 170/ 82 Achieved: 137/75	= Composite MI, HF, CV death, renal failure	= adverse side effects
SPRINT2017 (275)	Mean 68y USA, Haiti	n= 9,361 No DM/ Stroke F/u: 3.26y	B/L 140/78 Achieved: 121.4	↓MACE, ↓ACM	↑low BP, ↑syncope ↑AKI ↑e- abnormal =falls ↓OH
HOPE-3 (276)	Mean 66y Canada	n= 12,705 F/u=5.6y	B/L BP 138/82 Achieved sBP 128 v.s 124	= CV Death/ MI/ Stroke = Heart failure/ CV arrest/ revascularisation	↑hypotension ↑dizziness = syncope =renal failure = K^+ abnormalities

Table: Trials: AASK = African American Study of Kidney Disease and Hypertension; ACCORD = Action to Control Cardiovascular Risk in Diabetes; Cardio-SIS = Studio Italiano *Sugli Effetti CARDIOvascolari del Controllo della Pressione Arteriosa SIStolica;* HOPE-3 = Heart Outcomes Prevention Evaluation; JATOS = Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients; SPRINT = Systolic Blood Pressure Intervention Trial; SPS3 = Secondary Prevention of Small Subcortical Strokes; VALISH = Valsartan in Elderly Isolated Systolic Hypertension Study.

All abbreviations: All blood pressure recordings are in mm Hg; ACM= All-cause mortality; AKI = Acute kidney injury; DM = Diabetes mellitus ; e- = electrolyte abnormalities; ECG = Electrocardiogram; ESRD = End stage renal disease · GFR slope=ESRD = Glomerular Filtration Rate; HF = Heart failure; K+ = potassium; LVH = Left ventricular hypertrophy; I = Intervention; OH = Orthostatic hypotension; RCT = Randomised controlled trials; U = Usual treatment; y = years

Whilst older people are included in the age ranges of these trials, people with frailty, co-existing conditions and polypharmacy are less likely to have been recruited (277). Characteristic features of frailty include: dependence on others for activities of daily living, and having cognitive impairment. These characteristics often also form part of exclusion criteria in randomised control trials (278). Even when older people with frailty are targeted in trial recruitment as in the recent OPtimising Treatment for Mild Systolic hypertension in the Elderly (OPTIMISE) treatment withdrawal trial, a minority of those invited are enrolled (279).

The success of increasingly interventionist trial strategies is taken by some as evidence of a linear risk of BP, i.e. ‘the lower the better’. The SPRINT trial in particular does provide evidence, that for some older people, in terms of the end-points measured, lower sBP is associated with benefit. However, the general application of trial findings to the wide heterogeneity of risk and disease presented among older people with hypertension remains problematic. Concerns centre around two major limitations of the current trial evidence base:

1. Trial populations may not be representative of the patient population as a whole. Explicit or implicit exclusion of older people with competing health problems by trial design mean that the trial populations are highly selective (280), and particularly exclude people with multi-morbidity and frailty.
2. Outcomes measured prioritise cardiovascular end-points. It remains unclear how fastidiously adverse effects are asked about. There has only

been limited enquiry about the tolerability and degree to which patients suffered side effects (281).

3. BP measurement and titration of therapy in a trial setting is not necessarily replicable in routine clinical care.

A 2019 Cochrane systematic review and meta-analysis reported on randomised control trials of hypertension treatment specifically in people over the age of 60 (282). The synthesis involved 26,795 participants with a mean age of 73 years, in 16 trials with a mean duration of 4 years. The mean baseline blood pressure was 182/95 mm Hg. The synthesis of these trials demonstrated that treatment was associated with a reduction in all-cause mortality (from ARR 11% to 10%), and cardiovascular morbidity and mortality (from 13.6% to 9.6%). However, alongside there was an increase in the proportion withdrawing from the trial because of treatment side effects from 15.7% in the treatment arm, to 5.4% in placebo.

The reduction in mortality observed was due mostly to a reduction in the 60- to 79-year-old patient subgroup (RR 0.86, 95% CI 0.79 to 0.95). Cardiovascular mortality and morbidity was significantly reduced both in the subgroup aged 60 to 79 years old (moderate-certainty evidence; RR 0.71, 95% CI 0.65 to 0.77) and the subgroup aged 80 years or older (moderate-certainty evidence; RR 0.75, 95% CI 0.65 to 0.87). The reduction in vascular mortality and morbidity was primarily due to a reduction in cerebrovascular mortality and morbidity. The Cochrane synthesis identified that the magnitude of absolute risk reduction was

higher among 60- to 79-year-old patients compared to over 80 year olds (3.8% vs 2.9%).

1.7.2 Treatment harms

Treatment harm may relate to specific adverse effects relating to a particular drug or to the more general consequences of systemic BP lowering.

1.7.2.1.1 Drug side effects

Cardiovascular medications are among the most common causative treatments among adverse drug reactions (ADR) related hospitalisations (283). The principle known adverse treatment effects relating to BP-lowering medications are listed in **Table 1-3**.

Table 1-3 Principle adverse treatment effects of BP-lowering medications

Diuretics
Hypokalaemia in 5-20% (284) Urinary frequency, erectile dysfunction Disruption of magnesium, sodium, uric acid, calcium, glucose intolerance, insulin resistance Contributes to deterioration in renal function (285)
Angiotensin-Converting Enzyme inhibitors (ACE-i) or Angtiotensin Receptor Blockers (ARB)
ACEi: First dose hypotension, Disruption of potassium, glycaemic control Interference with erythropoietin, Deterioration of renal function, Cough and bronchospasm, Angioedema, ARB: rash
Calcium channel blockers
Short acting first generation drugs associated with increase in CV mortality, Pedal oedema Headaches flushing Gingival hyperplasia
Beta-blockers
Fatigue, bradycardia. diminished exercise tolerance, weight gain, Disruption of insulin sensitivity, triglycerides, potassium Bronchospasm;
Central sympatholytics
Depression, confusion, somnolence
Alpha blockers
Dizziness, syncope, orthostatic hypotension, Inferior cardiovascular risk reduction

1.7.2.1.2 General effects of BP-lowering

The trials demonstrate strong evidence for maintaining systolic BP lower than between 140 – 150 mm Hg depending on the population investigated and the outcomes measured. However much less is known on where the lower limit of treatment benefit lies: that is the BP level below which treatment may cause more harm than benefit (286). The J-curve describes the observation in some studies that at very low blood pressures there is an inversion of the normal positive linear association between increasing BP and adverse outcomes. Instead evidence of a J- curve would suggest that the association of BP and outcomes is non-linear: that below a certain BP threshold, the risk of outcome

starts to increase with lower BP. The J-curve was initially described in the Framingham cohort (287).

The J-curve also correlates with understanding of physiology that describes a lower BP threshold of auto-regulation which is elevated in chronic hypertension, so that low BP may cause under-perfusion of end-organs (288). Investigation of a J-shaped or U-shaped phenomenon for systolic BP has not been undertaken in trials. To do so, a trial would require a minimum of three thresholds (286), the exception is the Hypertension Optimal Treatment (HOT) trial which used three diastolic targets (226). It is evident from review of **Table 1-1** and **Table 1-2** that more recent interventions at lower BP in **Table 1-2** have demonstrated smaller treatment effects (286).

At which level of BP the J-point is located will also conceivably vary depending on the target organ of interest (289). For example, the myocardium is particularly at risk at low systemic blood pressure, because, unusually, it is perfused during diastole. Below a diastolic blood pressure of 60 mm Hg the risk of a Type II myocardial infarction increases (290). A type II myocardial infarction is defined as myocardial ischaemia in the absence of coronary artery disease when myocardial oxygen supply is insufficient for myocardial oxygen demand (291).

1.7.2.2 Ageing

Older people may come to harm because they are more vulnerable to the adverse effects of treatment and the adverse event itself may be more catastrophic. For example, orthostatic hypotension may lead to a younger person having a simple fall, but an older person fracturing their hip and requiring an emergency hip replacement operation.

Falls affect 1 in 3 people aged over 65 years in the UK every year (292), and represent the leading cause of emergency hospital admission in this age group (293). Falls are most often due to multiple interacting conditions (294), and risk factors for falls overlap with other geriatric syndromes (incontinence, delirium, poor mobility), but include postural hypotension.

The lower baroreceptor responsiveness seen in old age, as well as seen in chronic hypertension, means that low BP does not induce immediate increases in heart rate and/or systemic vascular resistance to maintain BP in the face of a hypotensive trigger. This makes older people more susceptible to BP variability leading to episodes of hypertension and hypotension. Hypotension is defined by as “a blood pressure that is below the norm expected in a given environment” (295). Hypotension may be absolute (systolic < 90 mm Hg, diastolic< 65 mm Hg); relative (drop in BP > 40 mm Hg); orthostatic (>20m mm Hg in systolic or 10 mm Hg diastolic on standing)(296), or may be a feature of shock. Low blood pressure is not problematic unless it is associated with other symptoms (e.g. vasovagal or post-prandial syncope), leading to syncope and falls. Orthostatic hypotension is exacerbated by particular BP-lowering treatment and contributes significantly to falls in older people.

1.7.2.2.1 Drug side effects

Adverse drug reactions (ADR) are a significant burden in later life. In a meta-analysis of 17 studies comprising a total of 7,553 hospitalisations of older adults, an average 16.6% of admissions were judged to be related to adverse drug reactions (297). BP lowering treatments are commonly prescribed and contribute significantly to the polypharmacy seen in old age, increasing the overall risk of harm (298). Whether the associated harm of BP-lowering medication is modifiable with de-prescribing is unclear (279, 299, 300).

1.7.2.2.2 General effects of BP-lowering

Recent epidemiological studies demonstrating a non-linear association of BP and outcomes (the J-curve): are listed in **Table 1-4** whereby low BP is associated with higher risk of adverse outcome (301-304). These studies are in populations which have explicitly included older adults with high multi-morbidity and high cardiovascular risk. Post-hoc analyses of trials have also extended the finding of a non-linear association between BP and outcome to people with high cardiovascular burden (305-307). The non-linear association described in these studies has generally been interpreted to be the consequence of the harms of treatment or to reverse causality. Reverse causality describes that low blood pressure in the context of disease burden is a marker of proximity to death due to failure of multiple physiological systems. This latter interpretation may have recently been challenged by the finding that risk associated with low sBP is reversible with revascularisation of the coronary arteries (305).

Table 1-4 Observational Cohort studies demonstrating non-linear associations between BP and Outcomes

Study 1st author, location	Cohort/ design	Findings
Mattila (308) Tampere, Finland Recruit:1977	Age: >85y n: 561 F/u: 5y	Systolic BP < 120 mm Hg was associated with longest survival
Heikinheimo (309) Tampere, Finland Recruit 1981-4	Age: 84– 88y n: 541 F/u: 3y	Mortality rate was higher in those with very high and very low sBP levels
Satish (30) USA Recruit 1981, 1987	Age: >65y n:12,802 F/u: 6y	Among those >85y risk of death was higher with an sBP < 130 mm Hg than with an sBP >180 mm Hg, not in the sub-population < 85 years.
Langer (310) Finland Recruit 1984	Age: >80y n:795 F/u 3y	Increased dBP was associated with reduced all cause and cardiovascular mortality
Rastas (311) Vantaa, Finland Recruit 1991	Age:>85y n: 601; F/u 9y	sBP < 140 mm Hg associated with increased risk (HR 1.35 (95% CI 1.04 – 1.74)) compared to sBP 140 – 159 mm Hg
Kagiyama(312) Japan Recruit 1997	Age: >80y n: 639 F/u: 4y	dBP < 70 mm Hg associated with increased risk of death compared to dBP > 90 mm Hg (RR 2.47 (95% CI 1.07 – 5.70))
van Bemmel (313), Leiden, Holland Recruit 1997	Age: >85y n: 571 F/u: 4.2y	sBP < 140 mm Hg, with a diagnosis of hypertension associated with an increased risk of mortality
Molander (314) Sweden Recruit 2000-2	Age: >85y n: 348 F/u 4y	sBP > 164 mm Hg (95% CI 154 –183.8) associated with lowest mortality, increased risk associated with sBP lower and higher than this
Poortvliet(315) Leiden, Holland Recruit 2002-4	Age: >90y n: 267 F/u: 5y	sBP < 150 mm Hg associated with increased mortality HR 2.0 (95%CI 1.1, 3.4) compared to an sBP > 150 mm Hg
Badia Farré (316) Spain Recruit <2007	Age: >80y n: 323 F/u 4y	sBP <130 mm Hg associated with increased risk of death compared to sBP 140 to 159 mm Hg (HR 0.39; 95% CI: 0.21 - 0.72)
Douros (317) Germany Recruit 2009-11	Age: >70y n: 8,853 F/u: 6y	In treated hypertension, BP < 140/ 90 mm Hg increased risk of all-cause mortality (HR 1.26 (95% CI 1.04 – 1.54), compared to BP >140/90
Lv (318) China Recruit 2011	Age: >80y n: 4,658 F/u: 3y	U shaped association between BP and all-cause mortality: lowest mortality risk associated with a sBP of 129 mm Hg

1.7.3 Balancing benefit over risk with age

International treatment guidelines indicate treatment for hypertension on the basis of at least two factors: the level of a person's BP, and the level of a person's overall cardiovascular risk.

Regarding BP target, current guidelines diverge (**Table 1-5**). For adults over the age of 80 years for example, the UK National Institute for Healthcare Excellence (NICE) guidelines (8), and the American Academy of Family Physicians (9) recommend treating systolic blood pressure to less than 150 mm Hg; the American College of Cardiologists recommend treatment to a target of less than 130 mm Hg systolic blood pressure (10); and, the European Society of Cardiology recommend maintaining systolic blood pressure below 140 mm Hg above 130 mm Hg (11).

Cardiovascular risk models were initially developed in the Framingham cohort, following which more than three hundred predictive models have been developed to anticipate risk for developing cardiovascular disease (319). The level of cardiovascular risk at which treatment is deemed to have greater benefit over harm has been recently reduced in the majority of guidelines. A cardiovascular risk level of 10% over ten years is recommended by the most recent NICE guidelines to indicate treatment (320).

Table 1-5 Summary of the key English language hypertension guidelines and their application to older people

Guideline Body	**NICE (320) UK**	**Hypertension Canada (321)**	**ESC (322) Europe**	**AHA & ACC (323) USA**	**NHFA(324) Australia**
Year	2019	2018	2018	2017	2016
Maximum BP before treatment	ABPM: 149/94 Clinic: <80y: 140/90 >80y: 150/90	ABPM: <130/80 Clinic <140/90	>80: 160 60-80y & fit: 140-159	Noninstitutionalized ambulatory community-dwelling adults >65: 130 (av.)	Low CV risk: 160 Mod CV risk: 140
Minimum BP on treatment	135/85	None; Caution if Standing sBP < 110	<65: 120/70 >65: 130/70	None	None
Target BP	ABPM , standing BP: <80: <135/85 >80:<145/85	High CV Risk: <120 Low CV risk:<140 Diabetes mellitus: <130	Target ABPM <65 130/79; >65 139/79	Low risk < 140 Mod/ high risk<130	All: <140 High risk or >75y: <120
Recommend clinical judgment	80y with frailty or multi-morbidity	Institutionalised elderly	65y - 80y: clinical condition, concomitant treatments and frailty	>65y & multi-morbidity, limited life expectancy	75y

Guideline committees: ACC = American College of Cardiology; AHA = American Heart Association; ESC = European Society of Cardiology ; NHFA = National Heart Foundation of Australia; NICE = National Institute for Health and Care Excellence

Table abbreviations: av. = average; ABPM: Ambulatory Blood Pressure monitoring; av.: average; BP: blood pressure; CV Risk: Cardiovascular risk; sBP: systolic BP; y = years.

1.8 Considering ageing as central to cardiovascular risk

The evidence presented in this chapter demonstrates the relevance of the process of ageing both to the pathophysiology of hypertension and to the balance of treatment benefits and harms (**Figure 1-6**). This thesis will investigate the potential role of frailty as a measure of biological ageing to inform the management of hypertension. In the following section I will outline how frailty is defined and conceptualised in recent literature, and present grounds to consider a person's frailty status in the management of hypertension.

Figure 1-6 Hypertension in the context of ageing: A proposed modification of Page's original mosaic

1.8.1 What is frailty?

The concept of frailty describes a loss of physiological reserve with age and a failure of homeostasis to maintain a steady state in the face of stressors (325). Frailty develops because ageing physiological systems loose complexity: they become less dynamic; they are unstable and reactive to perturbations; and, this ultimately results in loss of physiological function (326). Clinically, people with frailty are characterised by prolonged and incomplete recovery to a stressor event. People with frailty therefore spend longer in hospital, experience more peri-operative complications, and are discharged from hospital with greater functional needs, long term disability and mortality (327).

The stressor may include a wide range of precipitants, examples include an infection, a fall, or a new medication. Disease in the context of frailty therefore often presents with features that are less typical for the disease process (328) but more typical for diseases characteristic of ageing (329). Older people with frailty, in the face of what should be a minor stressor can change dramatically from being lucid to delirious, mobile to being bedbound, independent to requiring cares for basic daily needs (325).

Allostatic load represents cumulative biological burden across the life-course, and the attempt of the body to adapt to this is allostasis (330). The accumulation of biological burden leads to multiple failures in signalling at the level of molecular mechanisms with ageing. As a result, the overall system loses its complexity and ability to respond to stressors (331). Adaptive

compensations fail and functional homeostatic mechanisms are in jeopardy. The clinical features of this process present as frailty.

The cumulative deficit model of frailty is an internationally established theoretical model, operationalised as the additive effects of health deficits on the overall health of an individual (332). It is based on the understanding that with ageing, people are more likely to accumulate a variety of general health deficits (325). Deficits may include diseases, but also more minor impairments that do not meet disease criteria, including biochemical aberrations or evidence of physiological decline (6). An accumulation of deficits going unrepaired leads to loss of reserve. Therefore, the frailty index (FI) represents a means of quantifying a person's relative health state, and has utility in considering a large number of small effects on a person's health status.

An alternative approach is the frailty phenotype method (333). This approach regards frailty as a clinical syndrome, whose criteria include: unintentional weight loss, muscle weakness, self-reported exhaustion, slow walking speed, and low physical activity (333). Using the frailty phenotype model, frailty is identified in individuals in whom three or more of these clinical features are present.

Advantages of the cumulative deficit model over the phenotype mode are that the FI:

- is on a continuous scale and therefore frailty can be graded;
- can be measured in a diversity of clinical studies including in trial and routine healthcare data; and,
- can be calculated retrospectively from available data if the data are sufficiently comprehensive (334).

1.8.2 Why consider frailty in hypertension?

1.8.2.1 Frailty as a measure to capture variation in population health

A combination of improved survival rates and falling fertility rates means that the large majority of countries internationally are anticipating an increase in the size of their older populations (335). This is evidenced in the striking rise projected in the number of people globally aged over 65 years old from 0.7 billion in 2019 to 1.55 billion in 2050, with the biggest regional increases in North Africa and Western Asia (120%) and smallest increases in Europe and North America (48%) (335). In the UK there are currently 12 million people over the age of 65, constituting 18% of the population and this is set to increase to 24.8% by 2050 (336).

However there is marked geographical variation within the UK, with inequalities in rates of survival to old age (337). Also, there is a large disparity between life expectancy (number of years that a person can be expected to live) and healthy

life expectancy (number of years that a person can be expected to live in “full health” taking into account years lived in less than full health due to disease or injury) (338). In the UK, a large percentage of men (44%) and women (47%) at the age of 65 years live in poor health (339). Approximately 55% of those over 65 years have two or more long-term conditions (LTC), commonly known as multi-morbidity (340).

Because people are living longer, and living for an extended proportion of that time with greater disability and comorbidity, there is a wide variation in the health of older people. Chronological age is insufficient to capture this variation in the ageing process among individuals.

Frailty is easily measurable and available to practitioners in the current UK health system. Frailty is also now more easily identifiable in the UK, since the recent development, validation and implementation of an electronic Frailty Index (eFI) (341). This enables robust identification of frailty at a population level using routine primary care electronic health record data.

A hypothesis explored in this PhD is whether frailty can characterise ageing in a way that is clinically applicable to hypertension management that is patient centred.

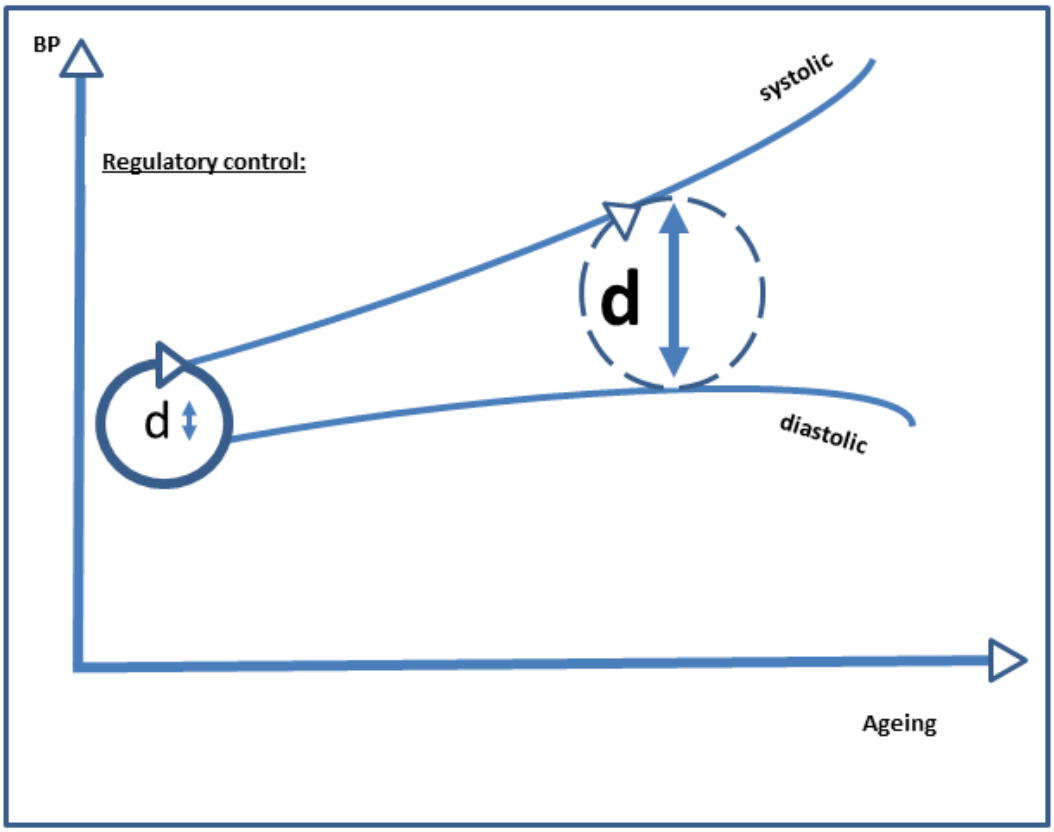
1.8.2.2 Frailty as a predictor of a range of adverse outcomes

There is significant variation in the rate of vascular ageing in later life throughout the population (342). The underlying aging process changes the substrate of the cardiovascular system in a way that lowers the threshold for common cardiovascular diseases to become clinically manifest in an individual. However, adverse outcomes, cardiovascular and non-cardiovascular in later life are predictable using measures that relate to the underlying ageing process (327).

Frailty is a global measure of multi-system failure associated with ageing that is relevant to the management of hypertension. Many of the structural and molecular changes involved in hypertension are changes of ageing. Vascular health is influenced directly by the health of end-organs. The integrated physiology underlying BP control is evidence that many organ systems failing, rather than the degree of failure of one single system is relevant in the context of hypertension (40) (**Figure 1-7**). For example, baroreceptor function becomes impaired with age, also there is reduced diastolic ventricular filling and reduced vascular compliance which all act to increase BP variability in the context of reduced preload. In such a context ageing represents the common factor of each of these system failures contributing to BP and the associated risk.

A hypothesis explored in this PhD is whether frailty can characterise ageing associated risk of key outcomes in relation to the management of hypertension in older people.

Figure 1-7 A schematic representation of the relationship between BP and frailty across the life course



Influences on BP control across the life course – these mechanisms of normal blood pressure control. Hypertension in younger life is characterised by increasing vascular resistance and relates to influences on increasing the set-point of stable blood pressure control (represented by the circle). Hypertension in later life is characterised by rising pulse pressure which represent changes to the dynamic blood pressure control (d). Negative feedback loop of blood pressure regulatory mechanisms may also be less sensitive than in younger life (represented by broken circle)

1.8.2.3 Frailty to identify a population in whom associations of BP and outcomes are different

The BP target, at which a favourable balance of benefit over harm exists remains the subject of debate, particularly for older people, in the context of competing risks. There is a divergence in the nature of BP associated risk reported in trial and epidemiological literature, which it is proposed, relates to the population in whom the association is measured. In populations with a low disease burden, including older people who maintain good health, increasing

BP is associated with a linear increase in risk of adverse outcomes. In populations with a high disease burden, particularly in older people, risk of low BP is also associated with harm so that the association between BP and adverse outcomes overall is non-linear.

A hypothesis explored in this PhD thesis is whether frailty can identify the population in whom BP associated risk is non-linear from the population in whom the BP associated risk is linear.

1.9 Research question

There is a evident uncertainty relating to the balance between benefit and harm of hypertension treatment for older people living with frailty. This is a clear research gap which is contributing to the divergence in guidelines which in the absence of evidence rely on expert opinion. Indeed the need for research in this area has been highlighted by all of the leading hypertension guideline committees worldwide (320, 322, 323).

From the biological and clinical perspectives outlined in this chapter, it is evident that the relevance of a BP measurement depends on its context. Targets for treatment vary based on the clinical context: for example the choice of target BP is different whether it is in the context of diagnosis or long-term management, and whether it is in primary or secondary prevention. Therefore this PhD will investigate the role of frailty specifically in the context of patients

with hypertension which is being treated for the primary prevention of cardiovascular disease.

Secondly, guidelines currently balance the benefit and harm of treatment on two factors: the level of a person's overall cardiovascular risk and the level of blood pressure. This PhD will investigate the potential role of frailty in hypertension management in both respects:

1. Frailty as a prognostic factor which alters a person's level of overall risk of outcomes in relation to the management of hypertension
2. Frailty as a factor that modifies the association of the level of BP with outcomes such that the balance of risk and harm may be different at particular levels of BP conditional on a person's frailty status.

Finally, the PhD will adopt a mixed methods approach to investigate the role of frailty in hypertension management both from the perspective of routine primary care as recorded in electronic health data, and also from the perspective of older people themselves who live with hypertension and frailty

1.10 Aims and objectives

The research questions, and associated objectives are as follows:

1. What is the current level and quality of evidence to inform whether the association of blood pressure and outcomes is different in the context of frailty?

Objective 1: to undertake a systematic review and meta-analysis of the available evidence from observational studies investigating the association of blood pressure and outcomes in the context of frailty.

2. Is frailty useful as a prognostic marker in the management of hypertension in routine clinical care?

   Objective 2: to describe the normal blood pressure-outcome associations in this population

   Objective 3: to investigate in large scale routine primary care data whether frailty is a prognostic factor for relevant outcomes in the management of hypertension in older people.

3. Is there evidence the association of blood pressure and outcomes is different in the context of frailty?

   Objective 4: to investigate in large scale routine primary care data, whether frailty causes effect modification of the association of blood pressure or blood pressure lowering treatment and outcomes in older people.

4. Is frailty a useful measure to inform management of hypertension from the perspective of patients themselves?

   Objective 5: to explore the patient's perspective using a series of narrative interviews to reveal how the concept frailty can inform shared decision making in older people with hypertension.

Chapter 2 Literature review

2.1 Summary

Chapter 1 summarised the evidence base for hypertension treatment in the trial and observational literature. Chapter 2 specifically focuses the existing literature examining the role of frailty. Here I will address the first objective of this PhD which is to undertake a systematic review and meta-analysis of the available evidence investigating the association of blood pressure and outcomes in older adults with and without frailty. There is a paucity of trials recruiting older people with frailty and multi-morbidity, as discussed in the previous chapter (**Section 1.6.1**). Therefore, a summary of observational studies is necessary, albeit with the caveat that their interpretation must account for their higher risk of reverse causality and residual confounding. This work has been published (343).

2.2 Objective 1

To undertake a systematic review and meta-analysis of the available evidence from observational studies investigating the association of blood pressure and outcomes in the context of frailty.

2.3 Methods

Given the focus on observational evidence, the review methodology followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidance and is reported using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (344, 345).The protocol was prospectively registered with Prospero http://www.crd.york.ac.uk/PROSPERO/ (reference CRD42017081635).

2.3.1 Inclusion criteria

Observational studies involving community-living older adults (mean age >65), with frailty identified using a validated measure, and participant follow-up for at least six months were eligible. A frailty measure was considered to be valid if it had been validated against a reference standard (346). Blood pressure was required to be measured at baseline with or without treatment, using a measurement standardised within the study. If a participant was unable to complete the frailty test, their data were excluded from meta-analysis. This is because non-participation does not represent a validated measure of frailty – non-completion of the test may be for reasons other than frailty.

The primary outcome was all-cause mortality. A priori secondary outcomes included: falls; stroke; non-fatal myocardial infarction; secondary prevention outcomes (e.g. proteinuria); adverse treatment effects; non-cardiovascular mortality; and other markers of general morbidity (including unplanned hospitalization; institutionalization; function; and quality of life).

2.3.2 Search methods for identification of studies

An inclusive MEDLINE search strategy was developed with an experienced research librarian at the University of Leeds, and adapted for CINAHL, EMBASE, and Web of Science. All databases were searched for English language publications between 1st January 2000 and 13th June 2018. A start date of 2000 was chosen because the reference standard frailty measures first became available since then (332, 333). The search strategy for MEDLINE (Ovid SP) is available (**Appendix A**). Reference lists of included articles were also searched. PROSPERO, Research registry and NIHR research registries were searched for unpublished work. Authors were contacted if abstracts referred to unpublished work, and a forward citation search was undertaken of all included studies.

Study eligibility was determined by two independent reviewers (OT, and Dr Chris Wilkinson (CW), or Dr Mark Perry (MP), or Dr Matthew Hale (MH)) with any disagreements settled by consensus discussion with a third reviewer (Professor Andrew Clegg (AC)). Reasons for exclusion of articles at the full-text review stage were collated using Covidence software (347).

2.3.3 Data extraction

Hazard ratios (HRs) were extracted with 95% confidence intervals (CIs) for time to event data (e.g. mortality) for different categories of baseline systolic and diastolic blood pressure, with and without frailty, adjusted for a minimum of age

and sex. Two independent reviewers extracted hazard ratios (OT, CW). A third reviewer (AC) settled any disagreements by consensus discussion.

2.3.4 Assessment of risk of bias

Two independent reviewers (OT, and CW or MH) assessed risk of bias for each study using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) tool (348).

2.3.5 Meta-analyses

Data were synthesized for meta-analysis by calculating natural logarithms of HRs, with standard errors to create summary forest plots by generic inverse variance random effects modelling using RevMan 5.3 software. Statistical heterogeneity was assessed using the I^2 statistic to determine whether fixed effects (I^2<50%) or random effects (I^2≥50%) modelling should be used. Since fewer than 10 studies were identified to provide data for each outcome, assessment for publication bias with funnel plots was not appropriate (349).

Where studies used different reference categories for blood pressure, estimates comparing groups were re-categorised according to thresholds for treatment recommended by NICE guidelines (systolic BP of 140 mm Hg, and diastolic BP of 90 mm Hg) (320). Where there was more than one category on either side of the threshold, risk estimates from directly neighbouring categories were

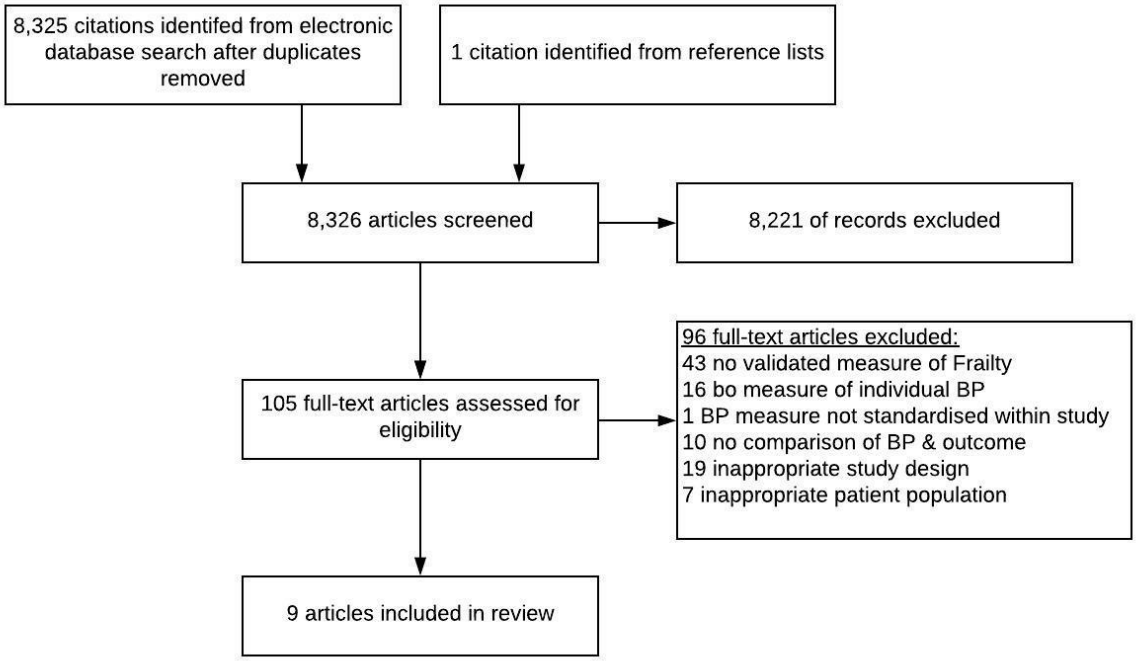
extracted and pooled using generic inverse variance methods (**Appendix B**). Data from ‘less than’ categories (<) were pooled with data from ‘less than or equal to’ (<=) categories and the same was done for ‘more than’ and ‘more than or equal to’ categories. Where continuous scales of measurement were used, the HR for events associated with 10 mm Hg difference in blood pressure at baseline was extracted.

2.4 Results

2.4.1 Literature search

Details of the study selection are presented in **Figure 2-1**. Following detailed assessment, nine studies were eligible for inclusion in the review; eight were included in the meta-analysis (350-357) of which seven required further information, which was supplied by study authors (350, 352-357). It was not possible to make contact with the author of one study, which therefore had to be excluded from the meta-analysis (318). A forward citation search on 8th March 2019 revealed 91 studies, none of which met eligibility criteria.

Figure 2-1 Flow chart of Included Studies



2.4.2 Study characteristics

The nine studies were all prospective cohort studies with a total of 21,906 participants and mean follow-up period of 6 years (range 3 to 11 years) (**Table 2-1** & **Table 2-2**). All studies were rated as low or moderate risk of bias (**Table 2-3**). Three studies were based on study populations in the United States (352, 353, 357), five in Europe (350, 351, 354-356) and one in China (318) with study periods between 1989 and 2014. The studies recruited a mean of 58% (range 20 – 92%) of eligible participants. The mean age was 81 years (74 – 92 years) and 59% (51-70%) were female. In the four studies in which it was reported, care home residents constituted 24% (10 - 39%) of the study population (354-356), in two studies care home residents were excluded (352, 357). Frailty was identified in 37% (13 - 64%) of participants, and use of BP-lowering treatment was reported in 52% (26- 81%), and where reported, a diagnosis of hypertension in 48% (25 – 70%) (318, 355). Median annual mortality for the whole study population was reported to be 7% (range 4-17%).

Table 2-1 Study characteristics Part A

Study	Study size Mean duration Recruitment	Exclusion criteria	Frailty measure & threshold	Blood Pressure (mmHg)				Confounders in addition to Age & Sex
				Readings	Categorical measures		Continuous measures	
					systolic	diastolic		
Gutierrez-Misis 2015 (350)	649 6 yrs 39%	Unable to consent; moved away; early death	Gait 0.8 m/s	2	<120 ≥120 & < 140 ≥140	< 80 ≥80 & < 90 ≥90		BMI; cholesterol; depression; CCF; cognition; stroke
Hospers 2014 (351)	1,411 11 yrs 53%	Refusal; early death; 'too frail'; not contactable	Gait 0.8 m/s	1	≤ 120 v >120 & ≤ 140 >140	< 70 ≥70 & < 90 ≥90		Education; BMI; smoking; alcohol consumption; cholesterol; cardiovascular disease; diabetes; and BP-lowering drug use
Lv 2018 (318)	4,658 3 yrs 60%	Age <79y; missing data; early death	OFI >2/3	2	<107 ≥107 & < 154 >154	< 70 ≥70 & < 90 ≥90		Marital status; education; residence; income; smoking; alcohol; cognitive impairment; restrictions on ADL; poor vision; BMI; central obesity; DM; CVD; stroke; respiratory disease; cancer.
Odden 2012 (352)	2,340 6 yrs 37%	Institutional living; early death	Gait 0.8 m/s	3 - 4	< 140 vs. ≥140	< 90 vs. ≥ 90	10 mm Hg difference	CCF; CHD; cholesterol; education; race; smoking; stroke; survey year
Peralta 2015 (353)	3,547 8 yrs 20%	Unable to consent; moved away; cancer	Gait 0.8 m/s	3	<120 ≥120 & < 150 ≥150	< 65 ≥65 & < 80 ≥80	10 mm Hg difference	Education; race; smoking physical activity; BMI; cholesterol; cystatin C; hypertension medications; and sBP or dBP respectively

Table 2-2 Study characteristics Part B

Study	Study size Mean duration Recruitment	Exclusion criteria	Frailty measure & threshold	Blood Pressure (mmHg) Readings	Categorical measures systolic	 diastolic	Continuous measures	Confounders in addition to Age & Sex
Streit 2018 (354)	570 5 yrs 81%	Early death; missing data	Grip *not defined*	2			10 mm Hg difference	CVD; BP medications
Vaes 2017 (355)	541 5 yrs 92%*	Dementia; palliative care; emergency	GFI 6+/15 Fried 3+/5 Puts 3+/9	2			10 mm Hg difference	Education
Weidung 2015 (356)	745 3 yrs 58%	Early death; missing data	Gait 0.5 m/s	1	≤ 125 >125 & < 140 ≥140 & < 150 ≥150 & < 165 ≥165	< 70 ≥70 & ≤ 75 >75 & < 80 ≥80		Follow-up time; CCF; AF; MI; cancer; depression; angina; BMI; MMSE score; adjusted for care facility residency; living alone; education; CVD; hip fracture; specific drugs and number of drugs.
Wu 2017 (357)	7,492 6 yrs 79%	Institutional living; missing data; fast gait	Gait *f* 0.52 *m* 0.6 m/s; Grip *f* 16kg *m* 26kg	3	< 140 vs.≥140 < 150 vs. ≥150	< 90 vs. ≥ 90	10 mm Hg difference	BMI; BP medication; cancer; cardiac disease; HbA1c; CRP; cystatin C; diabetes; education; ethnicity; smoking; stroke

AF = atrial fibrillation; BMI = body mass index; CCF = congestive cardiac failure; CHD = coronary heart disease; CRP = C-reactive protein; CVD = cerebrovascular disease; dBP = diastolic blood pressure; f = female; Gait = Gait speed; Grip = Grip strength; GFI = Groeningen Frailty Index; HbA1c = glycated haemoglobin; LAPAQ = Longitudinal Aging Study Amsterdam (LASA) Physical Activity Questionnaire; MI = myocardial infarction; MMSE = Mini-mental status exam; m = male; n = sample size; OFI = Osteoporotic Fracture Index; sBP = systolic blood pressure; yrs = years. * Estimate using information presented, but exact figures not provided.

Each study compared both systolic and diastolic blood pressures, as an average of between one and four readings, all at the start of the study. Five studies analysed blood pressure as a continuous variable (352-355, 357) and seven studies categorized blood pressure (318, 350-353, 356, 357) into 2-5 groups using thresholds used in the Joint National Committee (JNC) 7 (352), JNC 8 (357), or European Society for Cardiology (ESC) 2013 guidelines (350). In studies that did not report blood pressure categories using thresholds according to NICE guidelines (320) study authors were contacted to request access to the raw data. Frailty was measured using a variety of measures, and categorized using different thresholds (**Table 2-1**).

All nine studies reported all-cause mortality as an outcome, in eight as a primary outcome. One study reported cardiovascular morbidity as a primary outcome, and mortality as secondary outcome (353). Other secondary outcomes included disease-specific mortality (318), cardiovascular mortality (355), and change in cognitive function (354).

The consensus opinion of the PhD supervisory and collaborating team was that study eligibility criteria and included populations were sufficiently similar to allow pooling of findings from eight studies (n=17,248, mean duration 6 years) for comparison of all-cause mortality risk (350-357). There were too few studies to allow meta-regression (358). One study was excluded from meta-analysis because risk estimates were not reported for sub-groups with and without frailty (318).

2.4.3 Risk of Bias

Comprehensive assessment of the risk of bias using the RoBANS tool highlighted deficiencies, but overall risk of bias was low or moderate for each of the included studies (**Table 2-3**). Three studies gave incomplete information on cohort recruitment (351, 355, 357). Four studies were rated as at high or unclear risk of bias for the measurement of exposure. In these, the frail sub-cohort included participants who were unable to complete the frailty test (350, 353, 354, 356). In two studies the clinical or statistical justification for the choice of confounding variables was not reported (318, 357). None of the studies referenced a published protocol with pre-specified methods. In all studies, mortality was determined by robust means: either in death registries or by a primary care physician. Missing data for covariates were not accounted for with one exception (318). In one study, more than 20% participants had some missing data on relevant covariates (350).

Table 2-3 Risk of Bias Assessment

Study	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome	Incomplete outcome data	Selective outcome reporting	Overall judgement
Gutierrez-Misis (350)	Low	Low	High	Low	Low	Unclear	Mod
Hospers (351)	Unclear	Low	Low	Low	Low	Unclear	Low
Lv(318)	Low	Unclear	Low	Low	Low	Unclear	Low
Odden(352)	Low	Low	Low	Low	Low	Unclear	Low
Peralta(353)	Low	Low	Unclear	Low	Low	Unclear	Low
Streit(354)	Low	Low	High	Low	Low	Unclear	Mod
Vaes(355)	Low	Low	Low	Low	Low	Unclear	Low
Weidung(356)	Low	Low	High	Low	Low	Unclear	Mod
Wu(357)	Unclear	Unclear	Low	Low	Low	Unclear	Low

Risk of Bias Assessment using the Assessment tool for Non-randomized Studies (RoBANS) tool (348)

2.4.4 Primary Outcome - all-cause mortality

2.4.4.1 Categorical blood pressure comparisons

Systolic Blood Pressure: Synthesis of data from six cohort studies (350-352, 355-357) demonstrated that a systolic blood pressure less than 140 mm Hg had no association with mortality in older people with frailty compared to a systolic blood pressure more than 140 mm Hg (HR 1.02, 95% CI 0.90 to 1.16, n = 2,362) (**Figure 2-2**). However, in the absence of frailty, a systolic blood pressure lower than 140 mm Hg was associated with lower mortality compared to a systolic blood pressure of more than 140 mm Hg (HR 0.86, 95% CI 0.77 to 0.96, n= 8,012). There was no evidence of statistical heterogeneity across studies for sub-groups with frailty ($I^{2=}$0%), and low heterogeneity in sub-groups without frailty (I^2=42%).

Diastolic Blood Pressure: Synthesis of data from five cohort studies (350-352, 355, 357) demonstrated that a diastolic blood pressure lower than 90 mm Hg was not associated with a difference in mortality compared with a diastolic blood pressure greater than 90 mm Hg for those with frailty (HR 1.01, 95% CI 0.69 to 1.46, n = 2,000) nor in those without frailty (HR 0.90 95% CI 0.76 to 1.07, n = 8,267) (**Figure 2-3**). There was evidence of moderate heterogeneity for the sub-group with frailty (I^2=52%), but not the sub-group without frailty (I^2=7%) so a random effects meta-analysis was performed.

Figure 2-2 Forrest Plot demonstrating association between all-cause mortality and systolic blood pressure <140 mm Hg compared to >140 mm Hg in older people without frailty (i) and older people with frailty (ii).

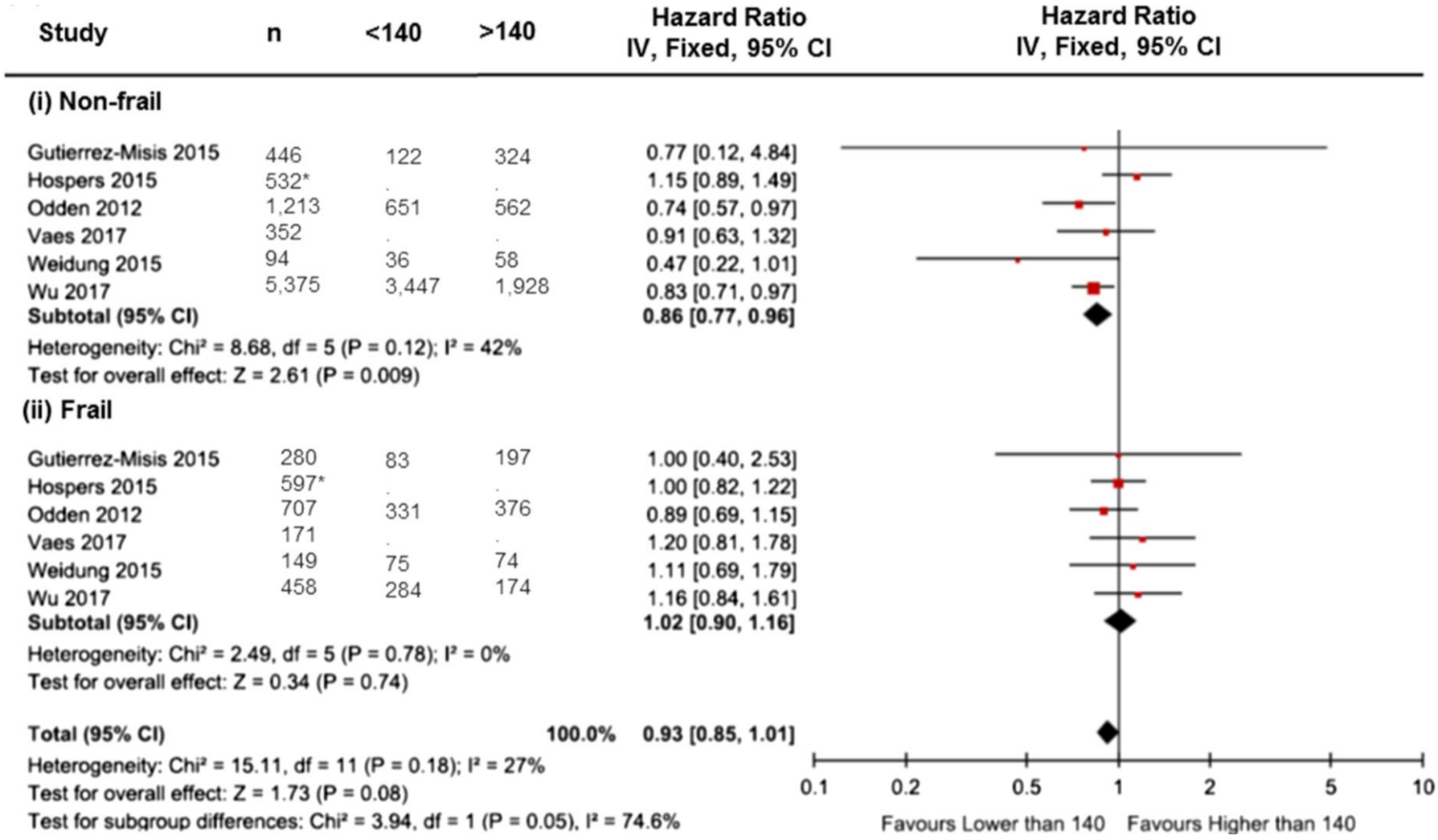
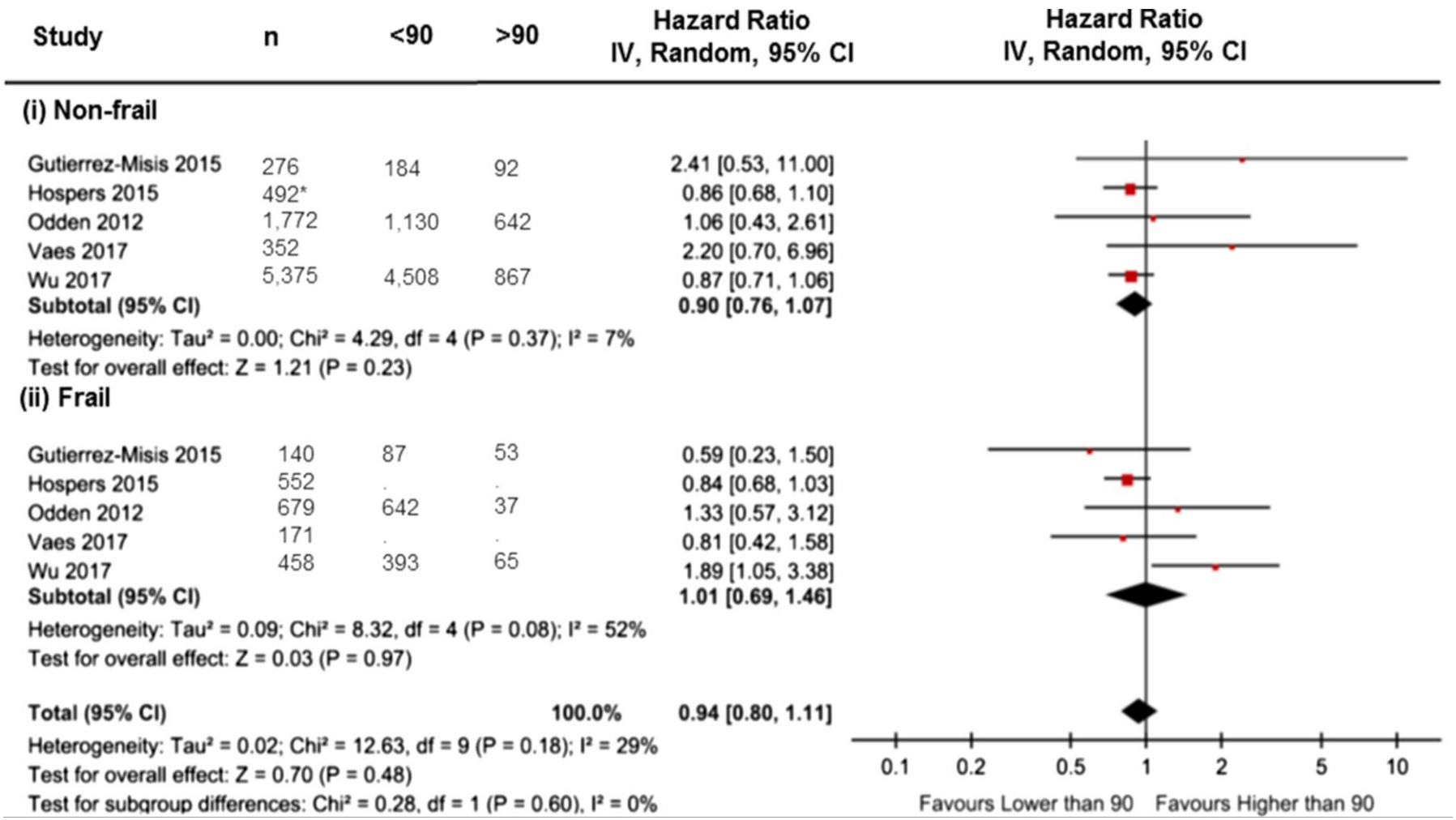


Figure 2-3 Forrest Plot demonstrating the association between all-cause mortality and diastolic BP <90 mm Hg compared to >90 mm Hg in older people without frailty (i) and older people with frailty (ii).



Legend for Figure 2-2 & Figure 2-3: <90 = diastolic BP <90 mm Hg; >90 = diastolic BP >90 mm Hg; <140 = systolic BP <140 mm Hg; >140 = systolic BP >140 mm Hg; CI = Confidence Interval; Fixed = Fixed Effects; IV = Inverse Variance; n = study population size; Random = Random Effects; * = these numbers are estimated using aggregate numbers reported.

2.4.4.2 Continuous blood pressure comparisons

Pooled risk estimates were calculated for a 10 mm Hg difference in systolic blood pressure (from five studies, n = 12,280) (352-355, 357) and diastolic blood pressure (four studies, n = 11,668) (352, 353, 355, 357).

Systolic Blood Pressure: A 10 mm Hg difference in systolic blood pressure had no association with mortality in people with frailty (HR 1.02, 95% CI 0.96 to 1.07, n = 3,138) or those without frailty (HR 1.00, 95% CI 0.97 to 1.04, n = 9,142). There was evidence of heterogeneity in the association of continuous measurements of systolic blood pressure and mortality for both the sub-groups with frailty ($I^{2=}$=68%), and without frailty (I^2=27%) so a random effects meta-analysis was performed.

Diastolic Blood Pressure: Similarly, a 10 mm Hg difference in diastolic blood pressure was not associated with mortality in people with frailty (HR 1.02, 95% CI 0.97 to 1.07, n = 2,748) or without frailty (HR 0.95, 95% CI 0.91 to 1.00, n = 8,920). There was no evidence of heterogeneity in the association of continuous measurements of diastolic blood pressure and mortality for both the sub-groups with frailty ($I^{2=}$0%), and without frailty (I^2=0%) so a fixed effects meta-analysis was performed.

2.4.5 Secondary Outcomes

Only one study reported cardiovascular-specific mortality with respect to blood pressure and frailty (351). In this study, lower diastolic blood pressure was associated with increased cardiovascular disease mortality in patients over the age of 80 years and in those with slower walking speed. By contrast, high diastolic blood pressure was reported to be associated with higher cardiovascular disease mortality in patients under the age of 72 years, and in those without physical and cognitive impairment. Data were not available for the other pre-specified secondary outcomes.

2.4.6 Sensitivity Analyses

A high or uncertain risk of bias was identified in four studies in the measurement of exposure. The exclusion of these studies did not change the pooled estimates significantly in any of the four meta-analyses. The exclusion from the meta-analysis of the largest study (n=5,375) (357) for categorical comparisons of diastolic BP, changed the pooled estimate for those with frailty (HR 0.84 95% CI 0.70 to 1.02) and for those without frailty (HR 1.08 95% CI 0.7 to 1.68). However, there was no significant change in pooled estimates with and without frailty for: comparisons of categorical systolic BP; or, comparisons of continuous systolic or diastolic BP.

2.4.7 Effect modification

Six studies assessed whether frailty had an interaction with the association of blood pressure and mortality. Only one study reported a significant interaction with systolic blood pressure ($p < 0.05$ (318)), but it is unclear if this interaction was in the context of an adjusted model. Five studies reported no significant difference with the addition of an interaction between frailty and blood pressure on outcomes (351, 354-357). Three studies assessed whether BP-lowering treatment (318, 350, 352) or self-reported diagnosis of hypertension (318) modified the effect of frailty on blood pressure and mortality, but they found no evidence of effect modification. One study stratified continuous comparisons of systolic BP by BP-lowering treatment and found that frailty did not modify the effect (354). Five studies reported sensitivity analyses to exclude those dying within 1 year (350, 352, 354, 356) and 2 years (357), to test for evidence of reverse causality, all showing no effect on the summary estimates.

2.5 Discussion

In this meta-analysis of 21,906 participants across nine cohort studies, in older people with frailty, a systolic blood pressure less than 140 mm Hg was not associated with a difference in mortality compared to a systolic blood pressure greater than 140 mm Hg. In contrast, in older people without frailty, a systolic blood pressure < 140 mm Hg was associated with a 14% lower risk of death compared to a systolic blood pressure > 140 mm Hg.

There was no association between diastolic blood pressure and mortality in older people overall (n=10,267), and this did not change when accounting for frailty. When measuring blood pressure as a linear variable, there was no difference in association with higher systolic (n=12,280) or diastolic blood pressure (n=11,668) and mortality after adjustment.

2.5.1 Strengths and weaknesses

The robust, inclusive search strategy identified studies that recruited an average of 58% of eligible participants. The study population was larger and more representative of community-dwelling older people than in recent randomised control trials (267, 359). Neighbouring categories were compared at thresholds defined by current NICE guidelines (320). This synthesis of adjusted data provides greater confidence in the meta-analysis findings.

Whilst I set out to investigate a number of other outcomes in addition to mortality the available studies did not report non-fatal outcomes to enable pooled estimates of risk to be calculated. The proportion of the study population who were care home residents was reported in a minority of included studies, limiting conclusions about this important group with advanced frailty in which there is also a high prevalence of hypertension at over 80% (360).

The study populations also included participants with hypertension and without, and those who were being treated for hypertension as primary cardiovascular disease prevention with those who were being treated for it as secondary prevention. This makes the findings of these studies difficult to apply to clinical care where these contextual factors influence how BP is measured and managed and therefore limits the external validity of these studies.

All studies measured blood pressure at one sitting, but measurement error and short-term variability of blood pressure mean that single readings are unreliable. Whilst there was no evidence of a linear dose effect of blood pressure, exclusion of a nonlinear association was not possible, due to a lack of reported data, which could be relevant considering the reported J-shaped relationship between blood pressure and outcomes in other populations (**Section 1.6.2.2**) (306).

Throughout the meta-analyses, patients were dichotomized as either frail or non-frail to allow us to compare patients across a number of different frailty

measures, however there is much evidence that frailty is graded. Frailty was inconsistently defined across studies with the use of a variety of measures.

It is possible that the association reported in this review may be the result of reverse causality (see **Section 1.6.2.2.2**) (32). Observational studies investigating blood pressure and outcomes in the context of frailty have demonstrated that low blood pressure out with the context of hypertension is likely to be a marker of poor overall health and not reversible (361). Therefore, it would be important to re-examine these associations in populations who all have a diagnosis of hypertension. Although several studies performed sensitivity analyses to test the possibility of reverse causality, the numbers included were small, and therefore the analyses to determine this may have been underpowered.

2.5.2 Findings in context of wider research literature

2.5.2.1 Randomised control trials

Findings of this systematic review contrast with the evidence from randomised control trials. There have been two treatment trials (267, 275) in which the modifying effect of frailty has been considered in retrospective analyses (359, 362). Both of which were included in the discussion in **Section 1.6.1.1.** It was not possible to pool the results because of differences between the trials in: baseline blood pressure; target blood pressure; and, the study populations.

The Hypertension in the Very Elderly Trail (HYVET) randomised individuals over the age of 80 years, to target a systolic blood pressure of less than 150 mm Hg using indapamide +/- perindopril (362). The post-hoc analysis of the HYVET trial was undertaken using a 60-item frailty index (FI) constructed according to established guidelines (334) using available trial data calculated at the time of study entry. This retrospective analysis was not powered or pre-specified. The study population was smaller than the original trial because calculation of the Frailty Index (FI) relied on quality of life questionnaires which not all patients completed.

The HYVET analysis was undertaken on 2,656 patients whose average age was 83 years, who were mostly female (61%), who had a median frailty index of 0.17 (IQR 0.11 – 0.24) which equates to mild frailty (362). Cox regression was performed, stratified by a patient's country of origin, adjusting for age and sex with the addition of frailty as a continuous variable as well as an interaction term between frailty and the treatment arm.

Overall, among these 2,656 patients, the findings of the main trial were maintained, an sBP < 150 mmHg compared to an sBP 150 mm Hg was associated with reduction in stroke (HR 0.65 (95% CI 0.43, 0.98), cardiovascular events (HR 0.59 (95% CI 0.45, 0.77)) and all-cause mortality (HR 0.83 (95% CI 0.66, 1.05)). Adjusted for frailty, these point estimates associated with treatment did not significantly change: for stroke (HR 0.64 (95% CI 0.42, 0.96), cardiovascular events (HR 0.59 (95% CI 0.45, 0.77)) and all-cause mortality (HR 0.83 (95% CI 0.66, 1.04)). When stratified by advancing

frailty, the treatment arm was associated with greater effect on stroke reduction, cardiovascular events and all-cause mortality (**Table 2-4**).There were also more withdrawals in the treatment arm among those with severe frailty.

Table 2-4 HYVET analysis stratified by frailty

Outcome	Frailty index	HR and 95% CI
Stroke	0.1	0.75 (0.40 – 1.38)
	0.2	0.66 (0.43 – 1.01)
	0.3	0.59 (0.36 – 0.96)
	0.4	0.52 (0.25 – 1.09)
	0.5	0.47 (0.16 – 1.33)
	0.6	0.41 (0.10 – 1.65)
CV events	0.1	0.62 (0.42 – 0.92)
	0.2	0.60 (0.45 – 0.78)
	0.3	0.57 (0.42 – 0.79)
	0.4	0.55 (0.42 – 0.79)
	0.5	0.53 (0.26 – 1.06)
	0.6	0.50 (0.20 – 1.27)
ACM	0.1	0.89 (0.63 – 1.25)
	0.2	0.84 (0.66 – 1.07)
	0.3	0.80 (0.61 – 1.04)
	0.4	0.76 (0.50 – 1.14)
	0.5	0.72 (0.40 – 1.29)
	0.6	0.68 (0.32 – 1.48)

The Systolic Blood Pressure Intervention Trial (SPRINT) randomised individuals over the age of 50 years, with increased cardiovascular risk but no history of diabetes mellitus to a systolic blood pressure target of less than 120 mm Hg (359).

A retrospective analysis of the SPRINT trial sub-population over 75 years old, developed a post-hoc 37- item FI, using as its basis an FI from the African American Health Study (AAHS), to which was added a further 20 items used in HYVET (363). Frailty was categorised as fit (FI < 0.1); pre-frail (FI 0.1 < 0.21) and frail (FI > 0.21). Additionally the trial had included gait speed (also a proxy measure of frailty), which took the maximum speed of two tests which were completed with the person's usual walking aid. A threshold of 0.8 m/s was used to distinguish those with slow versus normal walking speed. Cox proportional hazards analysis was undertaken with competing risks according to Fine and Gray sub-distribution hazards for Major Adverse Cardiovascular Events (MACE) outcomes with non-cardiovascular mortality as the competing risk.

The analysis was undertaken on the 2,636 patients over 75 years in the SPRINT trial, of whom 2,510 (952%) completed follow up (359). The average age was 79.9 years, 37.9% of whom were female. Participants had a median FI of 0.17, as in HYVET, equating to mild frailty. More than 30% of the patients over the age of 75 years were described as frail. The study population was classified: 13.9 % as fit; 55.2% as less fit; and, 30.9% as frail. 28.1% had slow walking speed (i.e. > 0.8m/s). The difference in the sBP achieved in the intensive versus the standard treatment arms reduced with advancing frailty. In those who were fit: sBP 121.4 (120.3, 122.5) intensive arm, 134.9 (133.9, 135.9) standard arm; less fit, sBP 123.3 (122.8 – 123.9) intensive arm, 134.7 (134.1, 135.2) standard arm; frail,124.3 (123.5, 125) in intensive arm, 135.0 (134.2 – 135.8) standard arm.

Analysis of the outcomes demonstrate findings of the main trial were maintained in the retrospective study population, with an achieved sBP of 121.5 mm Hg associated with a reduction in major adverse cardiovascular events and all-cause mortality compared to standard BP at 134.6 mm Hg, but with higher reported adverse effects in the intervention group. The sub-group analysis by frailty demonstrates more mixed results, with advancing frailty associated with less protective effects of BP lowering for major adverse cardiovascular events but not for all-cause mortality. However, numbers were small (**Table 2-5**).

			Intervention	Control
Outcomes	MACE	n (rate)	102 (2.59%)	148 (3.85%)
		HR	0.66 [95% CI, 0.51–0.85]	
	Deaths	N	73	103
		HR	0.67 [95% CI, 0.49–0.91]	
SAE	SAE	n (%)	637 (48.4%)	637 (48.3%)
		HR		
	↓BP	%	2.4%	1.4%
		HR	1.71 [95% CI, 0.97–3.09]	
	Syncope		3.0%	2.4%
		HR	1.23 [95% CI, 0.76–2.00]	
	e-		4.0%	2.7%
		HR	1.51 [95% CI, 0.99–2.33]	
	AKI		5.5%	4.0%
		HR	1.41 [95% CI, 0.98–2.04]	
	Falls		4.9%	5.5%
		HR	0.91 [95% CI, 0.65–1.29]	
	OH		21.0%	21.8 %
		HR	0.90 [95% CI, 0.76–1.07]	
	OH + dizziness		1.9%	1.3%
		HR	1.44 [95% CI, 0.77–2.73]	
Frailty	MACE	Fit	0.47 (0.13 – 1.39)	$p_{interact}$ = 0.52
		Less Fit	0.63 (0.43 – 0.91)	
		Frail	0.68 (0.45 – 1.01)	
		Norm GS	0.67 (0.47 – 0.94)	$p_{interact}$ = 0.85
		Slow GS	0.63 (0.40 – 0.99)	
	ACM	Fit	0.95 (0.27 – 3.15)	$p_{interact}$ = 0.88
		Less Fit	0.48 (0.29 – 0.78)	
		Frail	0.64 (0.41 – 1.01)	
		Norm GS	0.65 (0.43 – 0.98)	$p_{interact}$ = 0.68
		Slow GS	0.75 (0.44 – 1.26)	
	SAE		Higher in frailty, not presented	

Table 2-5 SPRINT analysis by frailty

ACM = All-cause mortality; AKI= Acute Kidney Injury e^-=electrolyte disturbances; GS = Gait speed; MACE = Major Adverse Cardiovascular Events; OH = Orthostatic Hypotension; p = p-value, significance test; $p_{interaction}$ = p-value of interaction term; SAE = Significant Adverse Events;

Limitations of both retrospective secondary analyses of HYVET and SPRINT include that neither was pre-specified nor statistically powered for the analyses by frailty status.

The frailty indices calculated retrospectively also deserve further scrutiny and may not generalise to frailty indices used in routine care. A recent study (which I co-authored) applied the SPRINT and HYVET eligibility criteria to a UK primary care population. The electronic frailty index (eFI) calculated of the corresponding UK population, was 0.09 which corresponds to fit (364). The frailty index developed both in SPRINT and HYVET did not include any non-cardiovascular morbidities.

Furthermore, of the 37 components of the SPRINT FI: 14/37 are cardiovascular risk factors although the population was recruited to all have moderate cardiovascular risk; 9/37 directly represent factors that are included in the exclusion criteria for trial recruitment; 11/37 are function measures but the choice may represent health behaviours more than functional abilities. For these reasons it is possible the frailty as measured in SPRINT may represent those with greater cardiovascular burden which may have a mediating role in the association between sBP and cardiovascular outcomes.

In summary, consistent with the findings from this meta-analysis, these two trials have reported persistent benefit from low blood pressure extending into old age for those without frailty. Both analyses also reported that there was no evidence that frailty modified the effects of BP-lowering treatment on mortality

(267, 359). In contrast with the findings of this meta-analysis, the HYVET trial analyses demonstrate that BP-lowering interventions maybe associated with greater reduction in cardiovascular outcomes. Importantly, neither of these two trial analyses were statistically powered and both used frailty indices which over-represented cardiovascular risk among their constituent items.

2.5.2.2 Routine data studies

Pooled findings from traditional cohort studies also contrast with those reported in large primary care studies (365, 366). The use of routine data from primary care mean that the study populations were highly representative of the overall population. However, the non-standardized measurement of BP in primary care meant that the routine data studies did not meet the criteria for inclusion in the meta-analysis. I will now examine both studies investigating whether associations of blood pressure and outcomes are different in the context of frailty.

Ravindrarajah et al studied 144,403 participants, recorded in the primary care electronic health records of the Clinical Practice Research Database (CPRD) during the period 2001-2014 (365). An eFI was used to measure frailty (341). All patients were over the age of 80 and study entry point was at their 80^{th}, 85^{th}, 90^{th} or 95^{th} birthday with random sampling to ensure weighting across age groups. Blood pressure was represented by monthly averages taken over the period of follow up to create trajectories. Frailty and BP-lowering treatment measurement was calculated during the first year of follow up. Covariates

included categorised forms of: smoking, body mass index, total cholesterol and comorbidity clusters. Cox PH models were undertaken and all-cause mortality was the outcome of interest over 5 year follow up. Subgroup analyses were undertaken on sex, frailty and BP-lowering medications. Missing data were replaced with dummy / indicator variables.

The study reported 51,808 deaths during 5 years follow up (35.9%) (365). Compared to a reference systolic blood pressure of 120 – 139 mm Hg, lower blood pressures were associated with higher mortality, and higher blood pressures with lower mortality. In the context of severe frailty, the association of low systolic blood pressure with higher mortality risk remained. In addition, with severe frailty, systolic BP categories above the reference range of 120-139 mm Hg were also associated with higher mortality.

There are several limitations of note which may have influenced the findings. The study extended over a long period of time during which hypertension treatment has changed, and no adjustment was made for study year in the analysis. Missing data were not imputed and the consequent direction of bias in routine data is difficult to predict. Non-fatal outcomes were not measured. The inclusion of BP readings and treatment variables during follow up is a recognised method of repeating measures to reduce the impact of regression dilution (367, 368). However, as a result, the findings of the study are difficult to interpret in clinical practice, because none of: the study start time; the measure of BP; nor, the method of cardiovascular risk assessment resemble the clinical encounter. Whilst the population was stratified by the presence or absence of

BP-lowering treatment, it was not clear if the indication of the BP-lowering treatment was for hypertension or another cause for which the therapy is also indicated.

Masoli et al also used CPRD data but with a different design (366). In this study, 415, 980 were included, all over the age of 75 years, with at least 3 BP measures in the 3 years prior to their 75th birthday, over a study period of 2000 to 2014. The source period for the eFI is not reported. Covariates include sex, age, deprivation as measured by Index of Multiple Deprivation (IMD), and only in a sensitivity analysis, a measure of cardiovascular risk and BP trajectory. BP-lowering treatment was not measured. Outcomes included incident cardiovascular disease and all–cause mortality. Follow-up was for 10 years. Survival analysis used Cox PH and Fine and Gray competing risks analysis. Subgroup analyses were undertaken according to groupings by age, hypertension, diabetes mellitus and heart failure, exclusion of events within 6 months, cancer. How missing data was handled was not reported.

For all-cause mortality, compared to a reference range of 130-139 mm Hg, lower systolic blood pressure was associated with higher risk. The pattern of association was not significantly different according to frailty status. The associations of sBP and cardiovascular outcomes are more diverse: for the risk of myocardial infarction, increasing frailty is associated with a more exaggerated increase in risk associated with increasing systolic BP. For stroke and heart failure, increasing sBP is associated with a J-shaped incremental risk of

outcome, except in the context of frailty where there is no association of sBP and outcome in the context of moderate or severe frailty.

Limitations of the Masoli study include: the lack of adjustment for BP-lowering treatment; that the method of handling of missing data is not reported; and, that moderate and severe frailty groups are combined in the analysis without it being pre-specified in the methods.

Furthermore, like the cohort studies analysed before it, both CPRD study populations are not recognisable as populations with hypertension for whom treatment is either targeting primary or secondary cardiovascular prevention.

In summary, the findings of these two routine data studies build on the findings of the meta-analysis. Consistent with the meta-analysis, the Masoli study demonstrated a loss of the association of higher blood pressure with risk of cardiovascular outcomes with advancing frailty, but moderate and severe frailty groups were amalgamated causing concern of bias in the interpretation of findings (366). The Ravindrarajah study demonstrated that the pattern of association between systolic blood pressure and all-cause mortality is inverted and does not significantly change conditional on frailty status (365, 366). There remain concerns about generalisability of these studies. Whilst routine data studies are more representative of the overall population, these two studies are difficult to translate to clinical practice because their designs do not mimic clinical practice. Study populations were not limited to people with hypertension and so included BPs are from a range of contexts. Furthermore the choice of

adjustments and handling of missing data mean that the interpretation of these studies must be cautioned by the strong possibility their findings are influenced by methodological bias

2.5.3 Interpretation

It is possible that residual confounding may explain the findings of observational cohort and routine data studies. The frailty index represents a composite measure of risk, and contains within it factors that cluster. Some deficits represent mediators of the effect of BP on mortality, and others are potential confounders. For example, hypertension and cardiovascular disease could have developed before or after the onset of frailty. In these cases if frailty was evaluated using a frailty index, it would be useful to include sensitivity analyses with and without the items that are related to cardiovascular disease.

The measurement of cardiovascular risk factors in routine data sets is potentially problematic given that high baseline values may lead to more intensive treatment and monitoring to reverse the baseline risk. To address this, summary measures of BP were used across the study period, but in so doing the BP measure is representative of BP trajectory, rather than a baseline measurement. Findings are therefore difficult to translate to clinical practice.

2.6 Conclusions

This systematic review of observational studies has identified an association between low systolic blood pressure and lower all-cause mortality in older adults without frailty, but not in those with frailty. These findings indicate that in the absence of frailty blood pressure targets should be considered independently of age. In the presence of frailty there is ongoing uncertainty. The use of routine data can enable the investigation of the association of systolic blood pressure and frailty on their continuous scales, with a range of outcomes measured in routine care. However, the findings of routine data studies to date are inconsistent with one another and with the findings of this meta-analysis. These differences may relate to choice of methodological approach, and this deserves further enquiry. The available evidence reported in this systematic review and meta-analysis indicates a personalised approach based on individual circumstances maybe appropriate.

Chapter 3 Methods

3.1 Summary

Chapter 2 summarised the current evidence base investigating the role of frailty in the association between blood pressure and outcomes in older people. Chapter 3 will now detail the methodology adopted in this thesis, which is informed by the literature to date. This chapter outlines the design of a secondary analysis of electronic health records (EHR) from linked primary care data in Wales, UK. A pre-analytic protocol describing the planned methods for this PhD study was published online (https://clinicaltrials.gov/ct2/show/NCT04662203). The methods have been selected to address three key objectives.

3.2 Objectives 2,3 & 4

Objective 2: To describe the normal blood pressure-outcome associations in this population

Objective 3: To investigate in large scale routine primary care data whether frailty is a prognostic factor for relevant outcomes in the management of hypertension in older people;

Objective 4: To investigate in large scale routine primary care data, whether frailty causes effect modification of the association between

blood pressure, or blood pressure lowering treatment and outcomes in older people.

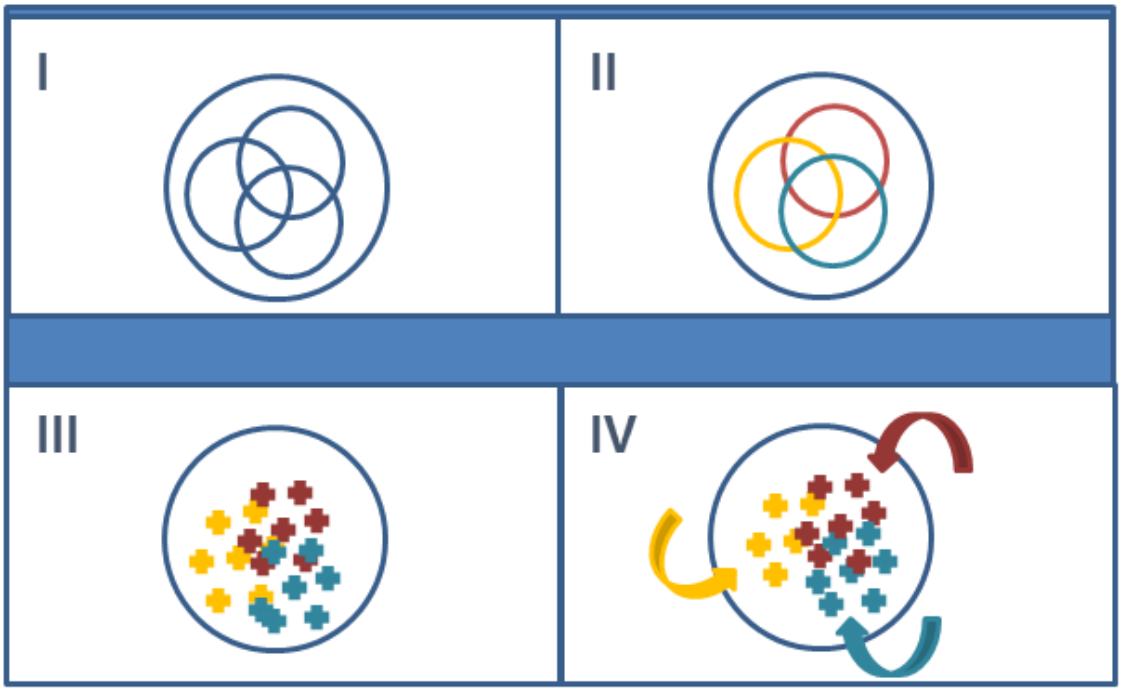
3.3 Research methods

The two research questions being asked in Objectives 3 and 4 require different methodologies. Objective 3 relates to an investigation of prognosis, while Objective 4 relates to an epidemiological investigation.

3.3.1 Prognosis research methods

Prognosis research aims to predict future outcomes in people with a given disease or health condition from the available data. Prognostic information can help anticipate outcomes: to prepare a patient for the occurrence of an outcome, or to indicate interventions to mitigate the risk of future outcomes. (369). The PROGnosis RESearch Strategy (PROGRESS) Partnership has outlined a framework for prognosis research, with four key themes, as depicted in (**Figure 3-1**) (370). The second of these themes is prognostic factor research which investigates which individual measure (a prognostic factor) at a given point, is associated with the outcome of interest, despite adjustment for the current best prognostic model.

Figure 3-1 Four prognosis research themes



I : Fundamental prognosis research describes the average clinical outcomes of patients with a certain disease, possibly distinguishing sub-groups; II: Prognostic factor research investigates the utility of individual measurements in predicting outcomes in order to identify different at-risk groups; III Prognostic model research combines prognostic factors to identify an individual's risk, using a method that can be replicated in different populations; IV Stratified medicine research identifies sub-groups for whom different interventions may be indicated to attempt to reverse their risk of an outcome occurring.(371-374)

This PhD applies prognostic factor research (PROGRESS II) methods to address Objective 3, to determine whether the measurement of frailty improves the prognostic utility of existing models such as QRISK-3 (373).

Prognostic effect size will be estimated with increasing frailty adjusted for all other standard prognostic variables. In addition, model fit, fully adjusted for established covariates, will be assessed with and without the addition frailty as the prognostic factor, to determine whether the addition of the prognostic factor improves model fit.

3.3.2 Epidemiological research methods

Objective 4 is a distinctly different research question, calling for epidemiological or causal inference methodology. Causal inference methods aim to determine the likely change in an outcome due to a change in risk factor (375). Causal inference methods are key to identifying what is reversible and should be the target of prevention and/ or treatment. These methods are appropriate when the research question asks whether the level of BP has a different association with outcomes, in the context of frailty. The validity of any estimate of causal effect of exposure on the outcome is only as good as the causal assumptions underlying it.

Effect modification by frailty of the association between BP and outcomes will be measured using the addition of an interaction term in a model already adjusted for known risk factors. Evidence of effect modification includes a change in the association of BP and outcome when frailty is added to the model, or evidence of improved fit when the interaction term is included in the model.(376)

3.4 Target study population

The study population targeted patients in whom hypertension was treated for primary prevention. These patients had a diagnosis of hypertension but had no previous diagnosis of established cardiovascular disease. The choice to restrict the study population to patients with hypertension only, was made to ensure a

degree of uniformity in the patient encounter and clinical practice, to which particular guidelines are applicable. Furthermore, it was hoped that investigating a more targeted population would lead to findings that have greater applicability to a specific but common clinical scenario.

The choice of a primary over secondary prevention was made for three reasons:

- Firstly, a focus on primary prevention replicates the design of the Framingham heart study with which BP-outcome associations in this cohort can be compared. The Framingham Heart study is a landmark epidemiological prospective cohort study based in Framingham, Massachusetts, USA, started in 1948, currently in its fourth generation of participants (28).
- Secondly, by excluding those with pre-existing vascular disease, the effects of vascular disease on blood pressure (reverse causality, see **Section 1.6.2.2.2**) are minimised (367).
- Thirdly, the absolute risk reduction from BP-lowering treatment for primary prevention is smaller than that for secondary prevention (377). Therefore, the potential role of frailty in informing hypertension management was considered greater in those where treatment is informed by cardiovascular risk (primary prevention) than in those in whom it is informed by established cardiovascular disease (secondary prevention).

The study focuses on the period between 2007-2008. This decision to focus on a narrow time period was made because of the potential influence of changing policies and guidelines altering hypertension practice, and the effects of these changes being difficult to predict and uneven over time. The time period 2007 – 2008 was chosen because:

- It enables ten year follow up of outcomes.
- It represents a period of time during which no new major guidance or policy was introduced. At that time the NICE/ British Hypertension Society (BHS) guidelines on Hypertension (Clinical Guideline 19, 2004 and Clinical Guideline 34, 2006) recommended treatment at a BP of >140/90 mm Hg in the context of a 10 year cardiovascular risk of > 20% (378, 379).
- It followed the introduction of the Quality Outcomes Framework (QOF) which was introduced in 2003/2004 (380) and motivated stricter adherence to BP targets in primary care.
- It preceded the introduction of the NHS Health Check in 2009, which involved more widespread BP review as part of general health screening (381).

3.5 Routine data in primary care

3.5.1 Primary care setting

This study uses routine data from primary care in the UK where most treatment of hypertension is undertaken.

3.5.2 Routine data

In the UK, most people presenting with a new symptom or health condition and most chronic diseases are managed by a general practitioner (GP) who are the ‘gate-keepers’ to the National Health Service (382). Therefore, the primary care electronic record contains comprehensive demographic information, as well as a patient’s presenting complaints, investigations undertaken, diagnoses made, prescriptions issued and any referrals. There are over 300 million consultations annually in primary care in the UK (383) and 96% of practices have been using electronic health records (EHR) since 1996 (384).

GPs in the UK use a variety of computer systems. (385). Of 7,526 GP practices in England in 2016: 56% used Egton Medical Information Systems (EMIS); 34% SystmOne; and, 9% Vision (385).

The use of routine data collected in healthcare for research purposes, although recently growing, has been ongoing in the UK for more than three decades (386). Consent for the release of a patient’s data to be used for research purposes that has been collected during the course of normal care, follows an opt-out approach, enabling the individual to withdraw their data from databanks used for research or planning purposes if they so wish (387). The European Union General Data Protection Regulation (GDPR) requires consent be unambiguous, and, clearly affirmative. Clear information must be provided on how to withdraw consent for data sharing at any time (388). A particular

challenge of the opt-out model in relation to older people is that there remains debate over whether people who do not have capacity have a realistic option of withdrawing their data.

There are a range of primary care data sets available in the UK. In England, they include: CPRD (389), QRESEARCH (390), ResearchOne (391), and The Health Improvement Network (THIN) (392). These research databases extract anonymised data from consenting records from the major clinical computer systems. There is crossover, so that one person whose GP uses EMIS maybe represented both in both THIN and CPRD for example. In England, with the exception of CPRD, research data sets are managed as public-private partnerships between a University and private company. In Wales and Scotland by contrast, research data is managed by the devolved governments. These are the Secure Anonymised Information Linkage (SAIL) databank (393) in Wales, and the Scottish Primary Care Information Resource (SPIRE), in Scotland (394). Using a unique patient identifier, primary care data are linked in some of the data sets to records from an individual's hospital attendances, social care interactions, census and death records.

The main characteristics of these data sets are presented for comparison in **Table 3-1**, with the exception of the Scottish Primary Care Information Resource (SPIRE) which is due to be ready for data access in 2020 (394).

Table 3-1 Major primary care research databanks in the UK

Key information	Coverage	Linkage	Access
CPRD England (Vision and EMIS**)**			
CPRD Gold Est: 1987 Profiled (395) CPRD Aurum Est. 2018 Profiled(396) Funding: Government	Gold (Vision) 674 GP, 11.3 m total, 4.4 m active (2015) (395) Aurum (EMIS) 738 GP,19.3m total, 7.1m active (2018) (396)	-HES -ONS -Mental health - Deprivation -MINAP (via CALIBER)	High cost (397)
QRESEARCH England (EMIS)			
Est: 1993 Profiled (398) Funding: PPP, University of Oxford/ EMIS	#: 1,200 GP; 30m total; 22m (2017) (398)	-Public Health England National Cancer Registry -ONS	Low cost [Data for external requests limited to n=100,000(397)]
ResearchOne England (SystmOne)			
Est: 2012 Profiled (399) Funding: PPP, University of Leeds & The Phoenix Partnership	#: unclear; approx. 8m active	-Care home residence	Low cost
THIN England (Vision)			
Est. 2003 Profiled (392) Funding: Vision-Quintiles MS© (Private) & University College London	# 744 GP; 15m total, 3.7m active (400, 401)	-Pharmacy coding (Multilex)	Cost: High cost (397)
SAIL Wales			
Est: 2006 Profiled (402) Funding: Government	# 5m, 3m active	-ONS; -HES -Demographic data; -Care home residence	Low cost

Table: CALIBER = Cardiovascular disease research using linked bespoke studies and electronic; Est. = Established; GP = General Practitioner; HES = Hospital Episode Statistics; m = million; MINAP = Myocardial Ischaemia National Audit Project; ONS = Office for National Statistics; PPP = Public Private Partnership; SAIL = Secure Anonymised Information Linkage· THIN = The Health Improvement Network

3.5.3 Comparison with cohort data

The studies synthesized in the meta-analysis in **Chapter 2** were traditional cohort studies, and did not include routine data studies. There are differences between traditional cohort and routine data studies worthy of discussion, as follows.

3.5.3.1 External validity

External validity is a measure of how generalisable study findings can be in their application to settings other than the specific circumstances applicable to that study. Participating in traditional cohort studies may be burdensome for an individual (403, 404). Participation rates were 58% on average among the studies included in the meta-analysis presented in this thesis which is relatively high for traditional cohort studies (**Section 2.5.1**). Older people may choose not to take part in such a study because: they feel too unwell; they are already overcommitted with hospital appointments; or, for literacy reasons. These personal factors may themselves correlate with risk factors for outcomes, hence participant selection bias can affect the results.

Routine data, by contrast, includes all patients presenting in a specified healthcare setting. Therefore use of routine data can overcome selection bias in this respect (405). Furthermore, use of routine data enables far larger study populations than would ever be affordable or practical in a traditional cohort design. This increases the power of analysis to discriminate associations in the

context of complexity and multiple confounding factors. This is important in ageing research where ageing increases the number of competing risks so the point risk estimates attributable to individual risk factors may be small and therefore missed in smaller sample sizes.

3.5.3.2 Internal Validity

Internal validity is a test of how confident we can be that the statistical model developed in a study represents the underlying truth. Traditional cohort studies and routine data studies each have their own advantages and disadvantages in terms of internal validity.

In traditional cohort studies, loss to follow-up can be significant, and data acquisition may rely on patient recall. The missing data resulting from non-response and loss to follow up may reduce internal validity. However, if the study is prospective in design, the choice of covariates can be determined to best account for confounding.

In routine data studies, the capacity for follow-up is higher because they do not require active participation on behalf of the patients. This means withdrawal is not so significant a problem as in the case of traditional cohort studies. The intensity and duration of follow-up provided by routine data would be prohibitively expensive in a traditional cohort study or in a trial based on participant-level data collection. However, in routine data, the choice of covariates to measure as confounders is restricted to what is currently

measured in routine care. Therefore there is significant scope for un-measured confounding to influence findings.

3.5.3.3 Sampling restrictions

Both traditional cohort and routine data studies will have sampling restrictions. In routine data studies, sampling may be informed by a start point which is more in keeping with the natural course of a person's illness – e.g. at the time of a patient's presentation with early signs and symptom ahead of a formal diagnosis. This lends routine data huge potential for prognostic research.

However as a result of sampling being determined by health service use, an individual's inclusion in routine data is not random: the individual is included in routine data because they are unwell and seek help from medical services. Therefore the population represented in routine health records is different from the general population. As such the findings of a routine data study must be interpreted in the context of informed presence bias. Informed presence bias describes the tendency for those assessed frequently in healthcare services, for example because of poor health, to have a greater recording of additional diagnoses (406).

Furthermore, routine data sets are positive recording data sets, that is diagnoses are recorded, but the absence of diagnoses are not. This distinguishes routine data from traditional cohort studies, where the absence of a diagnosis may be explicitly collected via a questionnaire for example.

3.5.3.4 Follow up

Follow-up in traditional cohort studies will occur at pre-specified time points, while events occurring in between these time points will not be captured at the actual time they occur. In routine data, follow-up data can be collected continuously as and when patients use healthcare services.

3.6 Study Data set

3.6.1 Choice of SAIL

The primary data source used in this PhD study to achieve Objectives 2, 3 and 4 is the Secure Anonymised Information Linkage (SAIL) Databank. The choice of SAIL as the data source for the analysis in this PhD was determined by factors: relating to the data set itself; the training opportunities afforded by collaboration with the SAIL team; and, data access.

Firstly, regarding the SAIL data set: the primary care data set in SAIL is linked to multiple secondary data sets which make outcome measurement more robust and reduces the risk of misclassification bias. Misclassification bias represents the risk a variable is incorrectly categorised, thereby altering the observation and potentially affecting overall research findings.

The electronic frailty index (eFI) is a measure of frailty (see **Section 1.7.2.1**), that is available and has been validated in SAIL (407). SAIL data include an

accurate method of identifying care home residence in SAIL (408). Care home residents are an important sub-population of older people with advanced frailty for whom there has been no clear evidence base from observational research to date (see **Section 2.5.1**).

Secondly, collaboration with data analysts and researchers at the SAIL Databank has been an important part of the training involved in this PhD fellowship. As part of the PhD fellowship, I spent a week with the SAIL team at the University of Swansea (hosted by Mr Ashley Akbari, Dr Joe Hollinghurst, and Professor Ronan Lyons), to learn how to link the data, and the basics of cleaning the data set using Microsoft SQL software.

Thirdly, remote data access was possible using encrypted software and a platform which was accessible on any laptop device.

3.6.2 Profile of SAIL

SAIL is the national data safe haven for de-identified data-sets concerning the 3.15 million people living in Wales (336). There is information posted at GP surgeries alerting patients to their ability to opt out so that their data is not included in SAIL. However, only 0.025% of the population had made this request by 2019 (409). Therefore, allowing for this small proportion and a minority who have had no contact with health services, the data set represents the country's whole population. SAIL is a longitudinal data set, containing linked

health and care data for more than 4 million people who have lived and received services in Wales since the database demographic records were created in 1990 (409).

SAIL uses the Universal International Business Machines (IBM) Database 2 (DB2) data warehouse because of its massively parallel processing architecture (MPP) which enables high computer processing power. Researchers access the data through a remote system using a VMware Horizon Gateway via a personal computer. This interface uses a Windows environment, alongside data analysis software, and on the interface there is access to the NHS Clinical Terminology Browser containing code dictionaries for codes commonly used in the primary care database (410).

Patient records in SAIL are linked across multiple data sets using an anonymized linkage field (ALF) code. Data sets provided to the Health Information Research Unit (HIRU), which hosts SAIL at Swansea University, are split into ‘File 1’ - data which is commonly identifiable (name, date of birth etc.) and ‘File 2’ which includes descriptive data (clinical and event based data) (402). ‘File 2’ data is stored in SAIL. ‘File 1’ data enters a repository managed by the NHS Wales Informatics Service (NWIS) acting as a trusted third party (TTP) (411).

An ALF is matched to a ‘File 1’ data set with minimal additional demographics to become the ‘File 3’ data set. ‘File 3’ is sent to SAIL for combination with ‘File 2’, creating a pseudonymised version of the original data set. On entry to SAIL, the

ALF patient code is encrypted and the data undergoes quality checks (410). A parallel process is undertaken for a person's address-related-information (e.g. care home residence status, deprivation code etc) using the regional anonymised linkage field per person (RALF_PE).

This 'split file approach' enables linkage of a person's various records including primary care data, secondary care data, demographic data-sets and mortality data whilst preventing identification of the individual (410).

3.6.3 SAIL data sets

The core data sets constituting SAIL are profiled in **Table 3-2**.

Table 3-2 Summary of SAIL core data sets

Sail data set	Information contained
General Practice Welsh Longitudinal General Practice (WLGP) data set Codes: CTV2/ Read	Symptoms, signs, clinical measurements (including blood pressure), previous history of disease, prescribed treatment and specialist referrals as well as social measures of a person's home environment. Coverage ~ 80% of the population in Wales (412). Each person can therefore have multiple records per visit, and multiple visits over a lifetime.
Accident and Emergency Emergency Department data set (EDDS) Codes: local	Demographic and attendance details, reasons for attendance and discharge location data from NHS Wales emergency department (ED) attendances in Wales. Available since 2009. Includes approximately 750,000 ED attendances per year.
Hospital Patient Episode Data Wales (PEDW) Codes: ICD10	Data recording demographics, admission details including length of stay, diagnoses and operations performed in secondary care (emergency, elective, maternity and day case services). Data collected by Central Patient Administrative System (PAS) available since 1997. Includes approximately 950,000 hospital admissions per year.
Demographics Welsh Demographic Service data set (WDSD)	Includes administrative data including LSOA data, demographics, dates of resident and registration in Wales including practice history, change of location, and RALF. These data are drawn from GP practices, acting as a proxy for the Welsh population register. Available since 1990. Coverage of approximately 5 million.
Birth data Annual District Birth Extract (ADBE)	This data set consists of all births recorded in Wales on the ONS register. Available since 2003. Recording of approximately 35,000 births per year.
Mortality data ONS Annual District Death Extract (ADDE)	This data set consists of death certification data from England and Wales, and therefore includes individuals who died in Wales as well as individuals from Wales who died in England. Data contain information regarding the approximate 32,000 deaths per year: date and primary cause and underlying causes of death as well as LSOA2011 location at time of death. ONS data used the ICD9 system until 2001 and the ICD10 thereafter.
Care home lists	Data using care home registry by Care Inspectorate Wales with missing details completed manually (413). Care homes were are assigned a RALF code (414) which can be linked to an individual's address data in WDDS, to determine who lives in a care home and the date they moved there.

Content retrieved from the SAIL website on 16th July 2020(415). CTV-2 = Read Version 2 codes. GP = General Practitioner; ICD-10 = International Classification of Disease manual, 10th edition. LSOA = Lower super-output area ; ONS = Office of National Statistics; RALF = Residential Anonymous Linking Field

3.6.4 Linkage process

NWIS matches data to the Welsh Demographic Service (WDS). The WDS is an NHS administrative database and acts as a proxy for a Welsh population database (393, 402) to allocate each patient record an ALF. Matching uses the Matching Algorithm for Consistent Results in Anonymised Linkage (MACRAL) algorithm (393). This applies an automated 'black box' method matching on the basis of a person's NHS number (where available), first name, surname, sex, date of birth and post code. The MACRAL algorithm has been tested and refined to reach a high degree of accuracy (99.85%) (393, 416). The process undertaken by NWIS results in five pre-specified levels of matching (393) (**Table 3-3**):

Table 3-3 Levels of matching in SAIL

Level	Matching required
'1'	Match to NHS number
'4'	Match on all of forename, surname, date of birth, sex, and postcode/address
'39'	≥ 90% Match
'35'	<90% but ≥ 50% Match
'99'	No Match

Level '1' represents deterministic matching, possible in the presence of an unique NHS number. In the absence of an NHS number, probabilistic matching is undertaken. This study will only include linked records where linkage has a probability above 90% of being correct, that is, only patient data with matching

levels of ‘1’, ‘4’ and ‘39’ will be included. The matching in the data set provided for this PhD is detailed in **Table 3-4**.

Table 3-4 Quality of linkage

Matching	Number	Total	Percentage
1 - NHS Number	4, 124, 808	4, 785, 194	86.2%
4 - Exact Match on all 5	273, 340	4, 785, 194	5.7%
39 - Probabilistic 90% Match	387, 046	4, 785, 194	8.1%

This linkage quality assessment represents data in the study extract ‘SAIL W0826V’, tested in Microsoft SQL between WLGP and WDS data sets

3.6.5 Coding

Clinical coding is the practice which translates medical terminology describing a patient’s presenting complaint, past medical history, diagnosis and management, into terms which can be organised and aggregated to enable statistical analysis (417). Taking into account the process of coding for each of the main coding systems is important to ascertain the presence and degree of potential misclassification bias (defined in **Section 3.6.1**).

3.6.5.1 Read Codes

The Welsh Longitudinal General Practice (WLGP) data set contains primary care data focused at the level of a ‘consultation’ which may represent an encounter face-to-face, over the telephone, or to another episode of involvement in a patient’s care (such as reading a hospital discharge letter). A consultation may therefore contain multiple records. Each record is date-

stamped and will be linked to: a patient's demographic details; practice demographic details; and staff description data. The clinical information coded includes: symptoms; signs; diagnostic tests; immunisations; diagnoses; referrals; treatments; and, operations. Numerical data (e.g. BP measurement) is linked to a parent code, where the parent code specifies a specific measurement variable ('BP measurement', 'Hypertension review' etc.).

Data entry may be completed as part of a variety of roles including: the general practitioner; the practice or community nurse; other healthcare professionals; the practice manager; or, practice administrators. During the consultation, some code entry uses automated text recognition, or provides the clinician with a number of options on the screen on entering first letters. GPs may also enter informative details about the patient as free text, but this information is not available to research as it may be identifiable (395). Prescription data is automatically entered using British National Formulary (BNF) codes, along with drug quantities and doses prescribed. Results from laboratory investigations similarly tend to be automatically linked, updating the WLGP records from other databases. Data fed back to GPs from other sources (e.g. discharge letters or outpatient letters) will most likely be entered by practice staff (395).

Coding systems used in WLGP records use Read Version 2 codes (CTV-2), and contain more than 96,000 codes (418). A key challenge of this coding scheme is that multiple codes relate to a single condition, so that an event such as a fall may be represented by over 100 different codes. This arises from the characteristics of the Read coding system which is a rigid hierarchy specifying

classes of disease within its own taxonomy that are limited to a fixed number of levels (each code may have a maximum of 5 offspring and 60 sibling data codes). Furthermore, the Read coding system has evolved over time: it was originally developed as 4 byte codes, later revised to 5 bytes (419). The next revision: Clinical Terms Version 3 (CTV-3) system is more flexible. UK primary care is currently transitioning to Systemised Nomenclature of Medicine-Clinical Terms (SNOMED-CT) codes. Read Version 2, CTV 3 and SNOMED codes will therefore not always map directly onto one another. Careful compilation of code lists is therefore required.

3.6.5.2 ICD codes

The Patient Episode Data Wales (PEDW) data set consists of hospital data, and represents the data warehouse for all inpatient activity in Wales. Originally PEDW, like Hospital Episode Statistics (HES) in England, was set up in 1989 for the organisation and planning of hospital services, but it is now used primarily for reimbursing hospitals for the care delivered (420). Data entry is undertaken, often post-hoc, by clinical coders who work according to the National Clinical Coders standards (417). The quality of coding varies. Whilst coding error fell from 16% to 11% in the 3 years prior to 2010, the rate of errors varied widely (between 1 – 30% of records) across NHS trusts during the time period of this study (421).

PEDW data fields include: clinical data, including diagnoses and procedures; patient information, including demographics such as age, sex and ethnicity;

admission information, including admission and discharge dates; and, geographical information used to ascertain area deprivation codes (422).

For diagnoses, coding in hospital records use the International Classification of Disease manual, editions 9th (ICD-9) and 10th (ICD-10) systems adopted by the World Health Organisation (WHO). Each episode is given a primary diagnosis, also when this is unknown, and the rest of the codes constitute comorbidities. For operations and procedures, hospital records use the Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, 4th revision (OPCS-4).

PEDW, as HES, records data in episodes of care, called Finished Consultant Episodes (FCE). Since 2007 each episode may be associated with up to 20 ICD-10 codes, and 24 operations. ICD-10 is a coding system using a logical hierarchy of codes using alphanumeric bytes – i.e. letters or numbers (423). ICD10 starts with a 3 byte rubric determining the category of disease such as disease of the nervous system. This is followed by a further 3 byte sequence determining the anatomical site/ laterality/ severity or aetiology. Finally, there is one character determining the visit encounter. Limitations of the ICD-10 coding system include: the lack of information provided on disease severity; lack of specific information on diagnosis, which affects some specialities of medicine more than others; and, the lack of capture of sub-diagnostic disease which includes symptoms and signs.

3.6.5.3 Death data

Deaths in England and Wales are recorded using a Medical Certificate of Cause of Death (MCCD), which includes two parts. Part 1 defines the primary cause of death and may constitute 3 more parts with the first of those being the precipitant or most proximal cause, and the last of those being the most distal or underlying cause. Part 2 reports associated conditions present in the individual that have not directly contributed to the death in individual. The MCCD is completed by a medical practitioner who was involved in that person's care within the last two weeks of life. Data entered into the Annual District Death Extract (ADDE), include data derived from this or additional information entered by the local registrar of births and deaths for the district, or the coroner in cases where further investigation of the cause of death is undertaken, such as in the event of a post-mortem (424).

The underlying cause of a person's death is defined by the WHO as the "disease or injury initiating the train of events directly leading to death", or, "the circumstances of an accident or violence producing a fatal injury" (425). This underlying cause of death is always singular, and most often derived from the lowest completed line on Part I of the certificate. Since 1993 the coding of this information to ADDE records has been automated in 80% of cases, with the remaining minority being undertaken by experienced coders (424). Since 2001, the underlying cause of death has been assigned an ICD10 code. Where the underlying cause is unclear, for example where the causal sequence of Part

1(a) to (c) is unclear, or where there are multiple causes entered, the choice of which is the underlying cause is made according to a computer algorithm. This computer algorithm until 2014 was provided by the US National Center for Health statistics Mortality Medical Data System ICD10 version 2001.2 (426), and since 2014 by the IRIS system (2013 version) initially developed by the EU statistical institute Eurostat, now based in the German Institute of Medical Documentation and Information in Cologne (427).

3.6.6 Ethical approval

No new data was collected for this research. This secondary analysis of routinely collected patient data was carried out in accordance with section 254 of the UK Health and Social Care Act 2012, and does not require Research Ethics Committee (REC) approval. This was clarified with Dr Alice Temple, the named advisor on the University Ethical Review at the Research and Innovation service, University of Leeds on 8th December 2017.

The data used in this PhD are available in the SAIL databank at Swansea University. The proposal for this research was submitted for review by an Independent Governance Review Panel (IGRP) to ensure proper and appropriate use of SAIL data (415). The IGRP comprises a mix of lay members, professional and regulatory body members (402). SAIL operates in accordance with the GDPR (388), UK Data Protection Act and the UK Common Law Duty of Confidentiality.

3.6.7 Data application

The data application was submitted to the SAIL IGRP on 28th August 2018. The project was approved by the IGRP as project reference SAIL0826 on the 12th September 2018. Applications were submitted for amendments to include care home residence data on the 10th September 2019 and to include ethnicity data, on 28th October 2019. Both amendments were approved by the IGRP.

3.6.8 Data access

To gain access to the SAIL databank, I undertook the Office for National Statistics (ONS) safe researcher training course on 3rd December 2018. Access to SAIL data is conditional on the completion of safe researcher training and assessment to ensure the safe and responsible use of sensitive data and awareness of data confidentiality breaches. Approved Researcher status was awarded following successful completion of an online assessment (AR reference number ONSF21146, expiring 3rd December 2023).

3.6.9 Data analysis software

Data cleaning was undertaken using Eclipse SQL Explorer software.
Descriptive analysis, including the estimation of crude outcome rates, was performed in R (R Statistical Computing Environment (http://www.r-project.org) (53). Imputation for missing data was undertaken in R. Survival models were built in Stata version 15 (54).

3.6.10 Security

The repository is hosted on the UK Secure Research Platform (UKSeRP) which is a customised technology and analysis platform. I was provided a user account to log into the Gateway via a Virtual Private Network (VPN), as well as a Yubikey which when inserted into a USB port of the computer transmits a one-time hidden password, as if entered by the keyboard (428). Data transfer from the Gateway VPN is only possible via a portal that requires every file to be reviewed by a SAIL data guardian for approval before being released.

3.7 Study design

3.7.1 Inclusion and Exclusion criteria

Individuals were included if they:

1. Had been registered with a GP contributing to SAIL for at least one year. This was set as a minimum requirement to allow time for any records from previous notes to be transcribed to avoid items from a person's past medical history being counted as early outcomes.
2. Had their blood pressure recording at any time in 2007. The first GP encounter where BP measurement was undertaken after 1st January 2007 and before 1st January 2008, was used as the individual's index start date.

3. Were aged 65 years or older at the time of study entry. A threshold of 65 years was chosen to define older people in this study because it is the minimum age of people for whom the eFI has been validated (341).

Individuals were excluded if they:

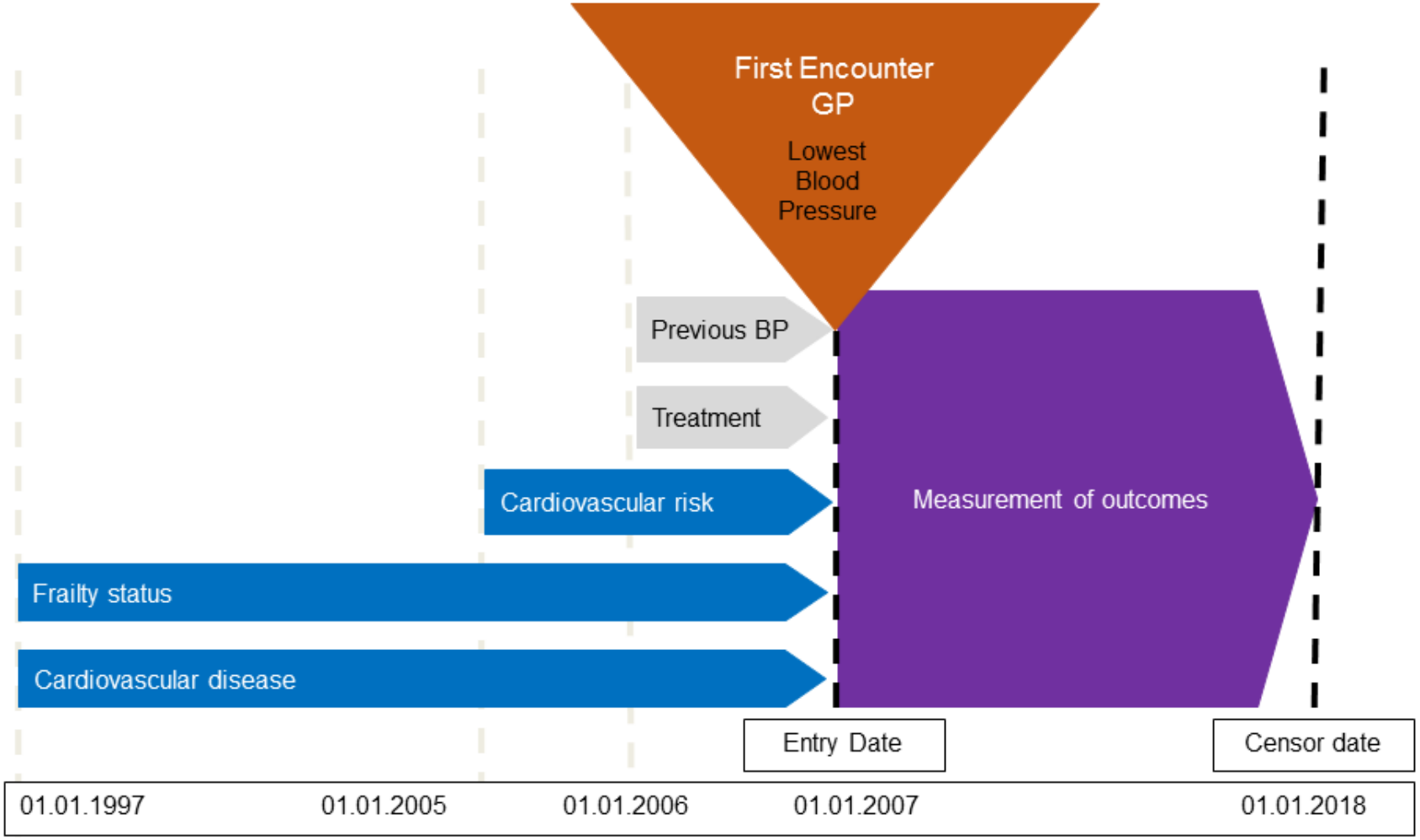
1. Did not have a diagnosis of hypertension or did not have blood pressure meeting criteria for hypertension (320);
2. Had an established history of cardiovascular disease (previous stroke, heart failure or myocardial infarction) prior to the start date.

These exclusions were applied to identify a study population of older adults with hypertension for whom treatment is for primary prevention.

3.7.2 Analytic Cohort Derivation

The study design is presented in **Figure 3-2**. A full definition of all study variables is given later in this Chapter (**Section 3.8**). Outcomes were measured during ten year follow up of primary care, secondary care and death records. Follow-up was censored at the earliest of: the date of the outcome occurrence; ten years since the index date; the date of de-registration from the practice; or, date of death. Total follow up time was 10 years, up to 1st January 2018.

Figure 3-2 Setting of PhD study cohort.



Entry date: First Encounter GP: date of first patient encounter at primary care where a BP was measured after 01.01.2007; Lowest Blood Pressure: BP reading with the lowest systolic reading recorded on that day was extracted; Previous BP measurements and treatment were extracted from 1 year prior to study start; cardiovascular risk measurement was extracted from 2 years prior to study start; Cardiovascular disease and frailty status from 10 years prior to study start; follow up was for 10 years or until censorship.

3.7.3 Missing data

Missing data refers to a situation where there is no information on a data point in the data set because of missing information (429). Missing data is a particular problem in routine health data (373). Data may be missing for multiple reasons: some patients do not appear in the database; some variables are not recorded (either predictors or outcome measures); or for others, values are simply missing in the record or implausible.

Most covariates in this analysis are recorded and interpreted on the basis that a positive recording (as defined in **Section 3.5.3.3**) is assumed to be sufficiently representative of the disease being present. For the purpose of this research I have assumed the absence of recording of a particular diagnosis represents the absence of diagnosis. The alternative would be to treat everything where a diagnosis is absent as missing data and the risk of misclassification bias is then higher.

However, this assumption cannot be made in cases of continuous variables which a person with a diagnosis of hypertension should ordinarily have measured according to guidelines, as part of a full assessment of cardiovascular risk (320). Continuous data that are part of cardiovascular risk assessment were therefore handled as missing data.

Identifying the pattern of missing data is an important means of determining which methods are appropriate to address missing data in a way that will cause

least bias in subsequent analysis. Missing data can be missing in at least three ways (430):

- Missing completely at random. For example this may apply where a study has extracted a randomised sample of a population (431). Those included in the study have complete data. The rest of the population is not represented in the study and has missing data. If all had the exact same chance of being included in the study, the missing data would be truly random and none of the observed data would help to predict information about the un-observed data.
- Missing at random. For example, this may apply in a study which involves a questionnaire, which upon completion, when asked some people don't disclose their income, but there is another question in the questionnaire which asks about privacy over such matters (431). In these cases, the missing data depends on some observed data and any systemic differences between the observed and missing data can, at least partially, be explained by differences in the observed data. The higher the number of relevant variables included in the observed data, the more plausible is the assumption that differences in the missing data may be explained by observed data patterns (432).
- Missing not at random. For example, this may apply to a study in which participants are asked about their attitudes about racial issues (431), missing data may relate to unobserved or partially observed variables in a way that cannot be fully predicted from the observed data because these factors have not been or have been inadequately measured.

There are several methods of addressing missing data. Each method has its own merits and flaws:

- Complete case analysis involves not including in the analysis participants for whom at least one data point is missing. However, unless the amount of missing is very small, this will reduce the study size (degrees of freedom) for any summary statistics as those with missing data would have been informative.
- Substituting missing with the mean or median of the existing observations in others. Whilst this method may not distort the mean, it will reduce the deviation from the mean (variance) and therefore cause bias.
- Multiple imputation. This is a method that uses the distribution of the observed data to estimate multiple possibilities for the missing data points, thereby accounting for the uncertainty of estimates (431). This method reduces bias, but only on condition the pattern of missingness can be assumed to be missing completely at random or missing at random.

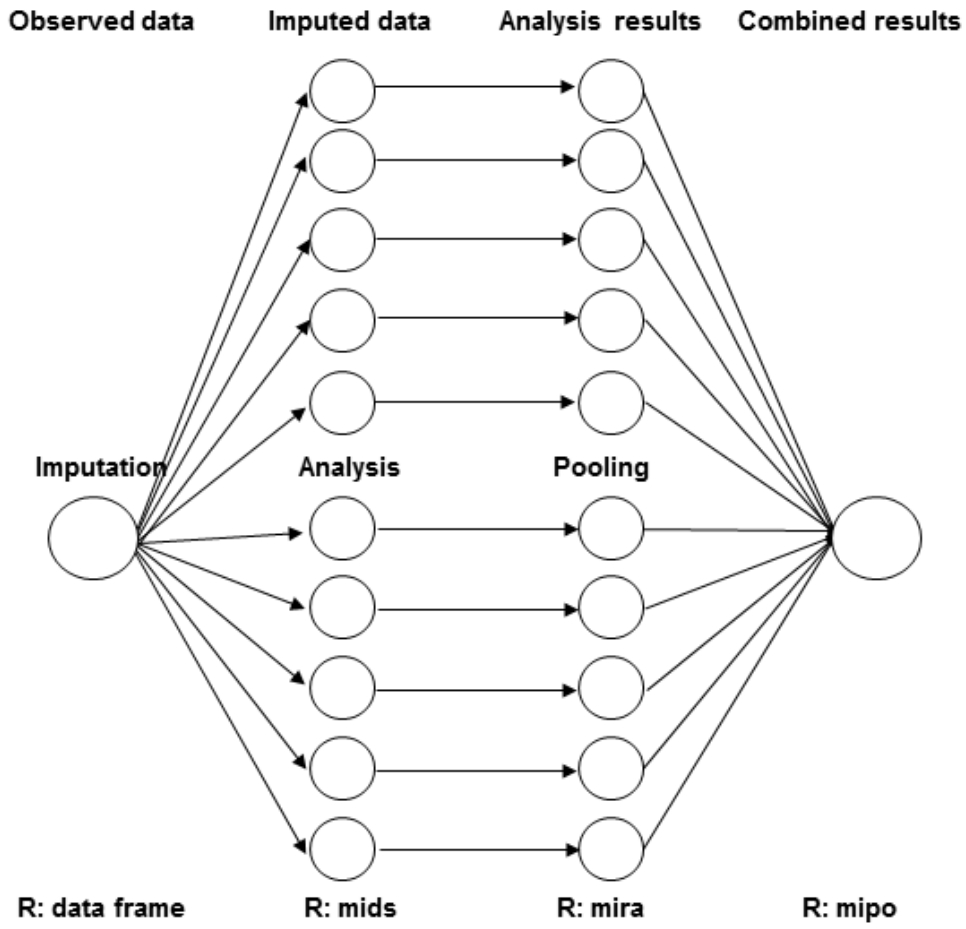
Rubin set out the key principles of multiple imputation (MI) analysis (433):

1. Values for missing data ascertained so as to keep the relationships in the observed data intact.
2. Independently drawn imputations of the data set are taken multiple times (e.g. ten times), and averages of these values calculated to derive single point estimates for the missing data points.

3. Standard error (SE) is estimated using the variation across the multiple data sets to account for the uncertainty of these estimates. The SE is calculated as a combination of the SE of each missing data estimate (average of squared SEs of each estimate); together with the variance of all the missing value parameters across the sample.

The choice of methods depends on the distribution of the data. If multivariate normal, joint multivariate normal distribution multiple imputation may be used (R packages **Amelia** and **norm**). Conditional multiple imputation represents an alternative, more flexible approach where missing values are replaced with plausible estimates (for example 10 imputations), each of which is modelled with different imputed values for the missing factors, and then these are pooled to give a combined result (**Figure 3-3**).

Figure 3-3 Key steps in multiple imputation process



Schematic describing multiple imputation corresponding R commands. Figure adapted from multiple sources: short course materials on multiple imputations delivered by the MRC Biostatistics Unit, Cambridge, PhD by Marlous van Laar (434), and online material from the University of Virginia (431). Abbreviations: mids = multiply imputed data sets; mira = multiply imputed repeated analysis; mipo = multiple imputation pooled object.

The stages of multiple imputations are as follows (431):

1. Identify the missing values and their proportion of the whole data set
2. Multiple imputation by chained equations (MICE) command completes multiple complete data sets, with each variable according to its own distribution. Complete data sets are stored in an object called **mids** (multiply imputed data set). These are copies of the original but with missing values replaced with plausibly imputed values generated by

mice. At this stage, these independent data sets have no measure of the collective uncertainty they represent as a whole.

3. Run a regression on each of these 10 data sets, using the **with_mids** command to run a regression coefficient for each data set. These analyses are stored in **mira** (multiply imputed repeated analysis).

3.8 Key study variables

This section defines key study variables for the analyses undertaken.

3.8.1 Health condition: hypertension

Hypertension is the health condition of interest in this PhD study, defined as either:

1. A diagnosis recorded in a person's EHR according to the code list (**Appendix C**) associated with a date, that precedes the study start date; or,
2. Routinely collected blood pressure readings indicative of hypertension at the study start date, according to reference thresholds defined by the NICE guidelines (320). These define hypertension as a systolic and diastolic blood pressure > 140/90 mm Hg under the age of 80 years, and >150/90 mm Hg over the age of 80 years.

3.8.2 Primary exposure: systolic blood pressure

Systolic and diastolic blood pressures were identified by code lists in the WLGP data set, and the associated numerical values for each code extracted. For descriptive purposes, the cohort is described by related measures of BP including the following calculations from the raw data:

- Pulse pressure (systolic blood pressure – diastolic blood pressure);
- Mean arterial pressure (diastolic blood pressure + 1/3 pulse pressure)

The analysis focuses on systolic BP. Diastolic blood pressure has previously been given precedence, but more recent epidemiological research has demonstrated that systolic blood pressure is a greater risk factor for cardiovascular disease (435, 436), particularly in people over the age of 50 years (40).

Where there is more than one reading on the same day, the lowest reading was extracted. The merits and limitations of alternative methods to represent BP were considered (**Table 3-5**). The minimum BP was chosen because (according to guidelines), it is this reading that informed the clinical decision making at the index clinical encounter.

Table 3-5 Profiles of alternative methods to represent BP

Method	Advantages	Disadvantages
Time-dependent correction for "regression dilution" (235, 365, 368) using information on repeat measures during prolonged follow up (367)	Can correct for effects of measurement error and short term variability in BP levels.	Requires information not available to the GP at the time of patient encounter.
Median BP of serial readings taken over a 2 – 3 year follow up (366)	Reduces effect of extreme values e.g. during concurrent illness	There is a risk that regression to the mean from the inclusion of multiple readings will lead to a 'concertina effect' – misrepresenting the true variability of BP present in a population (437-439). Exposure over a period of time rather than a clear clinical encounter.
Mean BP from each month (365), or year (32) of the duration of follow up included as trajectory	To allow for decline in BP with age – as described in Chapter 1.	Requires information not available to the GP at the time of patient encounter.
Combination of single reading and trajectory (440, 441)	May capture more information about BP associated risk	Not currently available to GP in the clinical encounter.
Minimum reading on day of measurement	This is the measure that currently informs practice, according to clinical guidelines in UK clinical care (320)	No correction for measurement error or BP variability over time, therefore may not represent person's true BP.

Where systolic BP was categorised in the analysis, eight categories were created either side of the European Society of Cardiology (ESC) guideline target range (130-139 mm Hg) in ten mm Hg categories, as follows: < 120 mm Hg; 120 – 129 mm Hg; 130 – 139 mm Hg; 140 – 149 mm Hg; 150 – 159 mm Hg; 160 – 169 mm Hg; 170 – 179 mm Hg; > 180 mm Hg. This replicates categorisation in similar studies using UK routine data (366). The ESC guideline was chosen because it is the only hypertension guideline that currently stipulates a lower limit to the systolic BP target range (322). The target range stipulated by the ESC is the central sBP category used as reference in the models.

3.8.3 Explanatory variable: frailty

There are multiple measures for frailty as outlined in Chapter 2. The choice in this study to use the eFI (341) as a frailty measure was made on the basis of its availability in routine UK primary care data (uniquely among the frailty measures), and the validation of eFI in SAIL and other routine data sets (407). The eFI is based on the cumulative deficit model of frailty (332), including 36 variables recorded as present or absent in the primary care electronic health record (**Table 3-6**).(341)**.** The eFI score is calculated as an equally weighted proportion of the number of deficits present in an individual relative to the total possible deficits measured.

In this study, the eFI score was measured over a period of 10 years on the basis that by 1997 the majority of GP practices in the UK had electronic records (384), allowing the eFI to be calculated retrospectively. This score will not have

been available to the clinicians at the time, so treatment decisions could not have been directly influenced by the eFI.

For the measurement of model fit, eFI is included as a continuous variable. Where frailty is categorised in the analysis, patients with an eFI score 0 < 0.12 are identified as fit; ≥0.12 < 0.24 as having mild frailty; ≥0.24 <0.36 as having moderate frailty; and, ≥0.36 as having severe frailty (341).

Table 3-6 Deficits included in the eFI

Category of deficits		Specific deficit
Symptoms		Dizziness
		Dyspnoea
		Falls
		Sleep disturbance
		Urinary incontinence
		Weight loss and anorexia
Comorbidities	Non-cardiovascular	Anaemia and haematinic deficiency
		Arthritis
		Foot problems
		Fragility fracture
		Osteoporosis
		Parkinsonism and tremor
		Peptic ulcer
		Respiratory disease
		Skin ulcer
		Thyroid disease
		Urinary system disease
	Cardiovascular	Atrial fibrillation
		Cerebrovascular disease
		Chronic kidney disease
		Diabetes
		Heart failure
		Heart valve disease
		Hypertension
		Hypotension/syncope
		Ischaemic heart disease
		Peripheral vascular disease
Polypharmacy		Count of medications prescribed
Functional impairments		Activity limitation
		Hearing impairment
		Housebound
		Memory and cognitive problems
		Mobility and transfer problems
		Requirement for care
		Visual impairment
Social vulnerability		Social vulnerability

Constituent deficits of the electronic frailty index (eFI) (341) Deficits are categorised to discern constituent parts of the eFI and allow comparison with the frailty indices developed in the post-hoc analyses of major trials SPRINT and HYVET (as discussed in **Section 2.5.2.1**).

3.8.4 Outcomes

3.8.4.1 Primary outcomes

Primary outcomes of interest in this thesis include major adverse cardiovascular events (MACE): myocardial infarction, new presentation of heart failure, stroke and cardiovascular death considered as a composite outcome. MACE was chosen as the primary outcome of choice given the relevance of cardiovascular risk in defining hypertension management, and its established use as a primary outcome in trials and observational data.

3.8.4.1.1 Myocardial infarction

Non-fatal myocardial infarction (MI) is defined as death of part of the myocardium due to coronary artery occlusion from any cause (spasm, embolus, thrombus, or rupture of a plaque) (442). This is recorded as either a diagnosis of an MI, or it's definitive treatment (percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)) from hospital records along with the date of the hospital admission.

3.8.4.1.2 New heart failure

Fatal or non-fatal heart failure is defined as an inpatient visit requiring treatment with intravenous therapy for a clinical syndrome that presents with multiple symptoms and signs consistent with cardiac decompensation or inadequate

cardiac pump function (443). The presence of such a diagnosis, including the date of the hospital admission were extracted from hospital records. Patients with a record of heart failure before the study start date were excluded, so the diagnosis could be assumed to be new.

3.8.4.1.3 Stroke

Fatal or non-fatal ischaemic and haemorrhagic stroke events are generally defined as a neurological deficit of cerebrovascular cause that has persisted beyond 24 hours or was interrupted by death within 24 hours (444). Codes that included terms for an episode of cerebral ischaemia, or intra-cerebral or subarachnoid haemorrhage were extracted from hospital inpatient records (PEDW) during follow up, together with the date of hospital admission.

3.8.4.1.4 Cardiovascular death

Death attributable to cardiovascular disease is defined in cases where the diagnosis of one of the above three cardio- or cerebrovascular diseases had been defined as the underlying cause of death on the death certificate. The underlying cause of death on the death certificate as well as the date of death were extracted from death records along with the death date.

3.8.4.2 Secondary outcomes

A range of secondary outcomes were chosen as being implicated by blood pressure or by BP-lowering therapy.

3.8.4.2.1 All-cause mortality

All-cause mortality was defined as death from any cause listed on the death certificate as recorded in the ADDE extract, with the associated date of death.

3.8.4.2.2 Falls

Defined as “an unexpected event in which the participant comes to rest on the ground, floor or lower level” (445), falls maybe the consequence of a trip, slip, overbalance, loss of consciousness or dizziness triggered by postural hypotension. Falls resulting in a hospital admission, usually as a consequence of fall related injury, were ascertained from hospital records using related ICD-10 codes and extracting the first fall and date of admission.

3.8.4.3 Additional descriptive outcomes

Additional descriptive outcomes included other non-cardiovascular outcomes. Whilst these outcomes listed below were not assessed in formal survival analysis models, the rates of this wider group of outcomes were described for the population by frailty and blood pressure category because they are of

relevance to clinical management of hypertension. However, numbers in this data set are likely to be too small for more formal detailed analysis. These outcomes include:

Orthostatic hypotension. This was identified from a related hospital admission during follow up.

Acute kidney injury. This was extracted from hospital admissions during which it was recorded in hospital records.

Delirium and new dementia. These were extracted from both primary (WLGP) or secondary care (PEDW) records, and considered valid where there was no record previously of a dementia diagnosis. When someone suffered delirium during a hospital admission this was also extracted from PEDW data.

Urinary incontinence. This was extracted from hospital admissions when it was recorded.

Functional decline. This was defined in patients who had a documented requirement for active rehabilitation resulting in or arising during a hospital admission.

Electrolyte disturbance. This was extracted from hospital records where it was reported as a cause or comorbidity during a hospital stay.

Hospital admission. This was recorded as the date of the first hospital admission for any cause during follow up extracted from the PEDW database.

Emergency Department admission. This was documented as the date of the first admission for any cause to Accident and Emergency department recorded in the EDDS database.

Care home admission. This was documented as a new transfer to a care home during the period of follow up where the previous address was not a care home. In SAIL there is a validated list of care homes in Wales, linked to primary care records which in turn are linked to RALF_PE codes. A new care home admission was identified by the change of a RALF_PE code to one identified as a care home residence using the SAIL care home registry (408).

3.8.5 BP-lowering treatments

Past prescriptions of BP-lowering drugs were extracted from WLGP according to the main five classes of BP-lowering medications, where the prescription predated the study start date and was within 2 years of study start date. (**Table 3-7**).

Table 3-7 BP-lowering treatment by class and drug name

Adrenergic neurone blocking drugs	
Alpha-adrenoceptor blocking drugs	Bethanidine; Clonidine; Desbrisoquine; Doxazosin; Indoramin; Methyldopa; Metirosine; Phenoxybenzamine; Prazosin; Terazosin;
Beta adrenoreceptor drugs	
Beta-blockers	Acebutolol; Atenolol; Betaxolol; Bisoprolol, Carvedilol; Celiprolol; Esmolol; Labetolol; Metoprolol; Nadolol; Nebivolol; Oxprenolol; Pindolol; Propanolol; Sotalol; Timolol
Compound beta-blockers	
Renin Angiotensin System drugs	
ACEi	Captopril; Cilazapril; Enalapril; Sodium Fosinopril; Imidapril; Lisinopril; Moexipril; Perindopril arginine; Quinapril; Ramipril; Trandolapril
ARB	Azilsartan; Candesartan cilexetil; Eprosartan; Irbesartan; Losartan; Olmesartan; Telmisartan Valsartan
Calcium channel blockade	
Calcium channel blockers	Amlodipine; Diltiazem; Felodipine; Isradipine; Lacidipine; Lercandipine; Mibefradil; Nicardipine; Nifedipine; Nimodipine; Nisolidipine; Slofedipine; Verapamil
Combination with ACEi	
Diuretics	
Thiazides	Bendroflumethiazide; Chlorothiazide; Chlorthalidone; Clopamide; Cyclopenthiazide; Hydrochlorothiazide; Hydroflumethiazide; Indapamide; Mefruside; Methylclothiazide; Metolazone; Polythiazide; Xipamide; Diuretics + Potassium supplements; Acetazolamide
Loop diuretics	Furosemide; Bumetanide; Etacrynic acid; Piretanide; Torasemide; Compound Potassium Sparing diuretic
Potassium sparing & Aldosterone antagonists	Amiloride, Potassium Canrenoate; Spironolactone; Triamterene; Eplerenone

3.8.6 Covariates

All relevant covariates including factors which may inform clinical management of blood pressure, are defined according to NICE guideline recommendations (320). UK NICE guidelines on hypertension management have been the subject of iterative changes during the period of this study's follow-up time. **Table 3-8** summarises NICE guidelines since the start of the study period.

Table 3-8 Summary of UK hypertension guidelines since 2007

	Diagnosis	Treatment indication	Target BP	Cardiovascular Risk		Shared Decision Making
				Definition	Measure	
North GC 2004	Office*>140/90 at the last two visits Home±>130/85	BP≥160/100 BP>140/90 & ↑CVr	<140/90	CHD ≥15% CVr ≥20% Past CVD TOD	Joint British Societies CVD risk chart	N/A
NICE 2006 #34	>140/90 at the last two visits			CVr ≥20% Past CVD TOD	Framingham	Consider preferences & needs
NICE 2011 #127	**Stage 1** Office >140/90 Home >135/85 **Stage 2** Office>160/100 Home>150/95	**Stage 1** if <80y +↑CVr **Stage 2**	Under 80y <140/90 Over 80y <150/90	As Above + CKD DM	Framingham QRISK2	Over 80y Consider comorbidities
NICE 2019 #136	**Stage 1** Home>135/85 to 149/94 **Stage 2** Home>150/95	**Start** Office>180/120 Home>150/95 **Discuss** Home: 135/85 - 149/94 &↑CVr **Consider** Home:135/85-149/94 ↓CVr/>80y	Under 80y **Office**<140/90 **Home** 135/85 Over 80y **Office** <150/90 **Home** 145/85	As Above but CVr>10%	QRISK 2	Patient Decision Aid Discuss uncertainty e.g. frailty, multimorbidity

All BP measurements are measurements in millimetres of mercury (mm Hg)
*Clinic: Office BP reading in the GP practice;
±Home: Ambulatory BP monitoring/ Home BP monitoring average. CG: Clinical Guideline; CHD: Coronary Heart Disease; CVD: cardiovascular disease; CVr: Cardiovascular risk; DM: diabetes mellitus; GC: Guideline Committee; NG: National Guideline; NICE: National Institute for Health and Care Excellence; OH: Orthostatic Hypotension; QRISK: Q-Research Risk prognostic model; TOD: Target Organ Damage; T2DM: Type II Diabetes Mellitus; y: years.

3.8.6.1 Cardiovascular risk

The assessment of cardiovascular risk uses the risk factors outlined by the QRISK-3 cardiovascular risk algorithm developed in the QRESEARCH database (446). QRISK is widely used in the UK and recommended by NICE hypertension guidelines. The overall cardiovascular risk for each participant at the study start was calculated using QRISK-3 independently using the available data according to a published algorithm (447). QRISK-3 is the latest iteration of QRISK, and includes 22 variables. Continuous variables included in the QRISK-3 score were extracted at their most recent date in the 2 years before study start from the WLGP database. Variables in QRISK-3 included in this study were:

Age

Age was measured at baseline as the difference between the index start date and the birth date, measured as a continuous variable, and recorded in whole years.

Sex

Sex was measured as a categorical variable, from WDDS, with categories of male and female.

Atrial fibrillation (AF)

AF was measured as a categorical variable. Hypertension increases the risk of atrial fibrillation through structural change of atrial remodelling (448), and atrial fibrillation is a major risk factor for stroke. Therefore AF also mediates some of the stroke risk associated with hypertension.

Atypical antipsychotics

As these are included in the NICE guideline on lipid modification and cardiovascular risk assessment (449), atypical antipsychotics were measured as present or absent in the prior 2 years.

Corticosteroids

Also included in the NICE guideline on lipid modification and cardiovascular risk assessment (449)**,** steroids were measured as present or absent in the prior 2 years.

Erectile dysfunction

Studies have demonstrated the prognostic importance of erectile dysfunction for cardiovascular risk estimation (450-452). Erectile dysfunction was measured as present or absent in the prior 2 years.

Migraine

Migraine is associated with increased cardiovascular risk in women (453) **.**Migraine was measured as present or absent in the prior 2 years.

Rheumatoid arthritis & systemic lupus erythematosus (SLE)

Atherosclerotic disease is increased in people with rheumatoid arthritis (454) and systemic lupus erythematosus where this disease is active, and in relation to some of the long-term treatment of inflammation, most prominently with steroids. NICE guideline on lipid modification and cardiovascular risk assessment recommends measurement of SLE (449). These were measured as present or absent in the prior 2 years.

Renal impairment

Renal impairment was recommended as a relevant prognostic factor according to NICE guideline on lipid modification and cardiovascular risk assessment (449). Challenges exist with using morbidity codes to identify chronic kidney disease given the limited capacity to stage chronic kidney disease (CKD) in CTV-2 coding. An alternative would have been to use Creatinine to calculate the electronic Glomerular Filtration Rate (eGFR) but there would be a risk with

this approach of misclassifying acute kidney injury (AKI) as chronic kidney disease. Renal failure was measured as present or absent in the prior 2 years.

Severe mental illness

Mental illness is included because it is recommended in the NICE guideline on lipid modification and cardiovascular risk assessment (449). QRISK-3 defines severe mental illness as moderate/severe depression, bipolar disease and schizophrenia. Moderate/severe depression may be identified by the prescription of anti-depressant medication. Codes for depression have been used in SAIL but it was not possible to grade the severity and therefore mild depression will have been included. Severe mental illness was measured as present or absent in the prior 2 years.

Type I and type II diabetes mellitus

The UK Prospective Diabetes Study Group (UKPDS) provided definitive evidence the incidence of micro- and macro-vascular complications of diabetes are significantly associated with blood pressure control. A10 mm Hg decrease in sBP was associated with a 12% (95%CI 10-14%) reduction of any complication of diabetes (455). Type I and type II diabetes were measured separately and collectively as present or absent in the prior 2 years.

Weight

Weight was recorded as continuous variable, measured in metres, and included the most recent recording in the prior 2 years.

Height

Height was recorded as continuous variable, measured in kg, and included the most recent recording in the prior 2 years.

Ethnicity

Self-assigned ethnicity was extracted from ethnicity coded data only available from hospital electronic health records. Therefore ethnicity data were only available for those who had had a hospital admission during follow up. The most recent of these records throughout the course of the study was extracted. Ethnicity in this study was coded according to the UK 2011 Census, in the following 9 categories:

1. White;
2. Indian;
3. Pakistani;
4. Bangladeshi;
5. Other Asian;
6. Black Caribbean;
7. Black African;
8. Chinese;
9. Other ethnic group.

For the QRISK-3 algorithm, those with ‘undeclared’ ethnicity data, are categorised with ‘White’ ethnicity.

Family history of cardiovascular disease

This was defined as a history of angina or heart attack under the age of 60 years old in a first degree family member recorded by the GP in the medical record as positive. Where this was missing it was assumed to be negative.

Total cholesterol: HDL ratio

Total cholesterol: HDL ratio is a better predictor of cardiovascular disease than total cholesterol alone (456). Recorded as the ratio of total serum cholesterol to high density lipoprotein, both were measured in millimoles per litre (mmol/l) within 2 years prior to the study start date. The most recent entry was extracted.

BP variability

BP variability was measured using the standard deviation of serial measures of blood pressure. Serial measures included the index BP recording and the most recent BP recording.

Smoking history

Smoking history was recorded as the most recent recording of any of the smoking codes describing smoking prior to the study start date. The most recent smoking status was then categorised according to the classification used in the QRISK-3 score, in the following 5 categories:

- never smoker;
- ex-smoker;
- light smoker;
- moderate smoker;

- heavy smoker.

Deprivation

Deprivation was measured by Townsend score developed by sociologist Peter Townsend (457) and applied widely as an index of deprivation. The Townsend score incorporates four factors relating to material deprivation: non-car ownership, non-house ownership, unemployment and over-crowding. The score is calculated by region defined as a Lower Super Output Area (LSOA) which equates to approximately 125 households. This study will use the Townsend score from the 2011 census for the most recent address in the patient's record prior to study start. The post-code may have a missing Townsend score if the person: has moved to newly built houses with new postcodes not yet linked to deprivation data; or, the person is homeless or has not been registered to a permanent address (192). Townsend scores at baseline for each individual were mapped to the individual's latest LSOA recorded prior to the individual's study entry date.

3.8.6.2 Clinical decision making

Covariates representing the clinical decision making process were characterised as follows:

Associated measures of BP

For descriptive purposes the total number of BP measurements in a 2 year period prior to the study start date were extracted, the minimum and average

reading on these dates, and an average of all readings during the two year period prior to the study start date.

Attendance to clinic and frequency of BP monitoring

The number of blood pressure recordings over the prior 2 year period were extracted; the interval between the index blood pressure recording and the subsequent one, and whether BP measured on the study start date was within the target set by NICE guidelines for hypertension.

Level of treatment

To calculate the QRISK-3 score, treatment was measured as present or absent where there was a prescription of any of the key classes of BP-lowering medications (458). BP-lowering medications were classified according to BNF categories (**Table 3-7**). Doses were not included. For inclusion as a covariate in the models, the number of classes of BP-lowering medication prescribed was included as a total drug count. The presence or absence of a prescription over the prior two years of lipid lowering therapy (statin, fibrate or ezetimibe) was also measured.

GP practice code

As guidelines recommend clinician discretion in older people, the role of the clinician is important and practices may vary. The GP practice code was extracted from the Welsh Demographic Data Service (WDSD) database.

The average number of patients registered at a GP practice in Wales was circa 5,000 patients between January 2000 and October 2014 (409). Each record included in the study was allocated a GP practice according to the most recently recorded practice ahead of the individual's study entry date.

Comorbidity

Comorbidity was measured according to clinical domains listed in the GP contract (459). There were 17 in total, excluding palliative care and hypertension. Categorical covariates qualified as present if the deficit was recorded in the patient's electronic health records and not removed prior to the study entry date. The list included: asthma; atrial fibrillation; cancer (within the last 5 years); chronic kidney disease; chronic obstructive pulmonary disease (COPD); coronary heart disease; dementia; diabetes mellitus; heart failure; learning difficulty; mental health illness; osteoporosis; peripheral arterial disease; rheumatoid arthritis; and, stroke.

Care home residence

Residential addresses were derived from the Welsh Demographic Service data set (WDS). The most recent address (represented by the RALF_PE code) in a participant's record on the study start date was extracted and matched to the care home registry.

3.9 Data extraction and cleaning

3.9.1 Code definitions

Code lists were created to derive variables from primary (WLGP) and secondary (PEDW) care records for risk factors and comorbidities recorded before or at study start, and for outcomes recorded after study start (**Figure 3-2**). The choice of code list was made from what was available depending on the particular variable, and prioritised, in order of preference:

(1) Code lists from an online clinical codes repository, including CALIBER (460), Clinical Codes (461) or Cambridge CPRD Code (462)
(2) Code lists used by existing studies (463-467);
(3) Recommended Read code lists from the UK Quality Outcomes Framework
(4) Code lists derived from a manual review of the codes accessed via the Technology Reference data Update Distribution (TRUD) Data dictionary (468)

Validated code lists from phenotype code repositories (e.g. CALIBER Phenotype) were given first preference, where they were available. However for outcomes, more sensitive lists (CALIBER Code lists) were also included to broaden inclusivity.

The sources of codes for each variable are listed in the **Appendix C**.

No code lists for BP-lowering treatments were available. Therefore, a novel list was created, as listed in **Appendix D**. Defining the code list for BP lowering

medications required a manual searching of the NHS Technology Reference data Update Distribution (TRUD) (468) code dictionary for relevant BP-lowering medications which were chosen according to the British National Formulary (469)

3.9.2 Code extraction

Code extraction was undertaken using Eclipse SQL Explorer within “IBM DB2” database architecture.

3.9.2.1 Continuous data

Continuous variables were extracted from a raw form in which they were combined in variable lengths of code. For example, BP was recorded as a total number combining systolic and diastolic readings. The number of digits was most commonly 8 but ranged from 1 to 10 numbers (**Table 3-9**) in the format ‘12000080’ which combined systolic (120 mm Hg) with diastolic blood pressure (80 mm Hg) values, with an interval ‘00’ to distinguish the two. However, this proved problematic if the systolic reading was 2 digits, i.e. any systolic BP reading < 100 mm Hg, such as in a BP reading of 95/55 mm Hg, entered as ‘09500055’. Because the system records values as numeric data, this would be saved as ‘9500050’, i.e. a 7 digit number. Other variations may also be the result of human error in data entry, such as a diastolic reading of 50 mmHg entered as 50 not 050.

Table 3-9 Raw blood pressure data according to integer length

Integers	Frequency	Proportion (%)
1	7	<0.1
2	517	0.2
3	595	0.2
4	1	<0.1
5	7	<0.1
6	15	<0.1
7	2,658	0.8
8	323,848	98.8
9	10	<0.1
10	1	<0.1

Listed are the numbers of integer number in the raw BP recording in the SAIL study from a total data extract of 327,659 individuals, frequency as a number and as a proportion of the population extract.

Explicit assumptions were made on what was deemed plausible: if the string started with a number more than or equal to 300, but less than or equal to 990, these were assumed unlikely to represent true systolic readings. They were more likely to represent systolic readings from 30 – 90 mm Hg. Therefore, only the first and second integer from the string were extracted to represent the systolic reading. Readings between 990 and 999 were not extracted, given the possibility these was entered to indicate the measurement was missing. If the three numbers at the start of the string were less than 300, the first, second and third were all extracted to form the systolic reading.

Similarly with diastolic readings, if the diastolic reading was more than or equal to 200, or less than or equal to 990, the 6th and 7th numbers were extracted. However, if the number was less than 200, then the 6th, 7th and 8th numbers were extracted.

3.9.2.2 Filtering outliers

A representative measurement was extracted per patient for each continuous variable. Filtering of outlying measures had to be undertaken before data extraction, to ensure, where possible, the reading extracted was that most likely to be reliably recorded. The limits in **Table 3-10** were pre-specified as the bounds of clinically plausible readings for all of the continuous variables in this analysis. Readings outside of these boundaries were considered unreliable and therefore treated as missing. All measurements extracted from specified time periods, were the first or a representative continuous reading where that reading was deemed plausible according to the pre-specified rules.

Table 3-10 Pre-specified thresholds defining outliers in continuous measurements

Variable	Outliers thresholds	Outlier rationale
sBP	< 50; > 300	Clinically implausible
dBP	< 30; >200	Clinically implausible
BP SD	calculated directly	
Age (y)	calculated directly	
BMI	<0.15% & > 98.5%	Statistical
Height (m)	<0.15% & > 98.5%	Statistical
Weight (kg)	<0.15% & > 98.5%	Statistical
Chol: HDL	<0.15% & > 98.5%	Statistical
Townsend	Not altered	

BMI = body mass index; BP SD = blood pressure standard deviation; dBP = diastolic blood pressure; Chol: HDL= Cholesterol to High Density Lipoprotein ratio: kg = kilograms; m = metres; sBP = systolic blood pressure

3.9.2.3 Categorical data

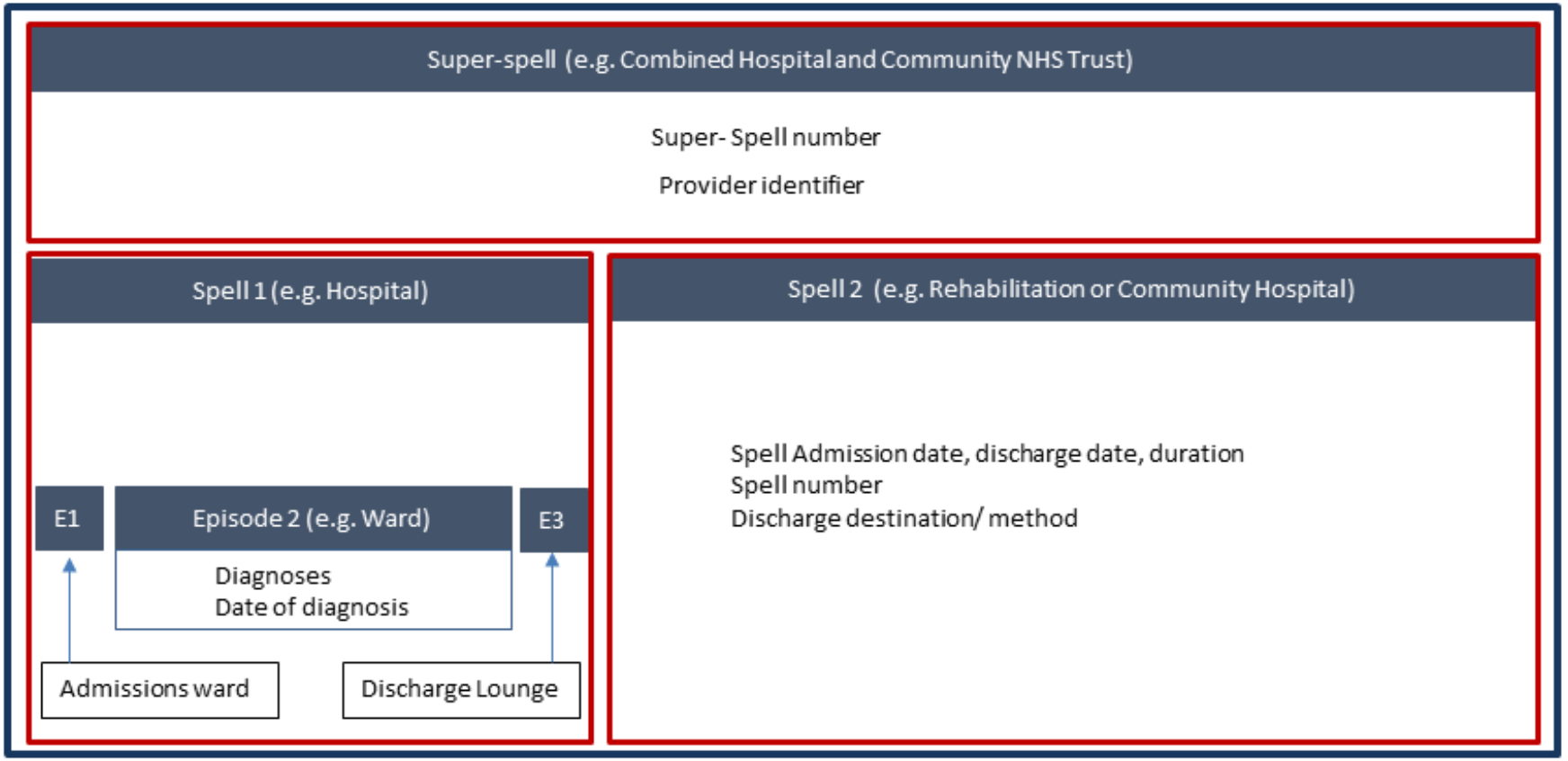
Given the positive recording assumption (see **Section 3.5.3.3**) where a categorical variable was missing it was deemed to be absent. For example, where a diagnosis of atrial fibrillation had not been made, the variable value was changed from missing to zero to indicate the absence of the AF diagnosis.

3.9.2.4 Hospital episode data

Primary and secondary outcomes were extracted from the Patient Episode Data Wales (PEDW) data set. Outcome data recording in PEDW is nested within the hospital database architecture, outlined in **Figure 3-4**.

Periods of patient care on a particular ward (e.g. Medical Admissions) or under a single consultant are recorded in PEDW as discrete *episodes* of care. A hospital stay may consist of several inpatient transfers, but the duration of stay in a single hospital is defined as a *spell*. Spells, in turn are linked together to account for inter-hospital transfers, within an NHS trust for example, creating *superspells*. In this study, an admission is counted as a continuous period of care (whether a spell or superspell). Diagnoses and their associated dates were extracted from episode data within an admission.

Figure 3-4 Architecture of Hospital Records in PEDW



This schematic attempts to explain the hierarchical architecture of PEDW hospital records using an illustrative example: where a patient is admitted from their GP to a Medical admissions ward (E1: Episode 1) before being transferred to a Geriatric Medicine Ward (Episode 2); thereafter waiting in the discharge lounge (E3: Episode 3) to transfer to a community hospital for rehabilitation which is undertaken at another hospital site but in the same NHS hospital trust. Episodes 1-3 represent Spell 1, and the stay in the community hospital represents Spell2. Spells 1 and 2 form 1 overarching superspell)

3.9.2.5 Preparing time to event data

If the event date for an outcome was valid, the outcome status was set to 1. If the event date for an outcome was not valid, the outcome status was set to zero. Time to event variables were then calculated as the difference in days between a person's index start date, and the earliest of: the event date; the censor date; the migration date; or, the death date (as defined in **Table 3-11**).

Table 3-11 Definitions of 'time-to-event' variables

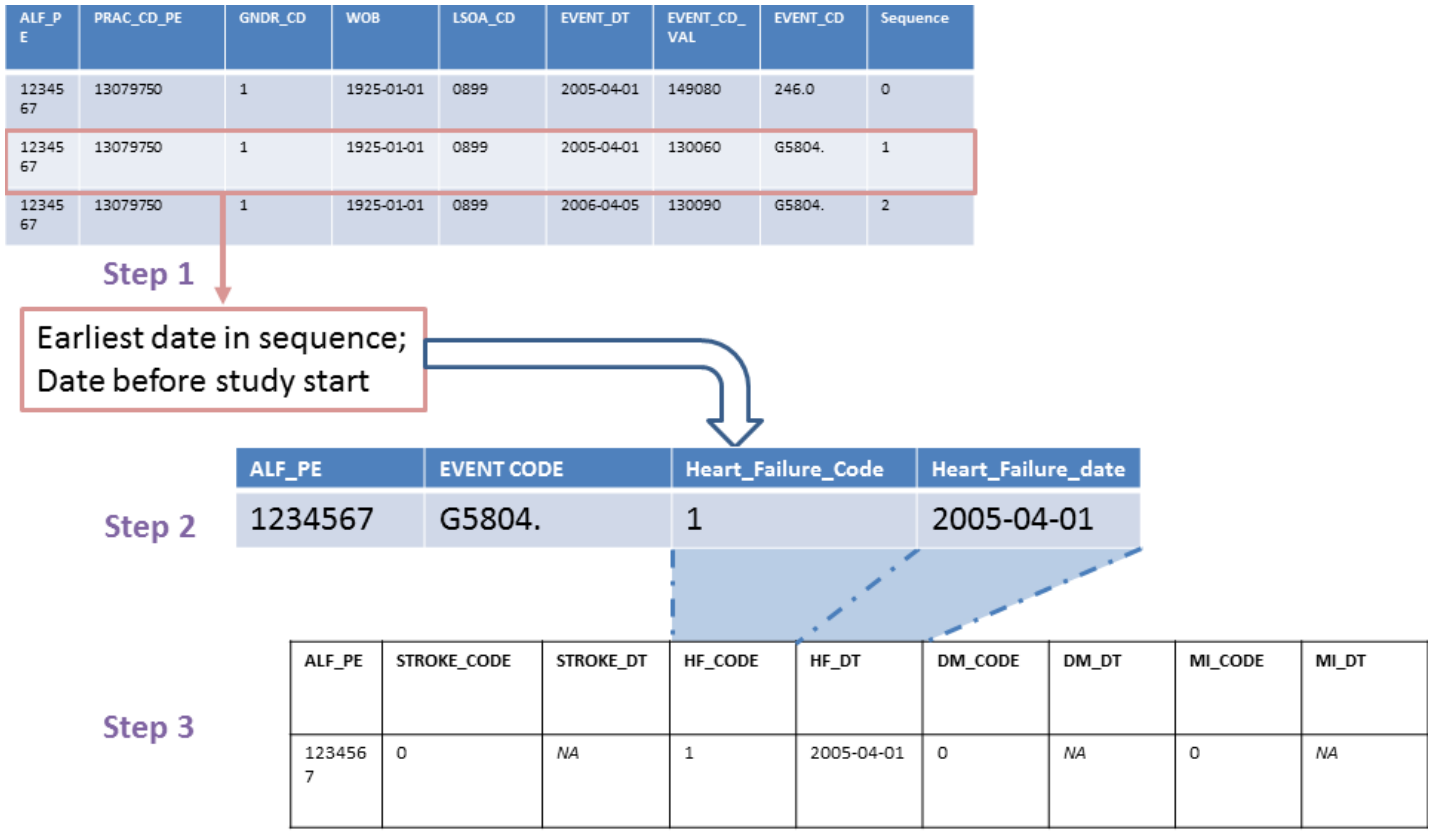
Date	Definition
Censor date	10 years after the study date;
Migration date	Move date, if predates death and censor dates, and post start date
Death date	Date of death, if predates censor, and post start date
Event dates	Date of event, if predates censor, migration and death dates

3.9.2.6 Transforming data from 'long format' to 'wide format'

Data were extracted from 'long format', that is lists of codes alongside dates and associated numerical variables with multiple rows per event and per patient, according to GP visit or hospital episode (396) (see **Figure 3-5**). Using the specified code lists, a specific diagnosis at a particular time point was extracted for each participant and entered into a dedicated table (Step 1). These new tables were created in 'wide format' data, so that each row represented an individual patient (Step 2). Each table represented only one variable with associated date stamps. These multiple relational tables were

linked using ALF_PE. All the tables were then combined per individual patient in an SQL data table (Step 3) and this table was exported for analysis to R .

Figure 3-5 Extracting Data from 'Long format' to 'Wide format'



The extraction of long format to wide is described using another illustrative example. Step 1 involves extracting from the WLGP database all event codes and their associated dates for the first diagnosis of heart failure between certain dates, using a series of heart failure codes. Step 2 involves collating all positive cases in a 'Heart Failure' table where each row represents one patient (a single ALF_PE). Step 3 combines variable tables (such as the heart failure table) with other diagnostic tables, for each patient. Where an ALF_PE is not represented in one of those tables, the corresponding column will be missing for that variable.

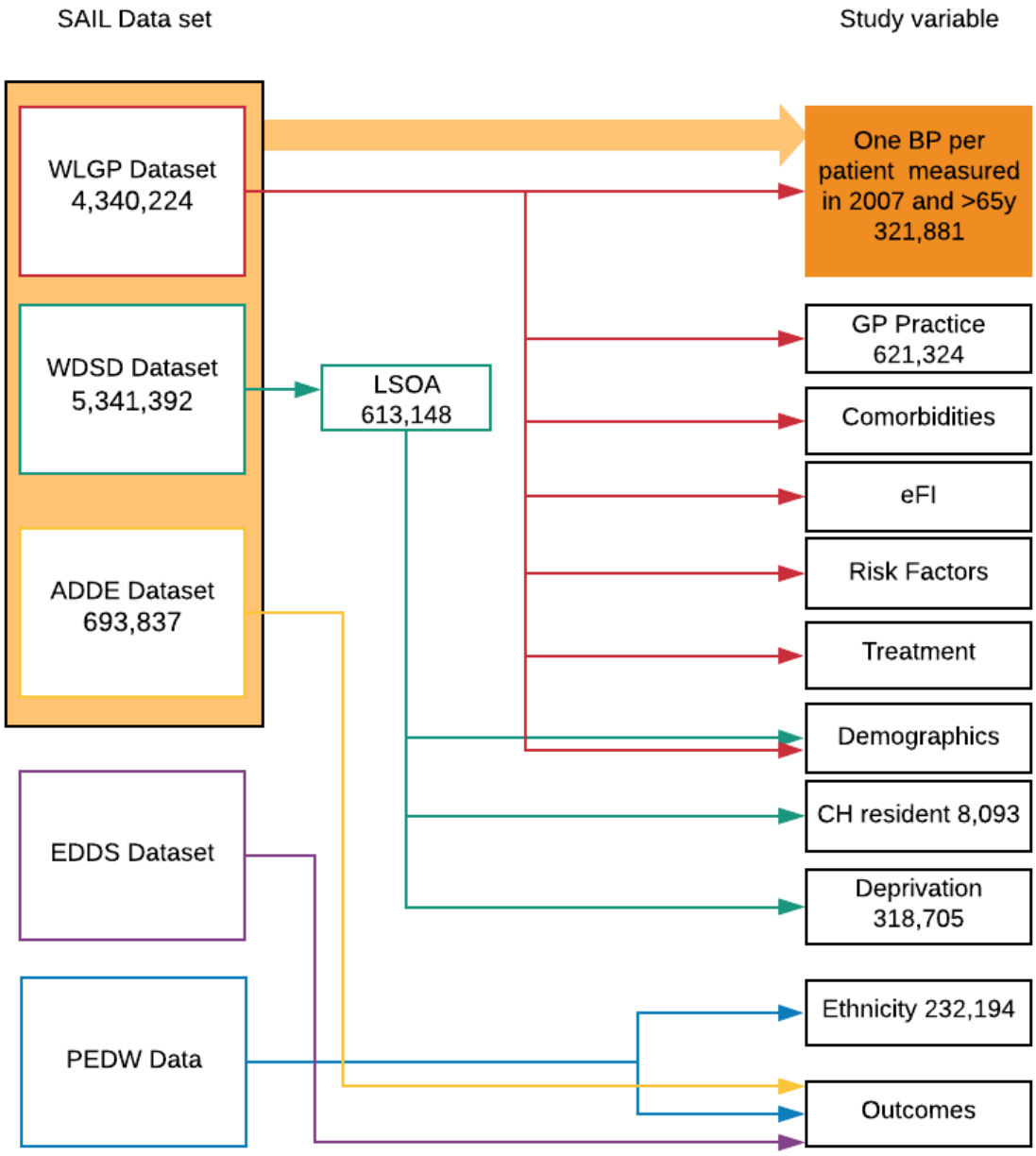
3.10 Statistical analysis

3.10.1 Deriving the study population

The study data set required the linkage of multiple data sets in SAIL, as described in **Figure 3-6**. The number of patients included at each stage of the study cohort derivation was summarised in a Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) diagram (**Figure 4-1**). This included the study cohort size:

- At initial data extraction;
- Following the application of exclusion criteria;
- Following assessment of data quality; and,
- At the end of follow-up, noting the numbers who died, migrated or dropped out.

Figure 3-6 Schematic describing linkage of core data sets within SAIL data extract



Schematic demonstrates on the left hand side: the core SAIL data sets from which the study data set extracted data for the study variables which are listed as groups on the right hand side. Linkage used the Anonymised Linkage Field (ALF) per individual, and for geographic information, and the Regional Anonymised Linkage Field (RALF) which indicated a person's address by Lower Super Output Area. Data sets: ADDE = Annual District Death Extract; EDDS = Emergency Department data set; PEDW = Patient Episode Data Wales; WDSD = Welsh Demographic Service Data set; WLGP = Welsh Longitudinal General Practice data set. Other abbreviations: CH = Care home eFI = electronic Frailty Index; GP = General Practitioner; LSOA = Lower Super Output Area.

3.10.2 Cohort description: the study population

The study population was summarised according to key demographics including age, sex, deprivation, care home residence, and ethnicity. Blood pressure; BP-lowering treatment; cardiovascular risk; and comorbidity status were characterised stratified by frailty status or baseline sBP. QRISK-3 was calculated where constituent data were available in the observed data set. Missing data were reported for each variable. Each parameter was checked for its distribution, whether normal or non-normal to determine whether respective parametric or non-parametric summary measures should be applied.

3.10.3 Missing data

Patients with complete data were anticipated to have a different health status and cardiovascular risk to those with missing data. However, it is also plausible these differences could be explained from the other factors measured, including other cardiovascular and clinical decision making covariates that are listed in **Section 3.8.6**. In this context and according to the guiding principles outlined in **Section 3.7.3**, missing data were assumed to be missing at random. Therefore, principle models were fitted on the basis of multiple imputation by chained equations with interaction (470-472).

A survival model was run using the observed data set to determine the quantity of observations excluded because of missing data. Each variable was named and characterised as: ordered categorical; non-ordered categorical; or,

continuous. All variables were treated as factors. Each variable was assessed for the level of missing data. Variables included in the prediction matrix included all components of the cardiovascular risk models. As an auxiliary variable, the number of attendances to primary care in the year preceding start date was added in.

All variables were included in the prediction matrix, and imputed with multiple imputations across 10 imputed data sets. All analyses were undertaken independently in each imputed data set before these were then combined according to Rubin's Rules (473). The **mice** algorithm in the statistical package R was used as described in **Section 3.7.3**. The imputations were then checked visually against the observed data using **stripplots** to ensure they were plausible.

3.10.4 Time to event analysis

The proportional hazards assumption was tested for each variable. The assumption states the hazards of different exposure groups remain constant over time, and that risk sets can be followed up until an event occurs and therefore hazards are proportional across time. Where variables are continuous they were dichotomised, with each proportional hazard plotted. The assumption of proportional hazards was tested, and if this assumption was not met, parametric models were deployed.

Parametric statistical methods rely on estimates of the distribution of the data (e.g. summary measures such as the mean and standard deviation). In contrast, non-parametric models do not make assumptions regarding the distributions of parameters. Instead they use ordinal measures to rank the order of observations (e.g. median and quartiles) (474).

Non parametric methods of modelling do not rely on estimates of the distribution of the data, but rely on assumptions that hazards are proportional throughout time (proportional hazards assumption). Parametric methods use different mathematical functions to estimate the baseline hazard function, to allow a hazard to be dependent on time. Models employing parametric methods are considered to be more robust as a result (475).

In flexible parametric models, the number of degrees of freedom or knots are estimated as the best fitting to model the baseline hazard (476). A visual inspection of function and comparisons to the non-parametric estimate, as well as measures Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) were used to determine the best fitting model.

AIC and BIC represent two methods of probabilistic model selection. The AIC was founded on Information theory which aims to quantify the amount of uncertainty in a random variable or outcome from a random process. The BIC is based on Bayesian theory whereby probability for a hypothesis is updated with information as the information becomes available. Although derived differently,

the AIC and BIC both give estimates of the amount of information lost in a model, the less information that is lost, the higher quality the model.

AIC and BIC estimate the likelihood of a model to predict future values using Maximum Likelihood Estimations, and both include a penalty for the complexity of the model (477). The absolute numbers calculated as AIC and BIC have no meaning in themselves, but the lower value across models indicates the best fitting model. Use of AIC and BIC rely on certain assumptions: that they are applied to models using equivalent data and outcomes; and that the sample is sufficiently large. Sufficiently large data has been estimated as the study number (n) where that has a ratio of at least 40 data points to each variable (477). All three assumptions were met in each of the applications of AIC and BIC in this analysis.

3.10.5 Non-linearity

Non-linear functions for nodes were considered for each of the continuous variables. Spline functions with 3, 4, and 5 knots for each variable were created and fitted to each in a Cox proportional hazards (semi-parametric) model. The linear predictors were saved using the locations recommended in methods established by Frank Harrell (478). Plots of functions were visually inspected, and model AIC and BIC statistics were calculated. The best fitting cubic spline was compared visually to the linear predictor, and used to represent that variable in the final model. The use of semi-parametric models is an accepted

method of model building, even when the final models used are parametric because of the proportional hazards assumption not being met.

3.10.6 Objective 2: What are the associations between BP and outcomes in this population?

3.10.6.1 Descriptive analysis

The number of events and the crude rates for events were calculated per 100 person years for all of major adverse cardiovascular events, for all-cause mortality and for injurious falls. Event rates were stratified according to category of systolic blood pressure and compared.

3.10.6.2 Definitive analysis

The association between systolic BP and all the outcomes measured was investigated, adjusted for known cardiovascular risk factors, BP-lowering treatment, and frequency of BP measurements at primary care. The hazard risk per sBP category for each of the primary and secondary outcomes was estimated in an unadjusted model and presented as Kaplan-Meier survival curves.

The estimates were then adjusted for known cardiovascular risk, the number of BP lowering medications and the frequency of primary care attendance. Comparisons were made to a central sBP category of 130 – 139 mm Hg. These

models were presented as forest plots for comparison of associations across different sBP categories for the three main outcomes.

3.10.7 Objective 3: Is frailty a relevant prognostic factor in the relationship between BP and outcomes?

3.10.7.1 Descriptive analysis

The number of events and the crude rates for events were calculated per 100 person years for all of primary and secondary outcomes stratified according to category of frailty and compared as forest plots. The hazard risk per frailty category for each of the primary and secondary outcomes was estimated in an unadjusted model and presented as Kaplan-Meier survival curves.

3.10.7.2 Definitive analysis

This study used methods to determine whether frailty is a prognostic factor in the management of hypertension. Specifically, it was assessed whether frailty presents additional risk in a model which included established risk factors for cardiovascular outcomes in the context of hypertension. The additional effect of eFI on the cardiovascular model performance was investigated following the addition of the eFI as a continuous variable based on improvement in model fit.

Measures of model fit and discrimination were assessed with and without frailty. In the event of a Cox model being used, measures of fit included the Wald

statistic, C-statistic (479) and D-statistic (480) compared using the DeLong comparison) and overall (R^2 (481)). In the event a parametric model was used, model fit was assessed using measures based on likelihood function, employing the AIC and BIC measures described earlier. In this analysis, variables in QRISK-3 were excluded if duplicated in the eFI (types I and II diabetes mellitus, hypertension, rheumatoid, SLE, renal failure).

3.10.8 Objective 4: Is blood pressure an effect modifier in any association between frailty and outcomes?

3.10.8.1 Descriptive analysis

The number of events and the crude rates for events were calculated per 100 person years for primary and secondary outcomes stratified according to category of frailty and baseline systolic blood pressure and compared as forest plots. The hazard risk per frailty category for each of the primary and secondary outcomes was estimated in an unadjusted model and presented as Kaplan-Meier survival curves.

3.10.8.2 Definitive analysis

The association of sBP and outcomes was measured in the context of frailty. Effect modification was assessed using two methods. Firstly, the relative hazards were examined for each systolic BP category in different sub-populations defined by frailty status to assess whether the association varied by frailty category. Secondly, a survival model was developed with the addition of

an interaction parameter to assess whether the effect of frailty is the same across different strata of systolic blood pressure. The model was tested with and without the interaction term, according to change in AIC and BIC measures of fit.

Effect modification was discerned as present:

- If the inclusion in the model of the interaction term led to a change in the point estimate of risk associated with BP;
- If the interaction term was significantly statistically associated with the outcome in the adjusted model; and,
- If the inclusion of the interaction term improved the model fit, defined by a significant Likelihood Ratio Test or a reduction in the AIC/ BIC measure.

This process was repeated for an interaction term between frailty and BP and frailty and BP-lowering treatment.

Sensitivity analyses were undertaken to assess whether the association of sBP and outcomes with different measures of frailty varied depending on subpopulation defined by sex.

3.10.9 Study size

The number of predictors in the model was estimated to be 55. This includes the 43 exposure and confounder variables plus an additional 10 for up to 10 non-linear terms for continuous variables, and 2 interaction terms on the outcome (sBP*frailty; treatment*frailty). To minimise overfitting of the model, a uniform heuristic shrinkage factor of >0.9 was estimated, so that overfitting is less than 10%. An overall mean risk of cardiovascular disease in this population is estimated to be at least 5% per annum (482). The model fit was pre-specified as measured by the Cox-Snell R^2_{adj} as 0.02193 informed by a recent study which tested a baseline cardiovascular model in a similar UK primary care population (482). My calculations used methods to estimate sample size for a multivariable prediction model for a time to event outcome (R package 'pmsampsize') (483). With an estimated mean follow up of 10 years, for estimates of risk at year 10, the minimum sample size was 16,617 participants. This corresponded to 11,631.9 person-years of follow-up with 686 outcome events per year, assuming an overall MACE event rate of 5.9% (95%CI 5.3%, 6.2%) estimating an event per predictor rate of 16.71. Given the prevalence of hypertension over 65 is estimated at more than 65% (484), I estimated the cohort size (145,598) was sufficiently powered to answer the research question described.

Chapter 4 Results

4.1 Summary

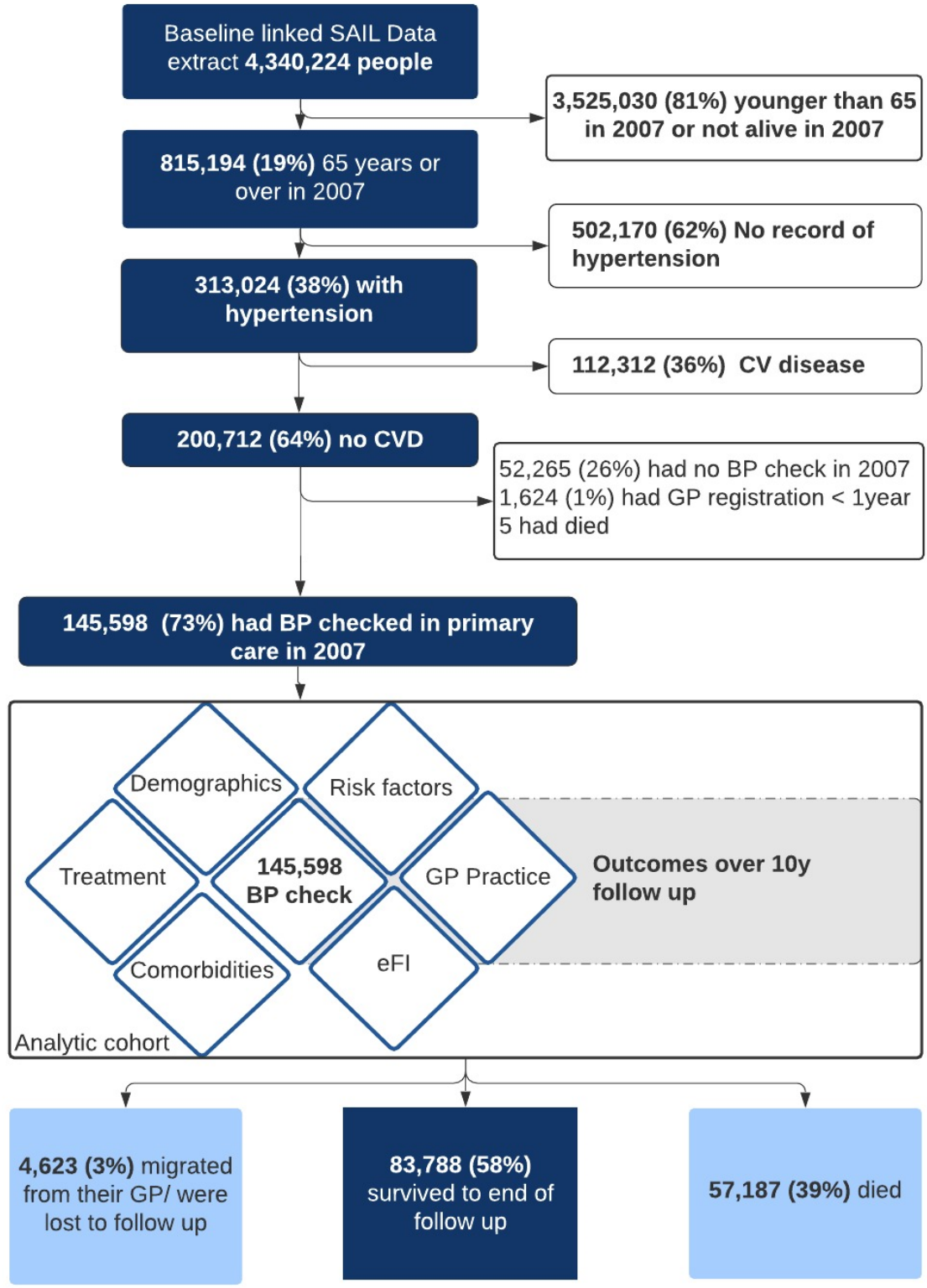
This chapter will present the results of the retrospective cohort study, the methods for which were outlined in Chapter 3. Detail is provided on how this study cohort was derived. Characteristics of the cohort are described with respect to systolic blood pressure, frailty and key demographic data. Findings that address three of this PhD study's objectives are presented. Firstly, associations of systolic blood pressure and outcomes in this routine data set are described. Secondly, evidence is presented that the measurement of frailty offers prognostic information for important cardiovascular and non-cardiovascular outcomes, in the context of hypertension management. Finally, it is demonstrated that the association of systolic blood pressure and outcomes is not significantly different in the context of frailty. Specifically frailty does not modify the effect of systolic blood pressure on outcomes. There is evidence however that frailty may modify the effect of BP-lowering treatment on outcomes. Sensitivity analysis demonstrated that these associations did not vary in men and women.

4.2 Study cohort derivation

The original data extract provided by SAIL consisted of 4,340,224 people in Wales (**Figure 4-1**). Following the exclusion of those who were under the age of 65 years at the start of 2008, this left 815,194 of whom 313,024 (38%) had a diagnosis of hypertension. From those with hypertension, people were excluded

with an established history of myocardial infarction, heart failure or stroke before study start, resulting in an analysis cohort including 200,712 individuals. Of this cohort, 73% had had their BP recorded in 2007 in primary care. There were 56,265 (27%) without a BP recording during this time period, 1,624 (1%) patients who had not been registered at their current general practitioner for more than 1 year at the time of BP measurement, and 3 patients who had died and were incorrectly in the database. Following the exclusion of these three groups, the study sample consisted of 145,598 individuals. During ten year follow-up: 4,623 (3%) migrated from the general practice to which they were registered; 57,187 (39%) died; and, 87,788 (58%) survived until the end of follow up.

Figure 4-1 STROBE flow diagram



Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) diagram to demonstrate the derivation of the study cohort.

4.2.1 Missing data

Ethnicity was recorded as one of the 17 NHS Wales ethnicity codes, of which 94,497 (64.9%) were coded ‘not declared’, and 12,902 (8.9)% were missing in this data set. Therefore ethnicity proportions were calculated of those with complete data which were available for 38,199 (26.2% of the cohort).

In the study cohort, the highest missing data was in QRISK-3 which was missing for 98,323 (69%) (**Table 4-1**). The QRISK-3 score was calculated from the raw derivative variables in the data set. Complete data is required for the calculation of a QRISK-3 score. Therefore a missing QRISK-3 is the result of missing of any of the 22 constituent factors contributing to the overall QRISK-3 score. Cholesterol: HDL was missing in 66,534 (46%); 5,409 (4%) had missing sBP variability measures; 4,470 (4%) had missing data for postcode meaning deprivation and care home residence were not possible to discern.

When stratified by frailty, it is evident that with advancing frailty, proportions with missing data were lower (**Table 4-1**). Those with missing data had lower frailty scores (mean eFI 0.13) compared to those with complete data (mean eFI 0.15) as shown in **Table 4-2**. Of those with missing data, fewer had diabetes mellitus type II and fewer were on treatment for hypertension.

Table 4-1 Summary of missing data according to variable and frailty status

Variable	Overall 145,598	Fit 72,744	Mild 58,747	Moderate 12,701	Severe 1,406
QRISK-3 n(%)	98,323 (69%)	52,813 (73%)	37,124 (63%)	7,562 (60%)	824 (59%)
Cholesterol: HDL Ratio n(%)	66,534 (46%)	34,885 (48%)	25,437 (43%)	5,589 (44%)	623 (44%)
Weight n(%)	42,329 (29%)	24,171 (33%)	14,905 (25%)	2,927 (23%)	326 (23%)
Height n(%)	10,864 (7%)	6,425 (9%)	3,672 (6%)	700 (6%)	67 (5%)
SBP variability n(%)	5,409 (4%)	4,448 (6%)	837 (1%)	116 (<1%)	<10 (<1%)
Ethnicity n (%)	12,902 (9%)	9,296 (13%)	3,150 (5%)	423 (3%)	33 (2%)
Smoking category	15,231 (10%)	9,073 (12%)	5,211 (9%)	872 (7%)	75 (5%)
Townsend score	4, 470 (3%)	2,245 (3%)	1,809 (3%)	377 (3%)	39 (3%)

Comparison of those with missing data overall and stratified by baseline frailty status, per key variable included in the analysis. Presented as raw numbers and as percentages of the total number in each sub-group. Abbreviations in the table: Chol: HDL = Cholesterol: high density lipoprotein ratio; SBP = systolic blood pressure

Table 4-2 Comparisons of populations with missing and with complete data

Variable	Missing data	Complete data
Frailty (eFI) Mean (SD)	0.129 (0.07)	0.148 (0.07)
Age n (%)	75 (7.3)	74 (6.3)
sBP mean (SD)	147 (17)	145 (16)
Female n (%)	64,693 (63)	27, 288 (59)
Townsend score n (%)	-0.433 (3.29)	-0.189 (3.17)
Never smoker n (%)	34,417 (34)	14,045 (31)
Diabetes mellitus II n (%)	10,058 (10)	13,660 (30)
FH CVD n (%)	20,072 (20)	11,672 (25)
CKD n (%)	11,691 (11)	6,608 (14)
BP-lowering treatment n (%)	83,382 (81)	41,860 (91)

Comparisons between the values of key variables in the sub-population with missing data, compared to the sub-population with complete data. Abbreviations used in the table: CKD = chronic kidney disease; eFI= electronic frailty index; FH CVD = family history of cardiovascular disease; n = number; SD = standard deviation;

4.3 Descriptive analysis

The analytic cohort included 145,598 patients who had had their BP recorded between 1st January 2007 and 1st January 2008 and were followed up for a median follow up period of 10 years. Patients were registered at a total of 502 GP practices/practice codes, each with median 380 patients per practice (IQR 94, 695) included in this study cohort.

The mean age was 74.6 years (SD 7.10) (**Table 4-3**). Average age increased with advancing frailty status: in those who were fit, mean age was 72.9 years

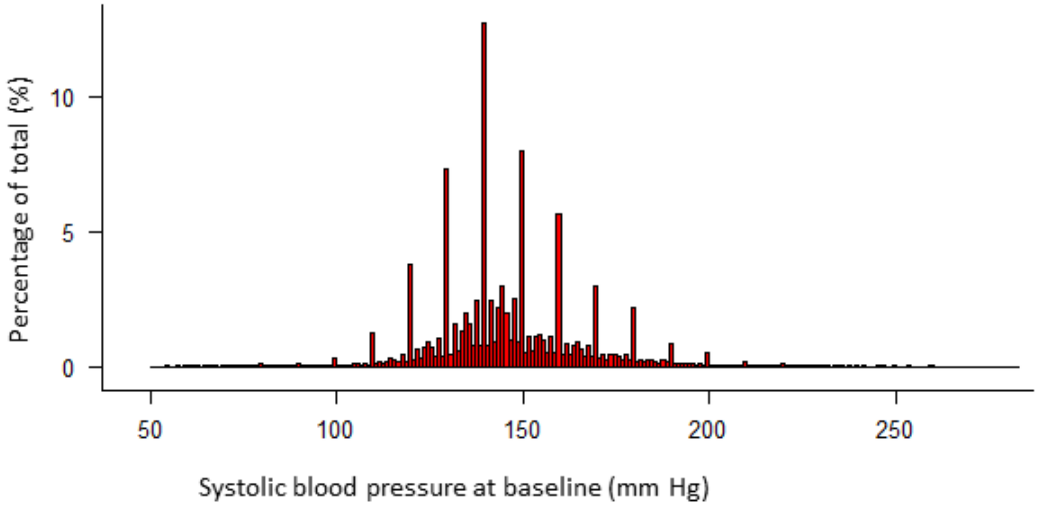
(SD 6.36), increasing to those who had severe frailty in whom the mean age was 81.5 years (SD 7.15). Overall, 61.9% of the study cohort were female: in those who were fit, 56.5% were female; this increased with frailty; in those with severe frailty, 81.3% were female. In this cohort, the least deprived quintile was not represented as well as in the general population (16.8% compared to 20%). However, with advancing frailty, those in the most deprived quintile increased as a proportion overall: in those who were fit, 14.1% were in the most deprived quintile; and, in those with severe frailty, 18.2% were in the most deprived quintile.

Cardiovascular risk was high in this cohort, with a median QRISK-3 score of 29.3 (IQR 21.1 – 39.1), which is a prediction of a cardiovascular event in that individual over the next 10 years. However, it was only possible to measure a QRISK-3 score in 47,275 (32.5%) of participants at baseline because of missing data among any of the constituent variables. 46,741 (98.9%) of those patients in whom a QRISK-3 score was measurable had a QRISK-3 score of higher than 10%. In the overall cohort the mean BMI was 28.1 kg/m^2 which is defined as overweight, 31,744 (21.4%) had a family history of cardiovascular disease, 62,229 (42.7%) were ex-smokers, and 58,038 (39.9%) were prescribed statins in the past 2 years. Mean Chol: HDL level ratio was 3.4 (IQR 2.8, 4.1).

4.3.1 Characterising systolic blood pressure

Systolic BP recorded in primary care in 2007 demonstrated three patterns (**Figure 4-2**)**.** Of the sBP recordings measured at baseline, 67,204 (46%) ended in 0, 80,527 (55%) of readings ended in 0 or 5; 117,861 (81%) end in an even number. The distribution of these three sBP patterns remain broadly similar, although there is greater asymmetry of numbers ending in even numbers after the population BP mean.

Figure 4-2 Frequency historgram of systolic blood pressure readings



Histogram presenting all baseline systolic blood pressure (sBP) readings by 1 mm Hg intervals: tallest bars represent systolic blood pressure readings ending with zero, thereafter readings ending with even numbers or 5 are most frequent.

Average systolic BP (sBP) in the study sample was 146 mm Hg (SD 19.2), and diastolic BP (dBP) 81 mm Hg (SD 11.0) (**Table 4-4**). The majority, 113,129 (78%) of participants had an sBP and dBP in keeping with NICE guideline

targets. On average, each participant was prescribed 2 classes of BP-lowering medications: 48% were on an ACEi/ ARB, 26% on beta-blockers, 37% on calcium channel blockers, and 52% on diuretics. The median interval between BP measures was more than 3 months, 103 days (IQR 28, 211).

4.3.2 Characterising frailty

Summary descriptive characteristics of the patient cohort, which are stratified by baseline frailty status, are presented in **Table 4-3**. In the study cohort as a whole, the median eFI was 0.139 (IQR: 0.083 to 0.167), mean 0.135 (SD 0.075, range 0 to 0.611), which both represent the equivalent of 5 out of 36 deficits, which would be categorised as mild frailty. In women, frailty was higher than men on overage: in women, median eFI was 0.139 (IQR, 0.083, 0.194), in men, 0.111 (0.083, 0.167). The eFI increased by 0.003 (95% CI 0.003 to 0.004) with every year older a person was at study baseline. Each 0.05 increase of eFI was associated with an increased risk of major adverse cardiovascular events (MACE) HR 1.12 (95% CI 1.11,1.13), adjusted HR 1.07 (95%CI 1.05, 1.09); all-cause mortality, HR 1.31 (95% CI 1.29, 1.33), adjusted HR 1.15 (95% CI 1.12, 1.17); and, injurious falls HR 1.37 (95% CI 1.34, 1.39), adjusted HR 1.14 (95% CI 1.12, 1.71).

Table 4-3 Descriptive table stratified by frailty status: demographics

	Frailty status		*Overall*	*Missing*	Fit	Mild	Moderate	Severe
	Number of participants		145,598		72,744 (50%)	58,747 (40%)	12,701 (9%)	1,406 (1%)
Demographics	Age, mean (SD)		74.6 (7.10)	-	72.9 (6.36)	75.7 (7.19)	78.9 (7.47)	81.5 (7.15)
	Women, n (%)		90,053 (62%)	-	41,065 (57%)	38,462 (66%)	9,383 (74%)	1,143 (81%)
	Deprivation	1) Most n (%) 2) n (%) 3) n (%) 4) n (%) 5) Least n (%)	24, 890 (17%) 29, 831 (20%) 31, 684 (21%) 28, 382 (19%) 32, 237 (22%)	*4, 470 (3%)*	10, 244 (14%) 14, 623 (20%) 14, 045 (19%) 15, 571 (21%) 16, 016 (22%)	9, 795 (17%) 11, 945 (20%) 11, 483 (20%) 12,045 (21%) 11, 670 UL(20%)	2, 321 (18%) 2, 570 (20%) 2, 491 (20%) 2, 555 (20%) 2, 387 (19%)	256 (18%) 296 (21%) 266 (19%) 260 (19%) 289 (21%)
	CH resident, n (%)		2,035 (1%)		278 (<0.5%)	955 (2%)	645 (5%)	157 (11%)
	White ethnicity n(%) excluding not stated: *94,497 (65%)*		37,496 (98%)	*12,902 (9%)*	16,035 (98%)	16,746 (98%)	4,209 (98%)	506 (98%)

Abbreviations: CH = care home; n = number; SD = standard deviation

Table 4-4 Descriptive Table stratified by frailty status: blood pressure

	Frailty status	*Overall*	*Missing*	Fit	Mild	Moderate	Severe
	Number of participants	145,598		72,744 (50%)	58,747 (40%)	12,701 (9%)	1,406 (1%)
Blood pressure	sBP mm Hg, mean (SD)	146 (19.2)	-	148 (19.1)	145 (19.4)	143 (20.4)	141 (20.9)
	dBP mm Hg, mean (SD)	81 (11.0)	*529 (<0.5)*	83 (10.7)	80 (10.8)	78 (11.1)	76 (11.4)
	MAP, mean (SD)	103 (12.0)		104 (11.9)	101 (11.8)	99 (12.3)	98 (12.9)
	PP, mean (SD)	66 (16.1)		66 (15.6)	66 (16.5)	66 (17.3)	65 (17.2)
	sBP SD median (IQR)	7.78 (3.54, 14.1)	*5,409 (4)*	7.07 (3.54, 13.4)	7.78 (3.54, 14.1)	8.49 (3.54, 14.8)	9.19 (4.24, 15.6)
	BP on target (NICE), n (%)	113,129 (78)	-	52,369 (72)	48,459 (83)	11,037 (87)	1,264 (90)
	ACEi/ ARB, n (%)	70,234 (48)	-	30,076 (41)	31,891 (54)	7,461 (59)	806 (57)
	Beta blockers, n (%)	38,094 (26)	-	19,547 (27)	15,339 (26)	2,882 (23)	326 (23)
	CCB, n (%)	53,568 (37)	-	24,561 (34)	23,511 (40)	4,969 (39)	527 (38)
	Diuretic, n (%)	75,646 (52)	-	34,145 (47)	32,879 (56)	7,734 (61)	888 (63)
	Treatment #, mean (SD)	1.75 (1.13)	-	1.58 (1.12)	1.91 (1.11)	1.99 (1.13)	2.01 (1.19)
	BP interval, median (IQR)	103 (28, 211)	*2,732 (2)*	109 (28, 226)	99 (29, 200)	91 (29, 178)	84 (29, 178)
	# BP in 2yr, median (IQR)	5 (3, 9)	-	5 (3, 8)	6 (4, 9)	7 (4, 10)	7 (4, 11)

Abbreviations: ACEi = Angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; dBP = diastolic blood pressure; IQR = inter-quartile range; MAP = mean arterial blood pressure; n = number; NICE = National Institute for Health and Care Excellence; PP = pulse pressure; sBP = systolic blood pressure; SD = standard deviation; yr = year;#=count.

Table 4-5 Descriptive table stratified by frailty status: cardiovascular risk

	Frailty status	*Overall*	*Missing*	Fit	Mild	Moderate	Severe
	Number of participants	145,598		72,744 (50%)	58,747 (40%)	12,701 (9%)	1,406 (1%)
Cardiovascular risk	QRISK-3, median (IQR)	29.3 (21.1, 39.1)	98,323 (68%)	24.6 (18.3, 32.6)	31.3 (23.2, 40.9)	38.5 (29.4, 49.3)	43.6 (34.2, 56.8)
	Chol: HDL ratio, median (IQR)	3.4 (2.8, 4.1)	66,534 (46%)	3.5 (2.8, 4.2)	3.3 (2.7, 4.1)	3.2 (2.6, 4.0)	3.2 (2.6, 3.9)
	Statins, n (%)	58,038 (40)	-	25,451 (35)	26,087 (44)	5,838 (46)	662 (47)
	BMI (kg/m^2), mean (SD)	28.1 (5.26)	48,061 (33%)	27.9 (4.87)	28.3 (5.47)	28.2 (6.00)	27.6 (6.02)
	FH of CVD, n (%)	31, 744 (21)	-	15,103 (21)	13,074 (22)	2,805 (22)	311 (22)
	Never-smoker, n (%)	55,738 (38)	15,231 (10%)	28,543 (40)	21,972 (37)	4,709 (37)	514 (37)
	Ex-smoker, n (%)	62,229 (43)		28,994 (40)	26,530 (45)	6,004 (47)	701 (50)
	Light smoker, n (%)	3,895 (3)		1,955 (3)	1,546 (3)	355 (3)	39 (3)
	Moderate smoker, n (%)	5,204 (4)		2,564 (4)	2,133(4)	464 (4)	43 (3)
	Heavy smoker, n (%)	3,301 (2)		1,615 (2)	1,355 (2)	297 (2)	34 (2)

Abbreviations: BMI = body mass index; FH of CVD = family history of cardiovascular disease; Chol: HDL = Cholesterol: high density lipoprotein ratio; IQR = inter-quartile range; kg/m^2 = kilograms per metre squared.

When frailty was categorised in the study population: 72,744 (50%) were fit; 58,747 (40%) had mild frailty; 12,701 (9%) had moderate frailty; and 1,406 (1%) had severe frailty. The proportion of the population living in a care home increased with greater frailty status (see **Table 4-3**). In the study cohort as a whole, 2,035 (1.4%) were living in a care home: as a proportion, this increased from 0.4% in those who were fit; 1.6% in those with mild frailty; 5.1% with moderate frailty; and 11.2% with severe frailty.

4.3.3 Baseline systolic blood pressure in the context of baseline frailty

In the study population overall, with advancing frailty category, systolic BP was lower. There was a 7 mm Hg difference in mean systolic BP and in mean diastolic BP between those who were fit and those with severe frailty: in fit, mean 148 / 83 mm Hg; in severe frailty, mean 141 / 76 mm Hg (**Table 4-4**). Consistent with these findings, mean arterial pressure fell from a mean, in those who were fit, of 104 mm Hg, to a mean in those with severe frailty, of 98 mm Hg. There was no difference in pulse pressure between the groups. Variability in sBP between readings increased with advancing frailty: median SD 7.07 in those who were fit; 7.78 with mild frailty; 8.49 moderate frailty; 9.19 in severe frailty.

The treatment count was not different between groups defined by baseline frailty. Proportions of participants prescribed ACEi/ ARB and diuretics increased with frailty (**Table 4-4**). Proportions prescribed beta-blockers and calcium

channel blockers were less marked in their difference by frailty status. The interval between BP measurements was 25 days shorter in those with severe frailty (median interval 84 days) compared to those who were fit (median interval 109 days). However there was a high degree of variation with wide inter-quartile ranges for BP intervals in all categories of baseline frailty. The proportion of people on target according to NICE guidelines for their age, increased with advancing frailty: from 52,369 (72%) of those who were fit; 48,459 (82.5%) with mild frailty; 11,037 (86.9%) with moderate frailty; and 1,264 (89.9%) who had severe frailty.

Cardiovascular risk increased markedly according to frailty category, as measured by QRISK-3 (**Table 4-3**). In those who were fit, median QRISK-3 score was 24.6%; mild frailty, 31.3%; moderate frailty, 38.5% ; and, severe frailty, 43.6%. There were not significant differences between groups conditional on baseline frailty in terms of: Cholesterol: HDL ratio, BMI, family history of cardiovascular disease and smoking history (**Table 4-7**). However, statin prescription increased with frailty: in those who were fit, 35% were prescribed a statin; mild frailty, 44.4%; moderate frailty, 46%; severe frailty 47.1%.

Inclusive of hypertension, 98,381 participants (67.6%) had multi-morbidity, where multi-morbidity is defined as having two or more long-term conditions. The number of co-morbidities in addition to hypertension ranged between 0-10 per person (**Figure 4-3**). Across baseline systolic BP, the median count of comorbidities did not vary conditional on sBP category (see **Table 4-8**). The sub-population defined by sBP < 120 mm Hg had higher proportions with co-

morbidity. The differences with other sBP categories were particularly evident in the frequency of type II diabetes, and dementia. The highest proportion of those who had moderate or severe frailty was among those with the lowest systolic BP: with an sBP < 120 mm Hg: 2,248 (38.3%) were fit; 2,984(46.9%) had mild frailty; 984 (15.4%) had moderate frailty; and, 153 (2.4%) had severe frailty. A higher proportion of those with sBP < 120 mm Hg were care home residents and lived with higher deprivation compared to those with higher baseline sBP (see **Table 4-6**).

Figure 4-3 Count of comorbidities per person (in addition to hypertension), n=145,598

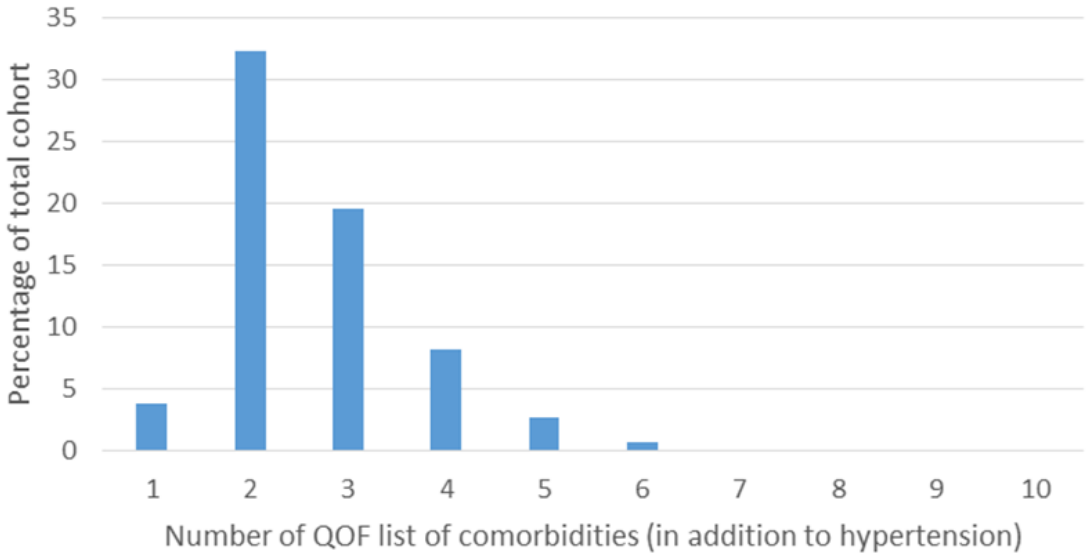


Table 4-6 Descriptive table stratified by systolic blood pressure: demographics

sBP category	Overall	<120	120-129	130-139	140-149	150-159	160-169	170-179	180 <
Participants, n (%)	145,598 (100)	6,369 (4)	13,130 (9)	27,057 (19)	41,180 (28)	22,589 (15)	16,156 (11)	8,975 (6)	10,1642 (7)
Age, mean (SD)	74.6 (7.10)	76.1 (7.87)	74.7 (7.37)	74.4 (6.93)	74.4 6.93)	74.4 (6.98)	74.6 (7.01)	74.8 (7.09)	75.7 (7.33)
Women, n (%)	90,053 (62)	3,902 (61)	8,090 (62)	16,283 (60)	25,173 (61)	13,888 (62)	10,102 (63)	5,675 (63)	6,940 (68)
Deprivation									
1) Most n (%)	22,616 (16)	1,094 (17)	2,163 (17)	4,261 (16)	6,246 (15)	3,415 (15)	2,416 (15)	1,434 (16)	1,587 (16)
2) n (%)	29,434 (20)	1,327 (21)	2,594 (20)	5,339 (20)	8,224 (20)	4,591 (20)	3,309 (21)	1,852 (21)	2,198 (22)
3) n (%)	28,285 (19)	1,269 (20)	2,585 (20)	5,206 (19)	8,062 (20)	4,397 (20)	3,089 (19)	1,729 (19)	1,948 (19)
4) n (%)	30,431 (21)	1,335(21)	2,674 (20)	5,556 (21)	8,763 (21)	4,726 (21)	3,377 (21)	1,882 (21)	2,118 (21)
5) Least n (%)	30,362 (21)	1,170 (18)	2,717 (21)	5,839 (22)	8,674 (21)	4,742 (21)	3,469 (22)	1,772 (20)	1,979 (20)
CH resident, n (%)	2, 035 (1)	410 (6)	354 (3)	418 (2)	404 (1)	174 (1)	117 (1)	78 (1)	80 (1)

Abbreviations: CH = care home; n = number; SD = standard deviation

Table 4-7 Descriptive table stratified by systolic blood pressure: cardiovascular risk

sBP category	Overall	<120	120-129	130-139	140-149	150-159	160-169	170-179	180 <
Participants, n (%)	145,598 (100)	6,369 (4)	13,130 (9)	27,057 (19)	41,180 (28)	22,589 (15)	16,156 (11)	8,975 (6)	10,1642 (7)
QRISK-3 median (IQR)	29.1 (21.1, 39.1)	26.6 (18.8, 36.6)	26.2 (18.7, 35.5)	27.3 (19.6, 36.7)	27.8 (20.2, 37.1)	29.6 (21.5, 39.2)	31.8 (23.8, 41.6)	34.5 (25.7, 44.8)	39.8 (30.2, 51.5)
sBP SD median (IQR)	7.78 (3.54, 14.1)	18.4 (11.3, 26.2)	10.6 (5.66, 16.3)	7.07 (2.83, 12.0)	4.95 (2.12, 9.19)	5.66 (2.83, 9.90)	8.49 (4.24, 14.1)	13.4 (7.78, 19.8)	21.2 (14.1, 29.0)
Chol: HDL median (IQR)	3.40 (2.78, 4.14)	3.30 (2.70, 4.10)	3.30 (2.70, 4.05)	3.35 (2.72, 4.10)	3.40 (2.80, 4.14)	3.40 (2.80, 4.17)	3.41 (2.80, 4.20)	3.48 (2.82, 4.23)	3.48 (2.80, 4.30)
BMI, mean (SD)	28.1 (5.26)	27.2 (5.40)	27.8 (5.32)	28.1 (5.21)	28.2 (5.20)	28.2 (5.28)	28.2 (5.24)	28.0 (5.37)	27.9 (5.40)
Never-smoker, n (%)	48,462 (33)	2,437 (38)	5,011 (38)	10,186 (38)	15,593 (38)	8,609 (38.1)	6,355 (39)	3,519 (39)	4,028 40)

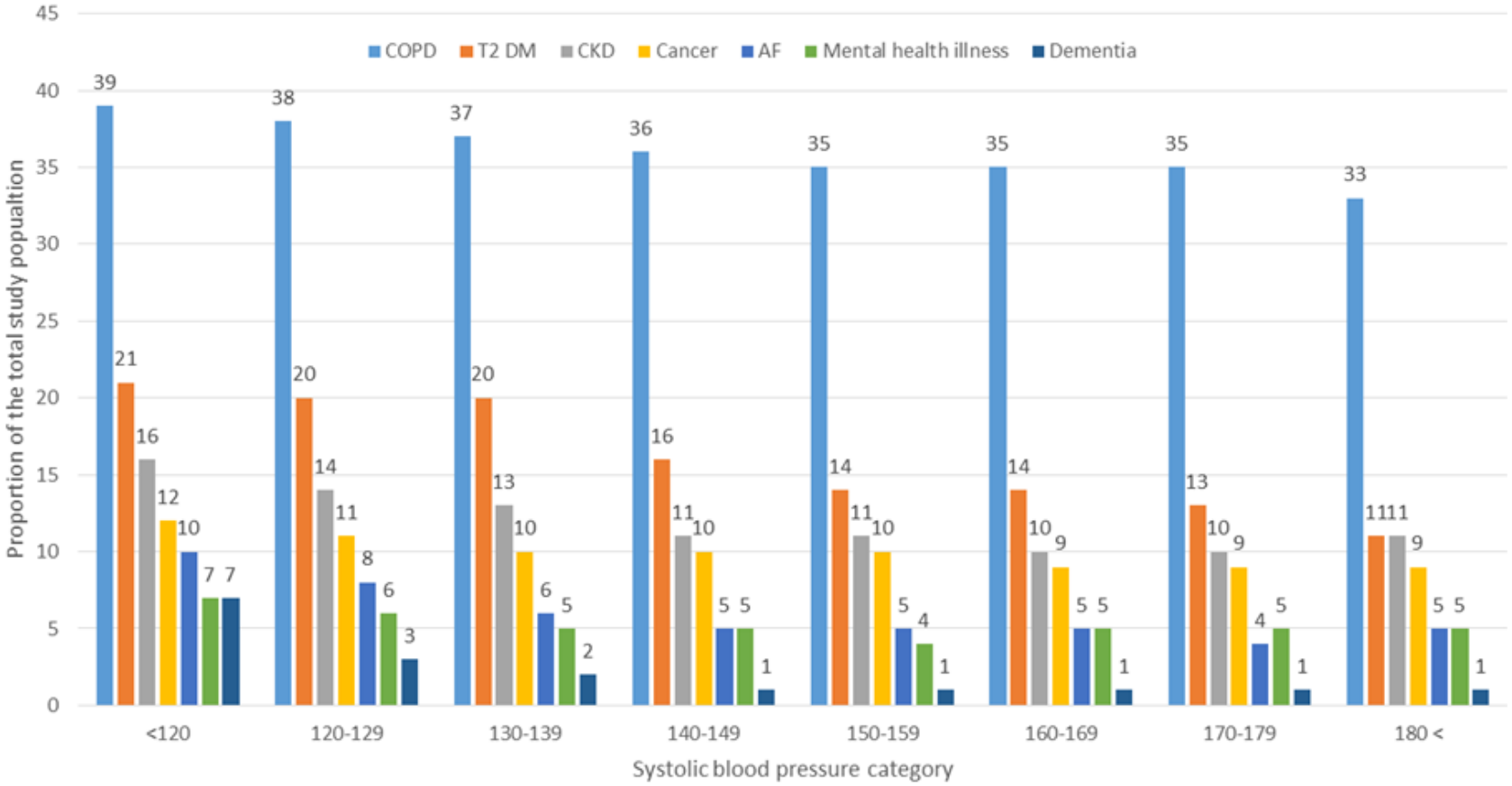
Abbreviations: BMI = body mass index; Chol: HDL = Cholesterol: high density lipoprotein ratio; IQR = inter-quartile range; n = number; sBP = systolic blood pressure; SD = standard deviation.

Table 4-8 Descriptive table stratified by systolic blood pressure: frailty and comorbidity

sBP category	Overall	<120	120-129	130-139	140-149	150-159	160-169	170-179	180 <
Participants, n (%)	145,598 (100)	6,369 (4)	13,130 (9)	27,057 (19)	41,180 (28)	22,589 (15)	16,156 (11)	8,975 (6)	10,1642 (7)
Fit, n (%)	72,744 (50)	2,248 (35)	5,536 (42)	12,535 (46)	21,093 (51)	12,022 (53)	8,750 (54)	4,998 (56)	5,562 (55)
Mild n (%)	58,747 (40)	2,984 (47)	5,881 (45)	11,585 (43)	16,461 (40)	8,749 (39)	6,093 (38)	3,258 (36)	3,736 (37)
Moderate, n (%)	12,701 (9)	984 (15)	1,519 (12)	2,633 (10)	3,304 (8)	1,645 (7)	1,197 (7)	650 (7)	769 (8)
Severe, n (%)	1,406 (1)	153 (2)	194 (2)	304 (1)	322 (1)	173 (1)	116 (1)	69 (1)	75 (1)
QOF median (IQR)	2 (1,3)	2 (2,3)	2 (1,3)	2 (1,3)	2 (1,3)	2 (1,3)	2 (1,3)	2 (1,3)	2 (1,3)

Abbreviations: n = number; QOF = comorbidity count according to those listed in the quality outcomes framework, * count includes the number co-morbidities in addition to hypertension disease.

Figure 4-4 Past history of comorbidity according to baseline categorised systolic blood pressure



This histogram demonstrates the baseline prevalence in participants past medical histories of important co-morbidities according to baseline systolic blood pressure. Co-morbidities are in order of prevalence for each sBP category with numbers representing the count of participants as a proportion of the whole population, n=145,598. **Abbreviations:** AF = atrial fibrillation; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; T2 DM = type II diabetes mellitus.

4.3.4 Characterising outcomes

Overall in this population over the age of 65 years with hypertension, 41,501 (28.5%) experienced major adverse cardiovascular events during a median follow up time of 1,162,286 person years. In those who sustained a MACE event, the event consisted of: 22,394 (15.4%) myocardial infarctions, 16,186 (11.1%) new diagnoses of heart failure; 9,192 (6.3%) stroke events, and 2,934 (2.0%) deaths specifically from cardiovascular disease.

Cardiovascular outcomes increased with frailty: of those who were fit, 17,193 (23.6%) had a MACE event; with mild frailty, 18,775 (32.0%); with moderate frailty, 4,940 (38.9%); and, those with severe frailty, 593 (42.2%). These 10 year event rates as a proportion of sub-populations defined by frailty status, are consistent with the QRISK-3 predictions which were in those who were fit, 24.6%, with mild frailty, 31.3%; moderate frailty, 38.5%, and severe frailty 43.6%.

For those developing an outcome during the 10 year period of follow up, median age at the time of myocardial infarction, 79 years (IQR 74 to 84 years); first stroke, 83 (IQR 77 to 87 years), new heart failure was 83 years (IQR 78 to 88 years), cardiovascular death, 86 (IQR 82 to 91 years); death of any cause, 85 years (IQR 79 to 90 years); injurious falls, 84 years (IQR 79 to 88 years), new care home admission 86 years (IQR 82 to 91 years).

Overall, 57,157(39.2%) died from any cause (**Figure 4-1**). Stratified by frailty: this included 21,301 (29.3%) deaths among those who were fit; 26,520 (45.1%) deaths with mild frailty; 8,227 (64.8%) deaths with moderate frailty; 1,119 (79.6%) deaths with severe frailty.

Overall, 33,311 (22.9%), sustained falls resulting in admission to hospital. Stratified by frailty, this included 12,602 falls (17.3%) among those who were fit; 15,756 (26.8%), falls with mild frailty; 5,163 (40.7%) falls with moderate frailty; and, 557 (39.6%) falls with severe frailty.

Descriptive outcome counts and proportions for the study population overall throughout 10 year follow up were as follows:

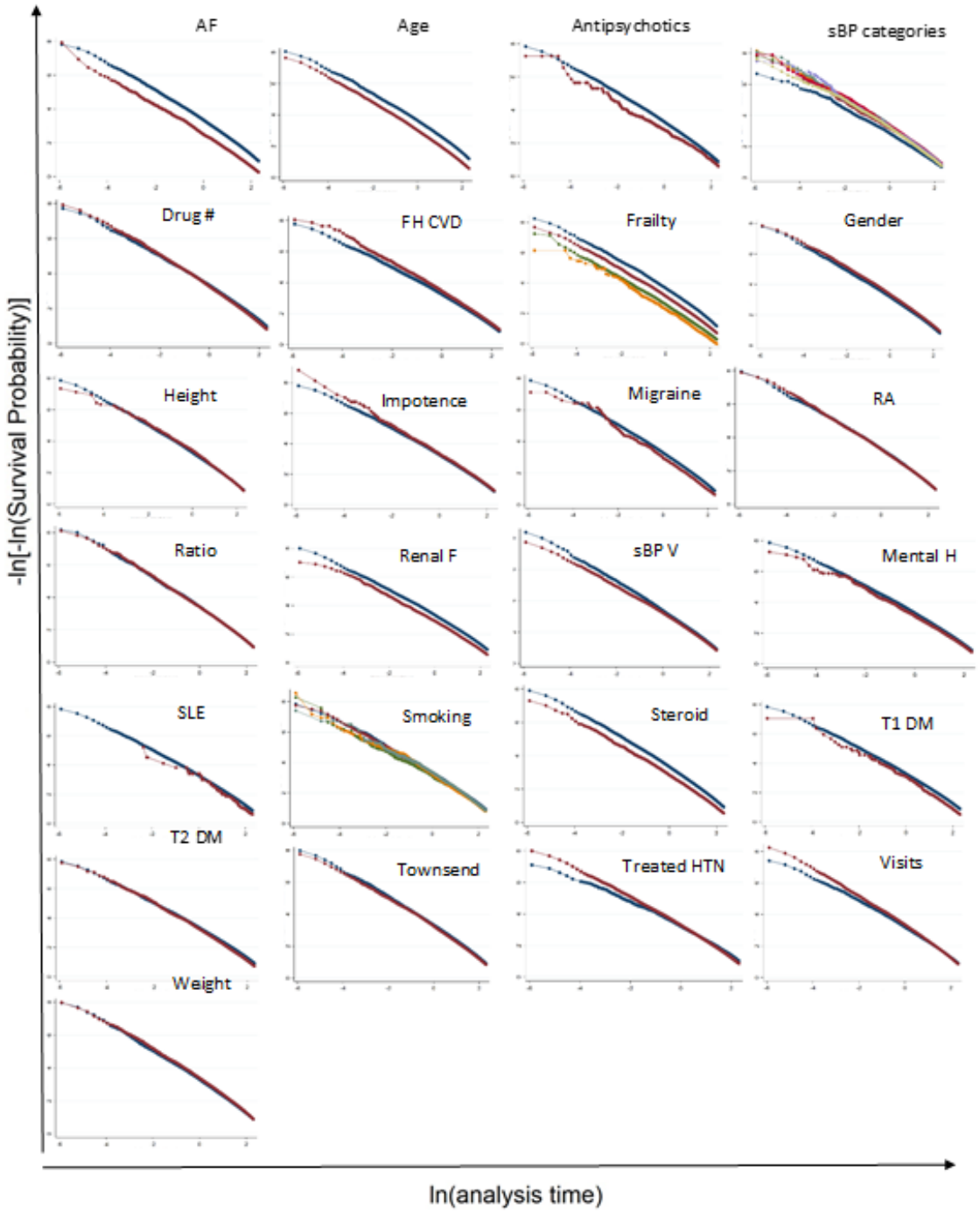
- 97,635 (67.1%) were admitted to hospital;
- 22,666 (15.6%) were admitted to hospital with hypotension;
- 14,969 (10.3%) were admitted to hospital with acute kidney injury;
- 11,445 (7.9%) were admitted to hospital with electrolyte disturbance.
- 3,733 (2.6%) had a hospital stay complicated by or because of urinary incontinence.
- 2,139 (1.5%) had delirium as a cause for presentation or developed during hospital admission;
- 16,827 (11.6%) had a hospital stay indicated by or causing functional dependence which required inpatient rehabilitation.
- 13,453 (9.2%) were newly admitted to a care home

- 12,528 (8.6%) developed dementia as recorded in primary or secondary care;

4.3.5 Model development

In the development of the model, each variable was tested for proportional hazards (**Figure 4-5)**. It is evident that the proportional hazards assumption could not be met for sBP categories, BP-lowering medications, family history of cardiovascular disease; rheumatoid arthritis, SLE, smoking categories and type I diabetes mellitus. Given the proportional hazards assumption was not met, flexible parametric models were used. Initially the model was developed with complete cases only before introducing imputed data into the models. The model development was undertaken separately for the primary and each of the secondary outcomes. The best fitting model using 3, 4 and 5 degrees of freedom, was tested by visual inspection and by comparing the AIC and BIC likelihood estimates. Thereafter each continuous variable was included individually as a linear and a non-linear term, and as a non-linear term using 3,4, and 5 restricted cubic splines. Spline functions were plotted and likelihood estimates measured and compared to find the best fitting measure of the non-linear, and three different splines. This was undertaken for all of the continuous variables included in the models including: age; systolic BP; weight; height; Cholesterol: HDL ratio; number of GP attendances; count of medications; systolic BP variability; electronic frailty index; and Townsend score for deprivation. The best fitting splines for each were then included in the models developed.

Figure 4-5 Test of each variable to check for proportional hazards



AF = atrial fibrillation; Antipsychotics = atypical antipsychotics; sBP categories = systolic blood pressure categories; Drug # = BP-lowering medication count ; FH CVD = family history of cardiovascular disease; RA = rheumatoid arthritis; Ratio = Cholesterol: HDL ratio; Renal F = chronic renal failure; sBP categories = systolic BP categories; sBP V = systolic BP variability; Mental H = severe mental health illness; SLE = systemic lupus erythematosus; T1 DM = type I diabetes mellitus; T2 DM = type II diabetes mellitus; Townsend = Townsend score of deprivation; Treated HTN = treated hypertension category; Visits = number of GP visits at which BP was measured.; ln = logarithm.

4.4 Objective 2: what are the associations of sBP and outcomes in this data set?

4.4.1 Rates of primary outcome events per sBP category

4.4.1.1 Major adverse cardiovascular events (MACE)

In the population overall, the rate per 100 person years of developing a MACE outcomes was 4.0 (95% CI 4.0 – 4.0) (**Figure 4-6**, in red). According to baseline sBP, rates demonstrated a U-shaped association: with a peak at sBP < 120 mm Hg, 5.0 (95% CI 4.8 – 5.3); nadir at 140 to 159 mm Hg, 3.9 events (95% CI 3.8 – 4.0); and a second peak at 160 mm Hg, 4.5 events (95% CI 4.3 – 4.6).

The association varied between constituent MACE outcomes. For myocardial infarction, the rate per 100 person years in the population overall was 2.1 (95% CI 2.1 – 2.1), and the pattern of association stratified by sBP was modestly J-shaped (**Figure 4-7**, in red). For new diagnosis of heart failure, the rate per 100 person years in the population overall was 1.4 (95% CI 1.4 – 1.5), and the pattern was more U-shaped with a nadir of risk at sBP 140 – 150 mm Hg (**Figure 4-7**, in blue). For stroke, the rate per 100 person years in the population overall was 0.8 (95% CI 0.8 – 0.8), and the pattern according to sBP was more modestly U-shaped (**Figure 4-7**, in green). For cardiovascular death, the rate per 100 person years in the population overall was 0.3 (95% CI 0.2 – 0.3), and there was no meaningful difference stratified by sBP (**Figure 4-7**, in black).

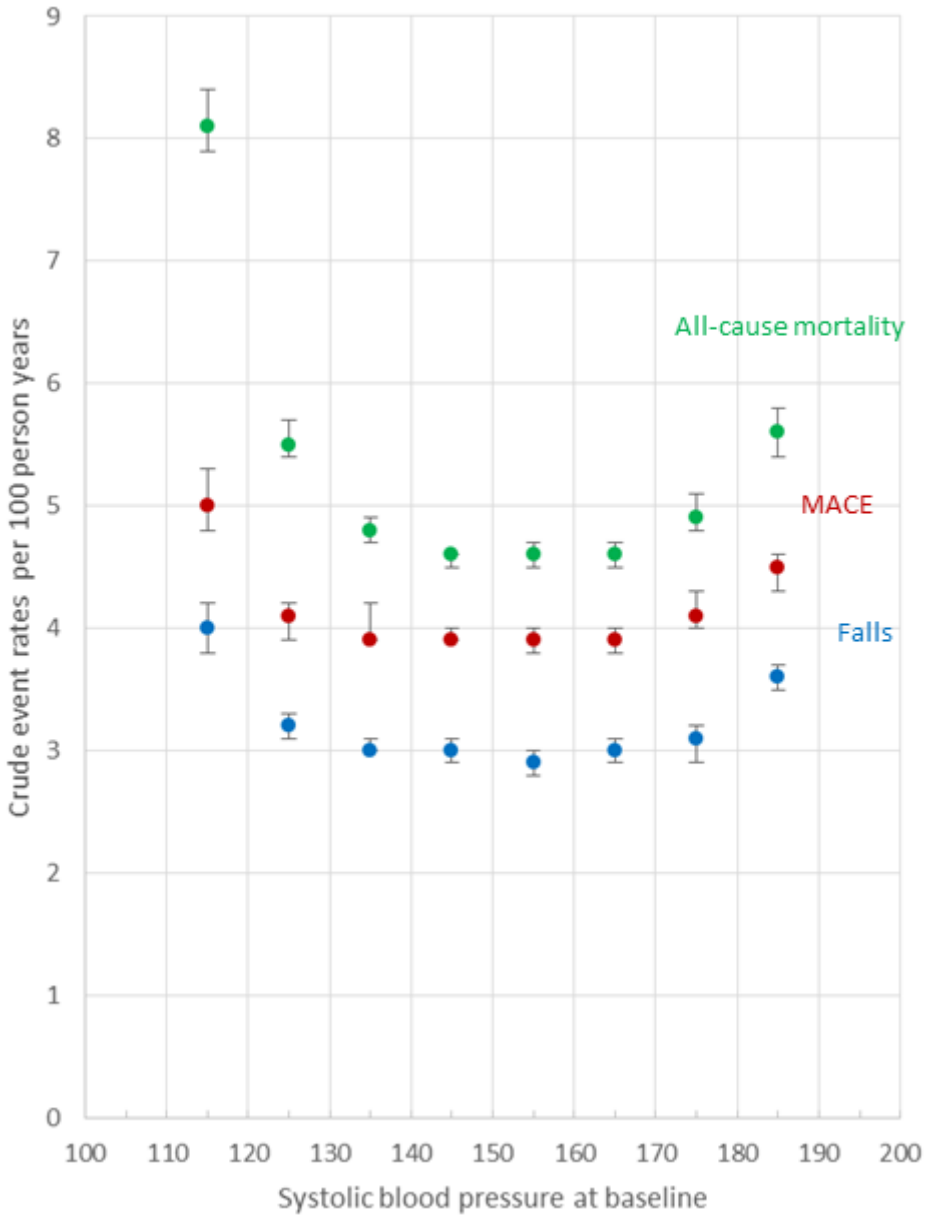
4.4.1.2 All-cause mortality

In the population overall, the rate per 100 person years of dying from any cause was 4.9 (95% CI 4.9 – 5.0) (**Figure 4-6**, in green). Stratified by sBP, the association was reverse-tick shaped: first peak at sBP < 120 mm Hg, 8.1 (95% CI 7.9, 8.4); nadir at 140 - 149 mm Hg, 4.6 (95% CI 4.5 – 4.6); with a second peak at > 180 mm Hg, 5.6 (95%CI 5.4 – 5.8).

4.4.1.3 Injurious falls

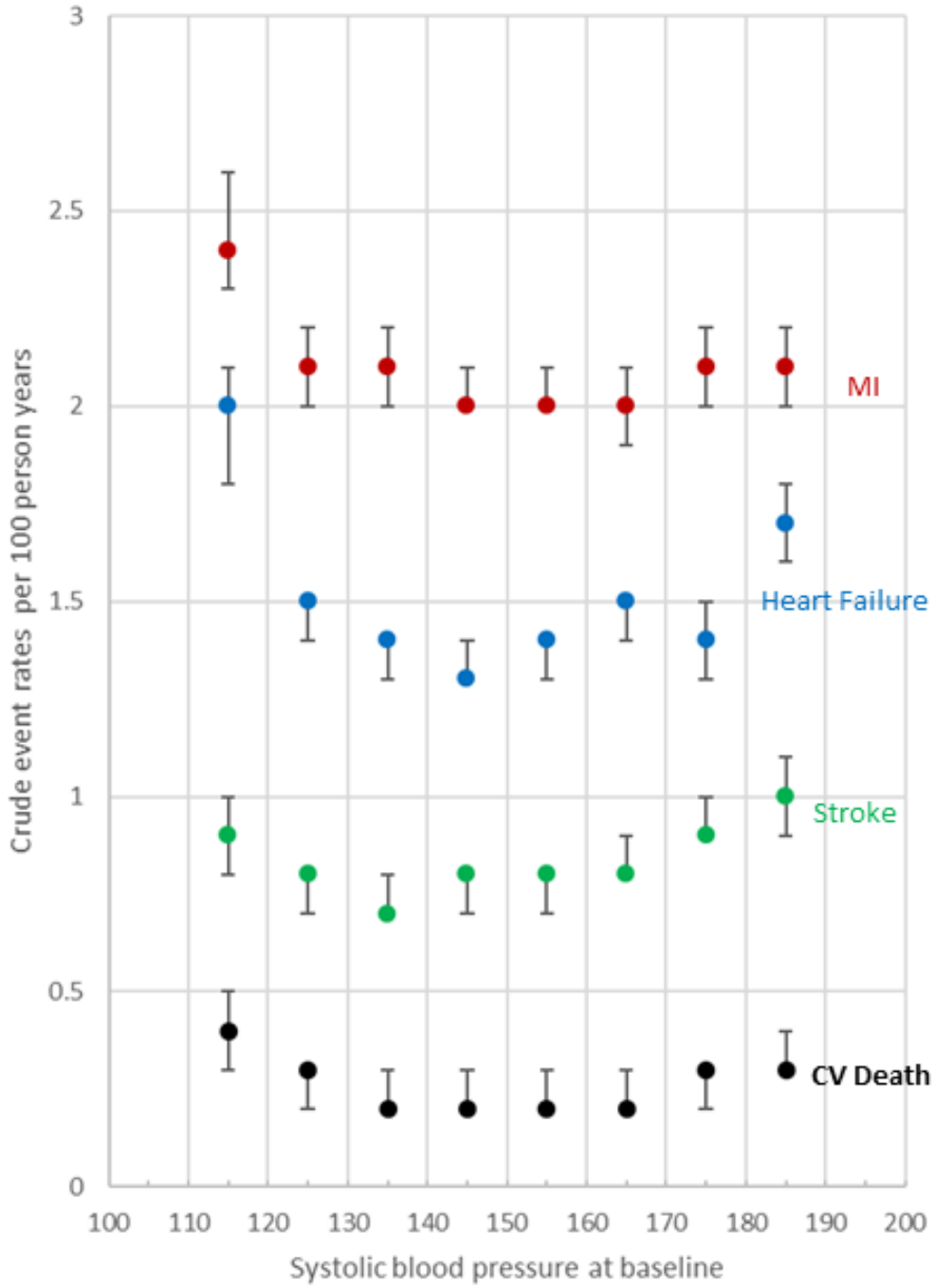
In the population overall, the rate per 100 person years of sustaining an injurious fall was 3.1 (95% CI 3.1 – 3.1) (**Figure 4-6**, in blue). For injurious falls, the crude rates varied more modestly conditional on sBP. Stratified by sBP: the first peak was at sBP < 120 mm Hg, 4.0 (95%CI 3.8 – 4.2); nadir at 150 to 159 mm Hg, 2.9 (95%CI 2.8 – 3.0); with a second peak at > 180 mm Hg, 3.6 (3.5 – 3.7).

Figure 4-6 Event rates with 95% confidence intervals for primary and secondary outcomes per 100 person years according to baseline sBP, n=145,598



Crude event rates with 95% confidence intervals are presented for the primary and secondary outcomes: all-cause mortality in green, major adverse cardiovascular events (MACE) in red, falls in blue, according to baseline systolic blood pressure.

Figure 4-7 Event rates with 95% confidence intervals for individual MACE outcomes per 100 person years according to baseline sBP, n=145,598



Crude event rates with 95% confidence intervals are presented for the major adverse cardiovascular events (MACE) individually: myocardial infarction (MI in red; heart failure in blue; stroke in green; cardiovascular death (CV death) in black.

4.4.1.4 Descriptive outcomes per sBP category

Overall rate of hospital admissions was 12.2 admission per 100 person years (95% CI 12.1 – 12.2) (**Figure 4-8**). Hospital admissions also demonstrated a reverse-tick shaped association: with a first peak at < 120 mm Hg, 17.0 (95% CI 16.5 – 17.5); nadir at 150 – 159 mm Hg, 11.6 (95% CI 11.4 – 11.7); second peak at > 180 mm Hg, 13.6 (95% CI 13.3 – 14.0).

Overall rate of care home admission was 1.2 per 100 person years (95% CI 1.2 – 1.2) (**Figure 4-9**) with a peak at < 120 mm Hg, 1.7 (95% CI 1.6 – 1.9); nadir at 140 – 160 mm Hg, 1.1 (95% CI 1.1 – 1.2); second peak at >180 mm Hg, 1.4 (95% CI 1.3 – 1.5).

Overall rate of hospital admissions with acute kidney injury was 1.3 per 100 person years (95% CI 1.3 – 1.3) (**Figure 4-10**) with a: peak at < 120 mm Hg, 1.7 (1.6 – 1.8); nadir at 150 – 159 mm Hg, 1.2 (95% CI 1.2 – 1.3); second peak at > 180 mm Hg, 1.6 (95% CI 1.5 – 1.7). Overall rate of hospital admissions with hypotension was 2.0 per 100 person years (95% CI 2.0 – 2.1) with a: first peak at sBP < 125 mm Hg, 2.8 (95% CI 2.6 – 3.0); nadir at 160 – 169 mm Hg, 1.9 (1.8 – 2.0); and second peak at > 180 mm Hg, 2.3 (95% CI 2.2 – 2.4). Overall rate of hospital admissions with electrolyte disturbance was 1.0 per 100 person years (95% CI 1.0 – 1.0) and there was not a meaningful difference according to sBP at baseline.

Overall rate of dementia diagnosis was 1.1 per 100 person years (95% CI 1.1 – 1.1) (**Figure 4-10**), with a first peak at sBP < 120 mm Hg, 1.5 (95% CI 1.4 – 1.6); and thereafter little difference above 120 mm Hg. Overall rate of delirium was 0.2 events per 100 person years (95% CI 0.2 – 0.2) with no difference in rates conditional on baseline sBP.

Overall rate of hospital admission with functional dependence was 1.5 per 100 person years (95% CI 1.5 – 1.5) (**Figure 4-10**) with a: peak at sBP < 120 mm Hg, 2.0 (95% CI 1.9 – 2.2); nadir at sBP 130 – 159 mm Hg, 1.4 (95% CI 1.4 – 1.5); and second peak at > 180 mm Hg, 1.9 (95% CI 1.8 – 2.0). Overall rate of hospital admissions with urinary incontinence was 0.3 events per 100 person years (95% CI 0.3 – 0.3), with no difference according to sBP.

Figure 4-8 Event rates for hospital admissions per 100 person years according to baseline systolic blood pressure, with 95%confidence intervals, n=145,598

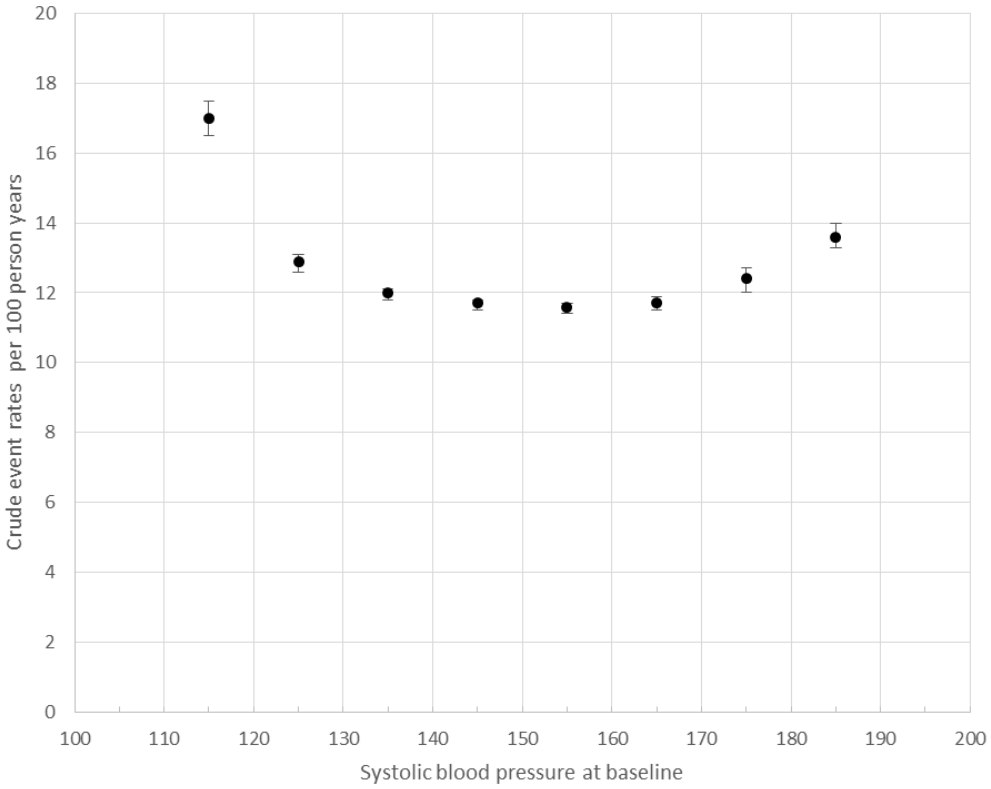


Figure 4-9 Event rates of care home admissions per 100 person years according to baseline systolic blood pressure, with 95% confidence intervals, n=145,598

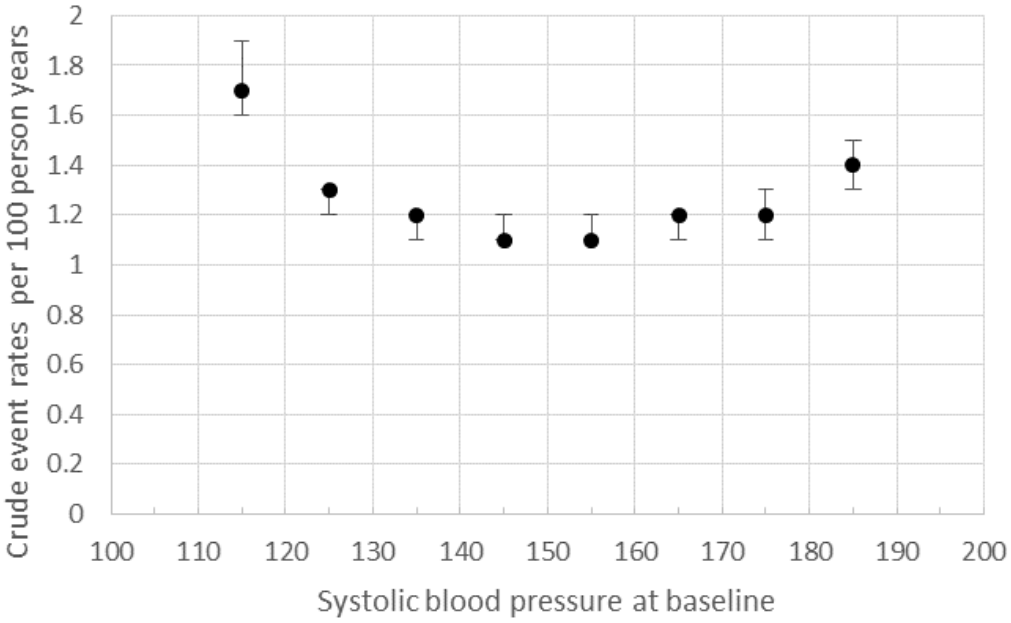
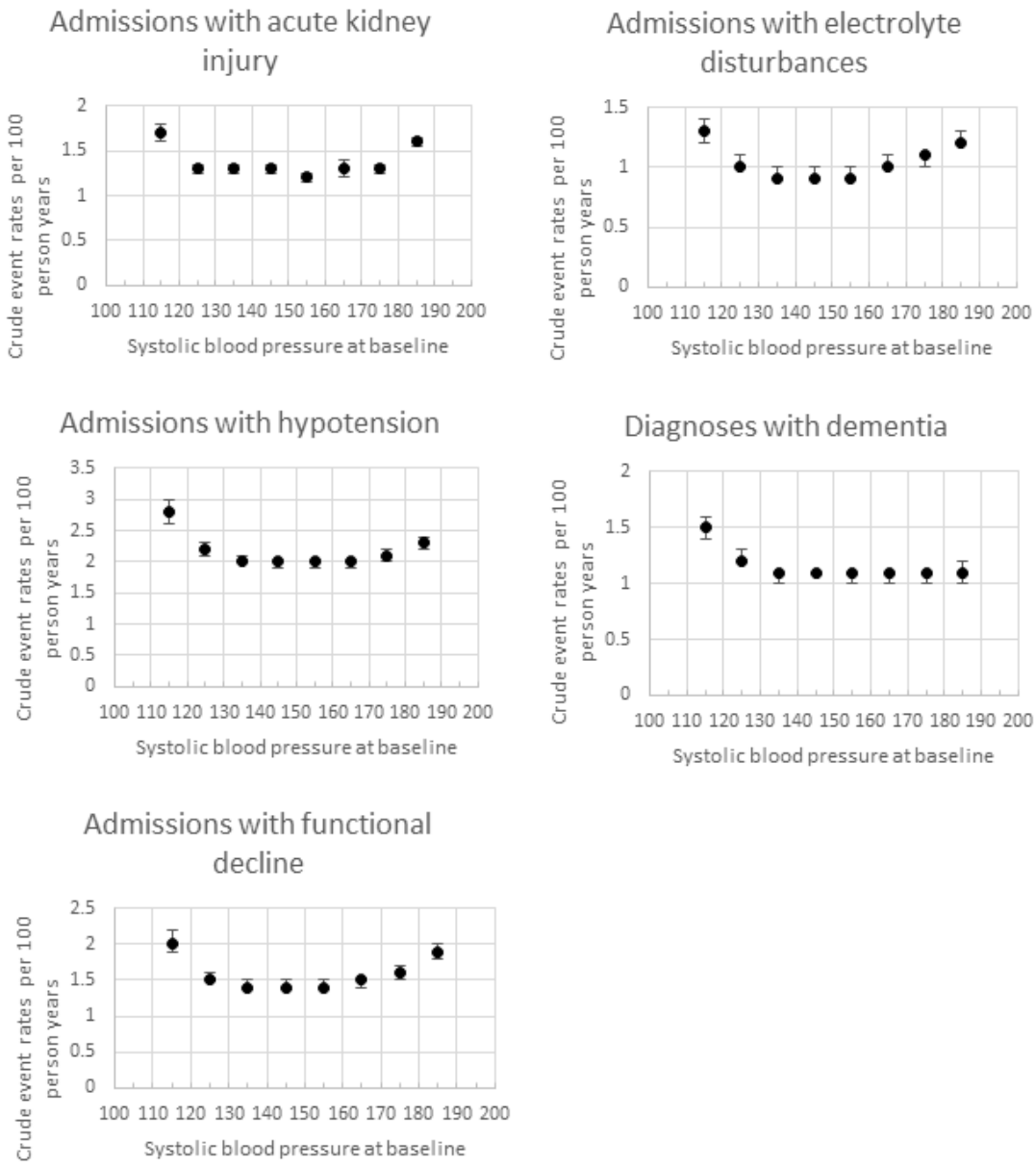


Figure 4-10 Event rates for descriptive outcomes per 100 person years according to baseline systolic blood pressure category, with 95% confidence intervals, n=145,598



4.4.2 Relative risks of outcomes per sBP category

4.4.2.1 Major adverse cardiovascular events (MACE)

Hazard ratios for the association of sBP category with MACE were estimated in a model adjusted for cardiovascular risk and BP-lowering treatment. Risk of MACE was higher than the reference category at both upper and lower extremes of the range of systolic BP (**Figure 4-11**). There was evidence of a non-linear association between sBP and MACE. Compared to a reference category of 130 – 139 mm Hg, a greater hazard was associated with an sBP < 120 mm Hg (HR 1.16, 95%CI 1.11 – 1.22), and an sBP > 180 mm Hg (HR 1.07, 95% CI 1.02 – 1.11). There were no significant differences between the reference category and sBP between 120 mm Hg and 179 mm Hg.

4.4.2.2 All-cause mortality

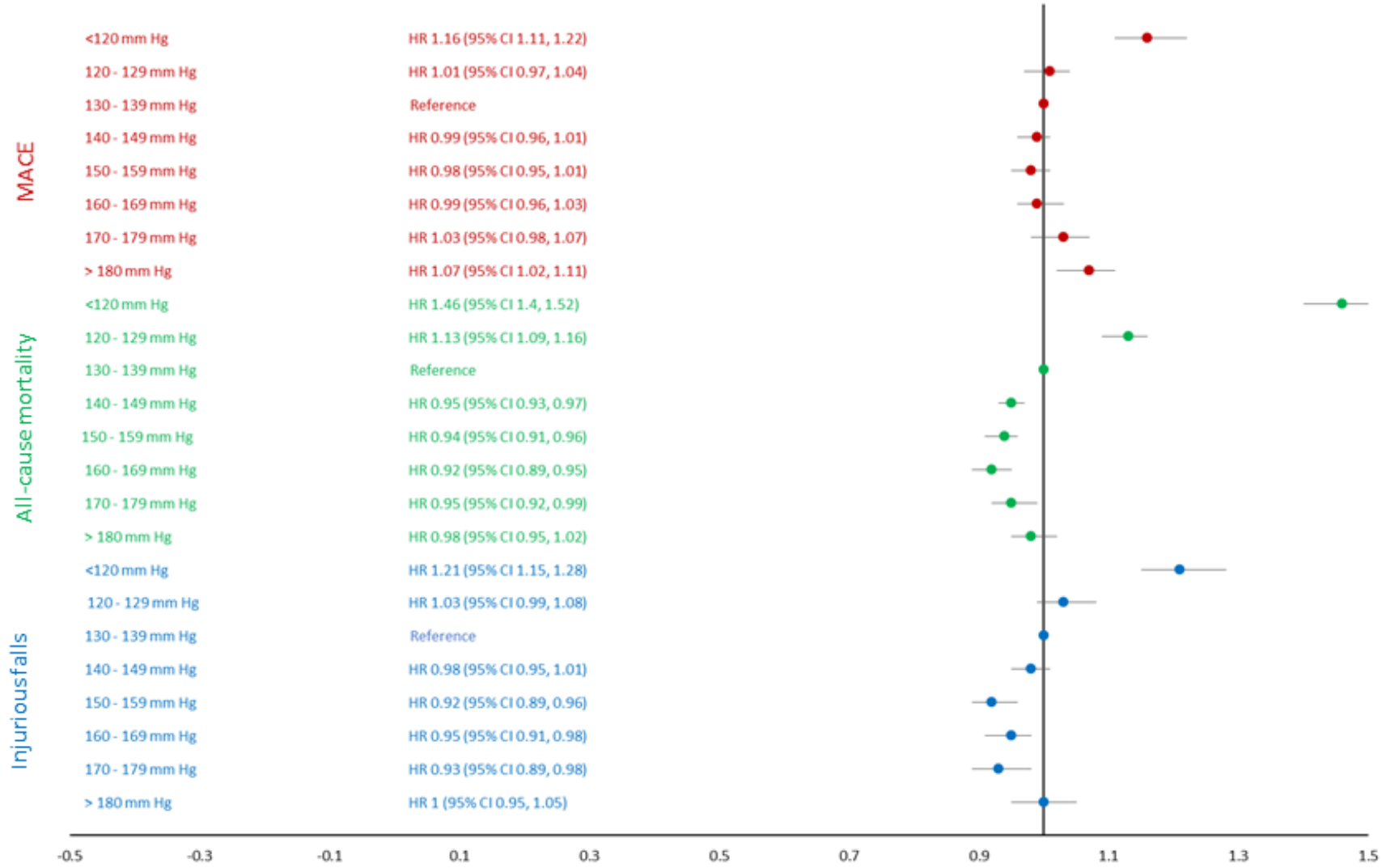
Hazard ratios for the association of sBP category with all-cause mortality were estimated in a model adjusted for cardiovascular risk and BP-lowering treatment (**Figure 4-11)**. Patients with an sBP < 120 mm Hg were associated with a 46% increase in risk of all-cause death compared to a reference of patients with sBP 130-139 mm Hg (HR 1.46, 95% CI 1.40, 1.52)). Patients with an sBP between 120 – 129 mm Hg were associated with a 13% increase in risk of all-cause death compared to reference (HR 1.13, 95%CI 1.09, 1.16)). People with an sBP over 140 mm Hg were associated with a reduced risk of mortality compared to reference (140-149 mm Hg, HR 0.95, 95% CI 0.93, 0.97; 150 – 159 mm Hg, HR 0.94, 95% CI 0.91, 0.96; 160 – 169 mm Hg, HR 0.92, 95% CI 0.89, 0.95; 170 –

179 mm Hg, HR 0.95, 95% CI 0.92, 0.99). However, at an sBP > 180 mm Hg hazard risk was not statistically different to the reference range (HR 0.98, 95% CI 0.95, 1.02).

4.4.2.3 Injurious falls

Hazard ratios for the association of sBP category with injurious falls requiring hospitalisation also in a model adjusted for cardiovascular risk and BP-lowering treatment (**Figure 4-11**). In common with the associations reported for all-cause mortality, patients with an sBP of < 120 mm Hg were associated with a 21% increased risk of sustaining an injurious fall compared to patients with an sBP between 130 – 139 mm Hg. People with an sBP > 150 mm Hg were associated with a reduced risk of falls compared to reference (150 – 159 mm Hg, HR 0.92, 95% CI 0.89, 0.96; 160 – 169 mm Hg HR 0.95, 95% CI 0.91, 0.98; 170 – 179 mm Hg HR 0.93, 95% CI 0.89, 0.98). Also, at an sBP > 180 mm Hg hazard risk was not statistically different to the reference range (HR 1, 95% CI 0.95, 1.05).

Figure 4-11 Association of systolic blood pressure with 95% confidence intervals with major adverse cardiovascular events (MACE), all-cause mortality and injurious falls, n=145,598



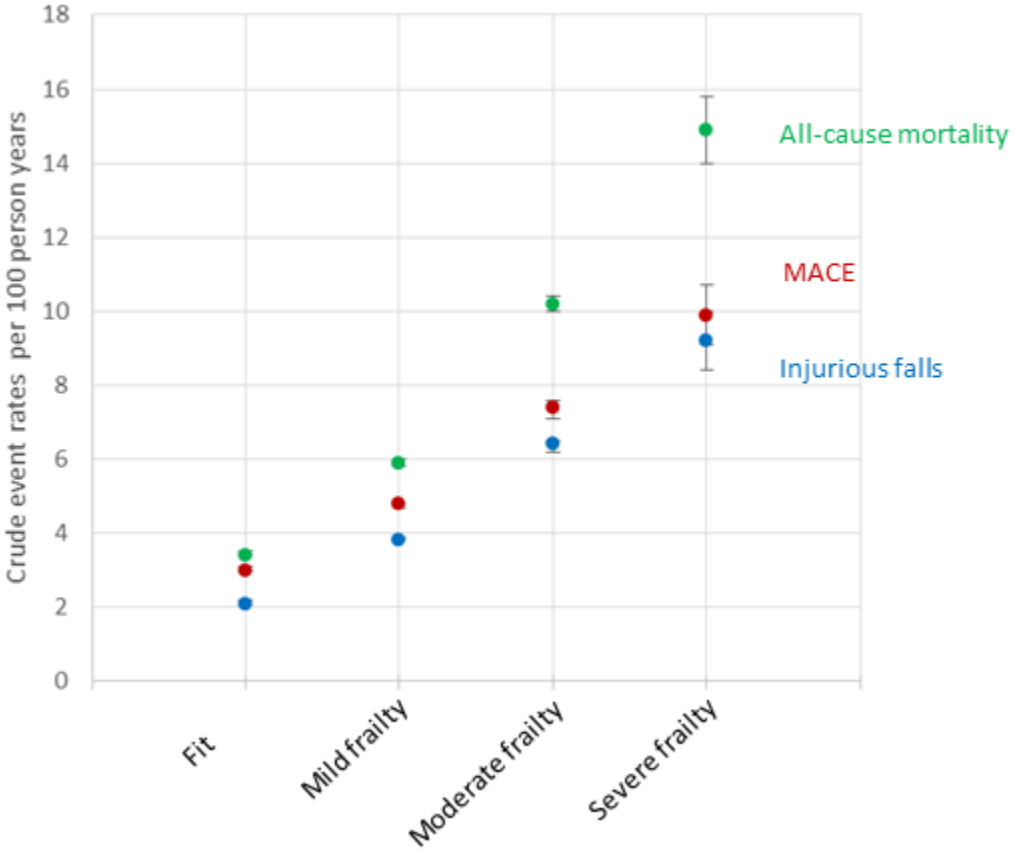
Adjusted for established cardiovascular risk factors & treatment. Association of systolic blood pressure as a categorical variable with the risk of Major Adverse Cardiovascular Event (MACE), all-cause mortality and injurious falls. Hazard ratios of the association between systolic blood pressure and risk of MACE (in red), all-cause mortality (green) and injurious falls (blue) with the corresponding 95% confidence intervals (black lines) (reference systolic blood pressure: 130 – 139 mmHg). Point estimates were calculated in a flexible parametric model with 3 degrees of freedom, using cubic splines for weight and Cholesterol: HDL ratio. HR, hazard ratio; CI, confidence interval; MACE, Major Adverse Cardiovascular Event; sBP, systolic blood pressure.

4.5 Objective 3: Is frailty a prognostic factor for key outcomes?

4.5.1 Event rates according to baseline frailty status

The crude rate of outcome events increased with advancing frailty status across primary and secondary outcomes (**Figure 4-12**). The rate per 100 person years of developing a MACE outcome increased with frailty status: in fit, 3.0 (95% CI 3.0 – 3.1); mild frailty, 4.8 (95% CI 4.7 to 4.9); moderate frailty, 7.4 (95% CI 7.2 to 7.6); severe frailty, 9.8 (95% CI 9.0 to 10.6). The rate per 100 person years of dying of any cause increased more steeply with frailty status: in fit, 3.4 (95% CI 3.4 – 3.5); mild frailty, 5.9 (95% CI 5.8 to 6.0); moderate frailty, 10.2 (95% CI 10.0 to 10.4); severe frailty, 14.9 (95% CI 14.0 to 15.8). The rate per 100 person years of being hospitalised with injurious falls also increased with frailty: in fit, 2.2 (95% CI 2.1 – 2.2); mild frailty, 3.9 (95% CI 3.8 to 4.0); moderate frailty, 6.5 (95% CI 6.3 to 6.7); severe frailty, 9.2 (95% CI 8.4 to 10.0).

Figure 4-12 Event rates with 95% confidence intervals for major adverse cardiovascular event (MACE), all-cause mortality and injurious falls according to frailty status at baseline, n=145,598



4.5.2 Relative risk according to baseline frailty status

The unadjusted risk for MACE, all-cause mortality, and falls were all increased with increasing severity of frailty (see **Figure 4-13**, **Figure 4-14**, **Figure 4-15**). The hazard risk for MACE adjusted for known cardiovascular risk factors, BP-lowering treatment and GP attendance also increased with frailty in comparison to those who were fit: mild frailty, HR 1.38, 95% CI 1.35, 1.41; moderate frailty, HR 1.84, 95% CI 1.78, 1.91; severe frailty, HR 2.17, 95% CI 2.00, 2.36 (**Figure 4-16**). The adjusted risk for all-cause mortality increased with frailty compared to those who were fit: mild frailty, HR 1.36, 95% CI 1.33, 1.39; moderate frailty, HR 1.86, 95% CI 1.81, 1.91; severe frailty, HR 2.18, 95% CI 2.05, 2.32 (**Figure 4-17**). The adjusted risk of injurious falls increased in comparison to fit: mild frailty, HR 1.44, 95% CI 1.41, 1.48; moderate frailty, HR 1.93, 95% CI 1.86, 2.00; severe frailty, HR 2.24, 95% CI 2.06, 2.44 (**Figure 4-18**).

Figure 4-13 Major adverse cardiovascular events (MACE), by frailty status at baseline with 95% confidence intervals, n= 145,598

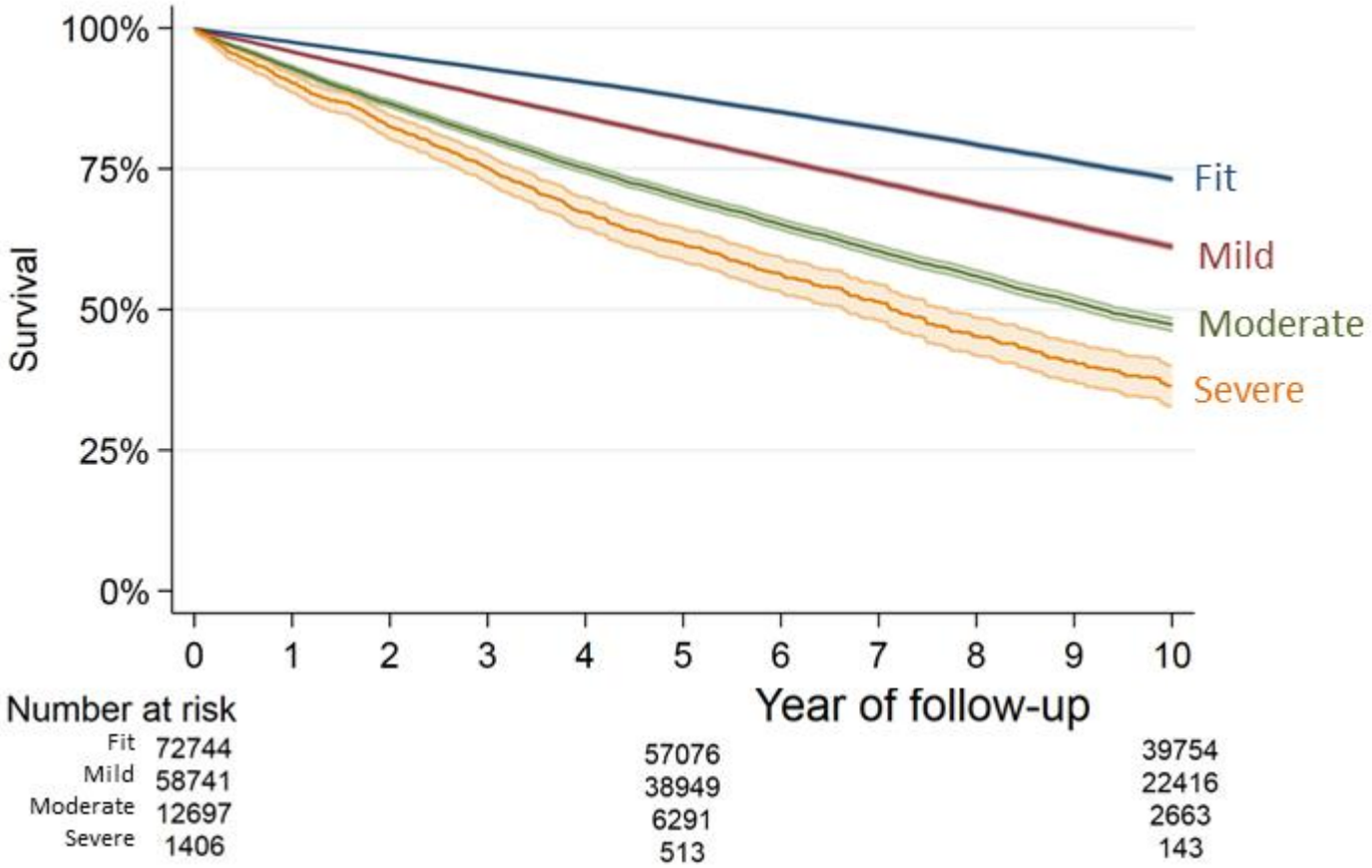
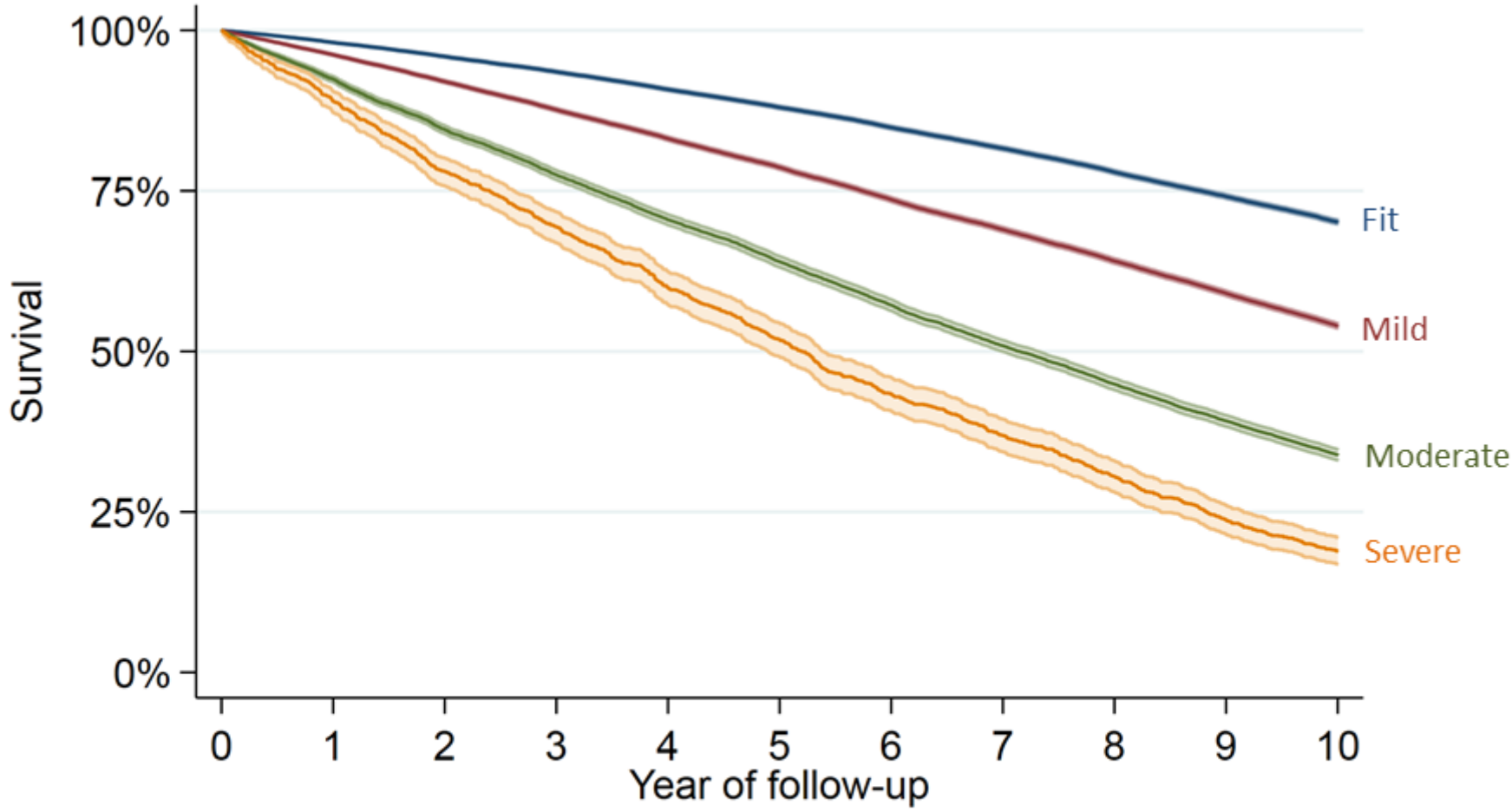


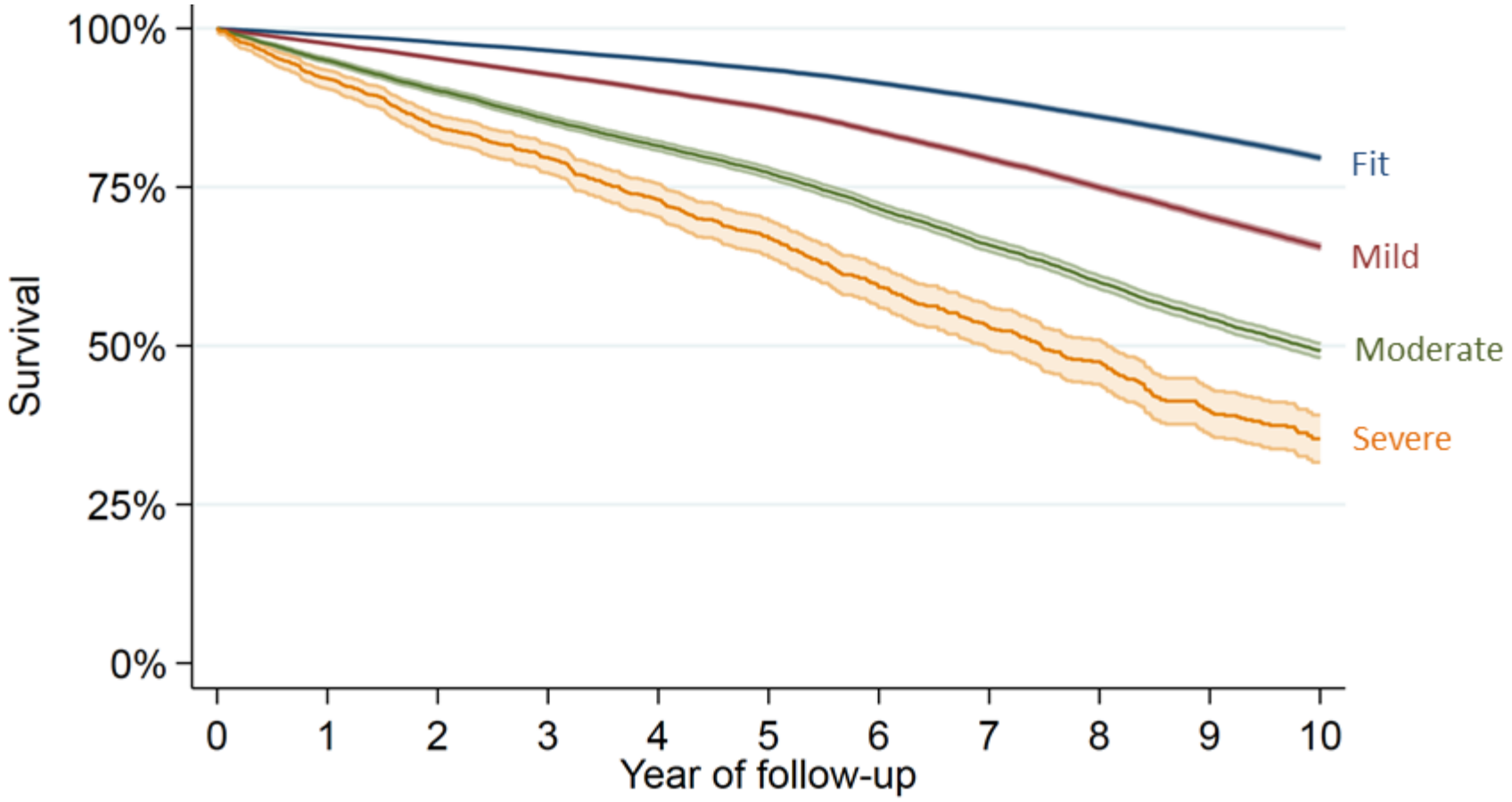
Figure 4-14 All-cause mortality by frailty status at baseline with 95% confidence intervals. n= 145,598



Number at risk

Fit	72744	63000	49096
Mild	58741	45390	30391
Moderate	12697	7949	4084
Severe	1406	712	253

Figure 4-15 First injurious fall by frailty status at baseline with 95% confidence intervals. n= 145,598



Number at risk

Fit	72730	59987	42911
Mild	58731	41387	24047
Moderate	12684	6682	2839
Severe	1404	534	149

Figure 4-16 Association between frailty status at baseline and major adverse cardiovascular events (MACE), unadjusted (grey), adjusted (black) hazard risks, n=145,598

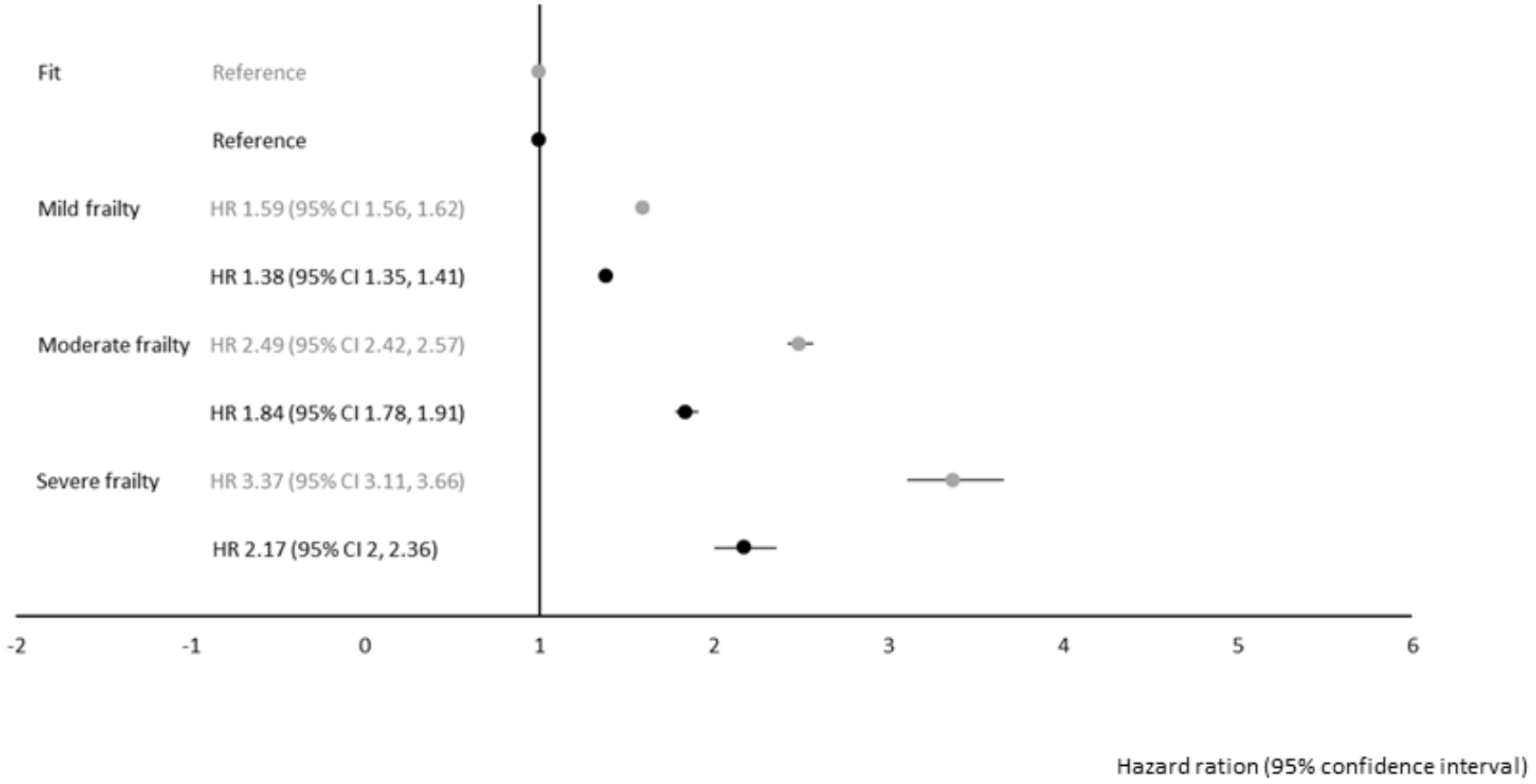


Figure 4-17 Association between frailty status at baseline and all-cause mortality, unadjusted (grey), adjusted (black) hazard risks, n=145,598

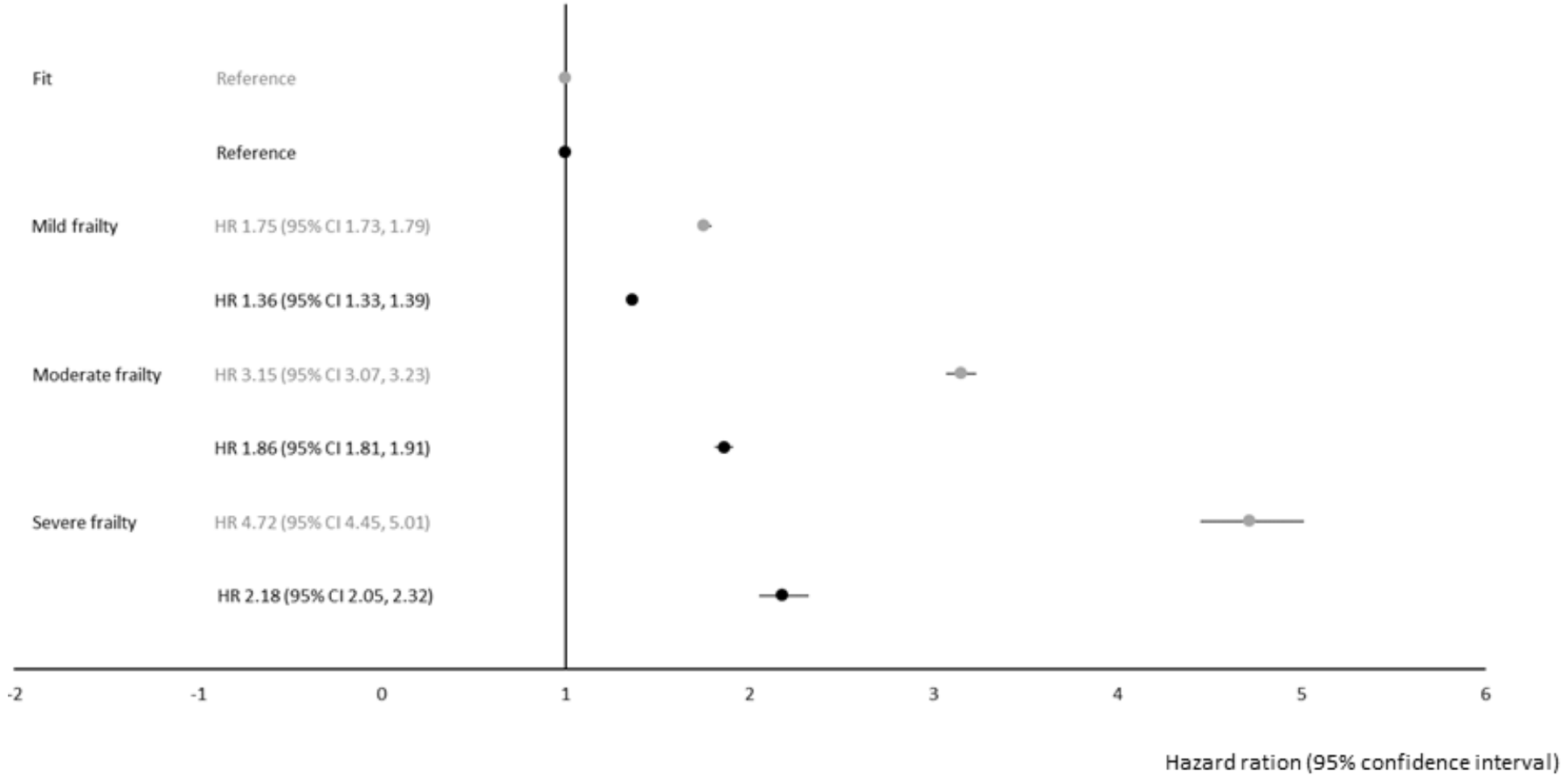
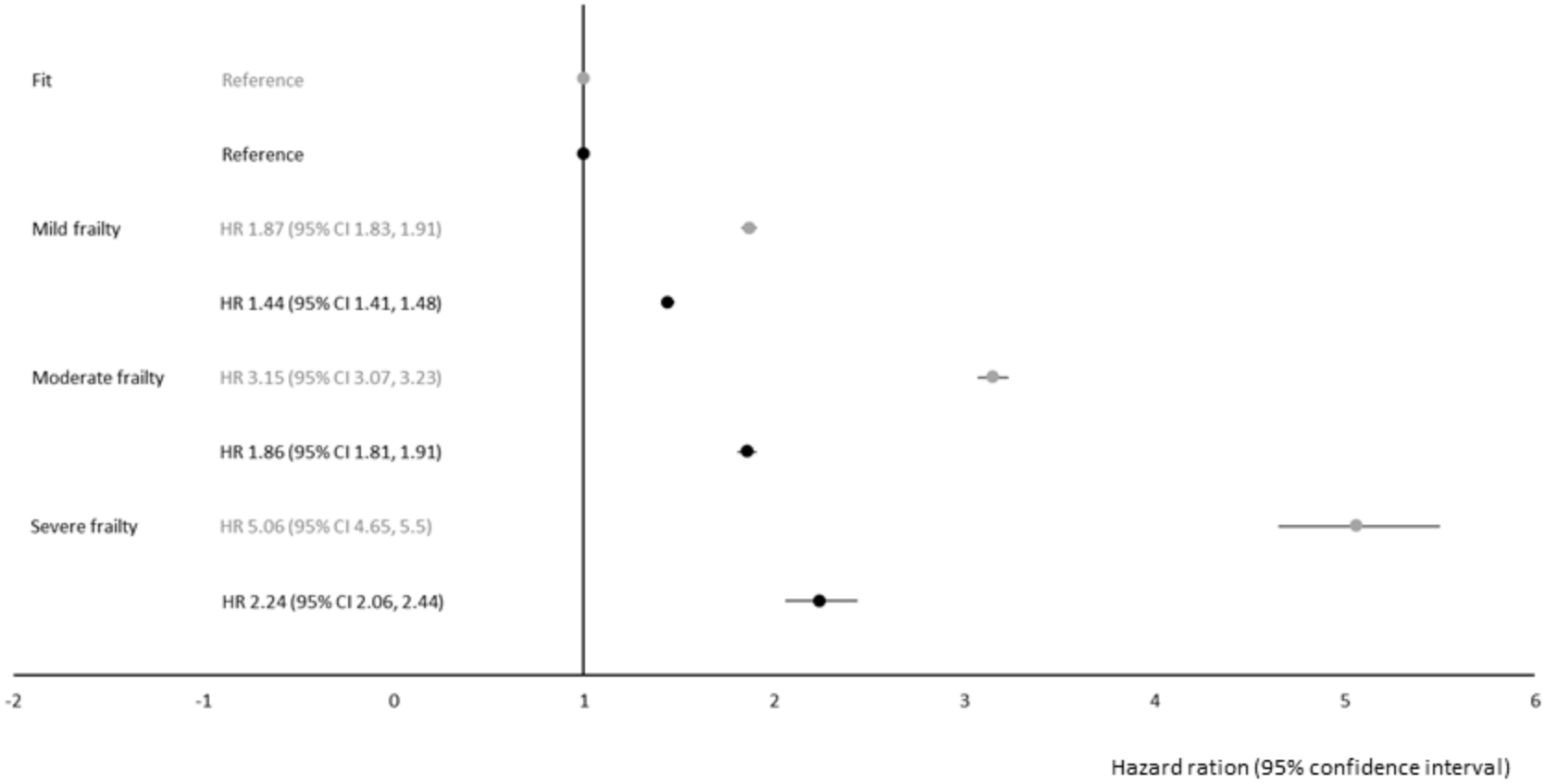


Figure 4-18 Association between frailty status at baseline and injurious falls, unadjusted (grey), adjusted (black) hazard risks, n=145,598



4.5.3 Change in model fit with adjustment for frailty

The model fit with and without frailty as a continuous term was tested (**Table 4-9**). For all outcomes both the AIC and BIC reduced with the addition of frailty to the model. For MACE, the best current model had an AIC of 248,829 and BIC of 249,023. With frailty this reduced to an AIC of 247,409 and BIC of 247,579. For all primary outcomes therefore, these are consistent with an improvement of model fit with the addition of frailty. For all-cause mortality, the best current model had an AIC of 260,202 and BIC of 260,396. The addition of frailty reduced the AIC to 259,252 and BIC to 259,422. For injurious falls, the best current model had an AIC of 183,481 and BIC of 183,675. There were similar reductions of AIC to 182,276 and BIC to 182,446.

Table 4-9 Survival models with and without the addition of frailty as a prognostic factor, adjusted for cardiovascular risk, BP-lowering treatment and GP attendance, for primary and secondary outcomes

Outcome	Prognostic factor	AIC	BIC
MACE	Without frailty	248,828.6	249,023
	With frailty	247,409.3	247,578.8
All-cause mortality	Without frailty	260,201.6	260,396
	With frailty	259,252.3	259,421.8
Injurious falls	Without frailty	183,480.9	183,675.3
	With frailty	182,276	182,445.5

AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; MACE = Major adverse cardiovascular event.

4.6 Objective 4: Does frailty modify the association between blood pressure and outcomes?

4.6.1 Event rates according to systolic blood pressure in sub-population defined by frailty status

4.6.1.1 Major adverse cardiovascular events (MACE)

The differential rate of MACE according to baseline sBP varied in pattern in different sub-populations defined by frailty status. MACE crude rates in fit and mild frailty groups were modestly U-shaped (**Figure 4-19**). In fit people, the crude rate was highest at <120 mm Hg, at 3.6 events per 1000 person years (95% CI 3.3 – 3.9) and at > 180 mm Hg, at 3.5 events (95% CI 3.3 – 3.6), and lower in-between. In mild frailty, the pattern was similar, with crude rates highest at < 120 mm Hg (5.6 (95% CI 5.2 – 6.0), lowest rate at 130 – 139 mm Hg (4.5 (95% CI 4.3 – 4.6), but a more gradual increase with increasing sBP thereafter until > 180 mm Hg, at 5.6 (95% CI 5.3 – 5.9).

However in populations defined by moderate and severe frailty, associations between sBP and MACE are broadly indifferent across sBP. Conversely among those with moderate frailty the crude rate varied only between 7 and 8 events per 1000 person years at all sBPs. In people with severe frailty crude rates varied between 9 – 11 events per 1000 person years but not in a clear pattern.

4.6.1.2 All-cause mortality

The crude mortality rate associated with sBP also varied in pattern according to frailty status but in a different manner to MACE. The pattern throughout was shaped as an inverted J, and this became more pronounced with advancing frailty (**Figure 4-20**). In fit people, crude death rates were not grossly different across sBP categories, ranging from highest rate at < 120 mm Hg, 4.7 (95%CI 4.4 – 5.1), to lowest rate at 130 – 139 mm Hg, 3.2 (95% CI 3.1 – 3.3), rising again at > 180 mm Hg, 4.2 (95% CI 4 – 4.4). The J shape becomes more pronounced in mild frailty, ranging from highest at < 120 mm Hg , 8.9 (95% CI 8.5 – 9.4) to a nadir at 140 – 149 mm Hg, 5.5 (5% CI 5.3 – 5.6), rising thereafter up to > 180 mm Hg, 6.9 (95% CI 6.6 – 7.3). In moderate frailty, rates were highest < 120 mm Hg 15.6 (95% CI 14.5 – 16.8), lowest at 150 – 159 mm Hg, 9.3 (95% CI 8.7 – 9.9), rising to > 180 mm Hg, at 11.1 (95% CI 10.1 – 12.1). In severe frailty, rates peaked at < 120 mm Hg, 21.2 (95% CI 17.8 – 25.1), then reduced with increasing sBP, with a nadir at 160 – 169 mm Hg at 12.5 (10 – 15.3).

4.6.1.3 Falls

The pattern in the crude risk of falls remained U shaped in those who were fit or who had mild frailty (**Figure 4-21**). However in those with moderate frailty, and particularly in those with severe frailty, the sBP-falls association became more of the conventional J-shaped association. In those who are fit, crude rate of falls was high < 120 mm Hg, 2.6 (95% CI 2.4 – 2.9) and again > 180 mm Hg, 2.7 (95% CI 2.5 – 2.8), and in-between, rates were between 2 and 2.1. In mild

frailty, similarly, rates were highest < 120 mm Hg, 4.4 (95% CI 4.1 – 4.7) and > 180 mm Hg 4.5 (95% CI 4.2 – 4.8) , and in-between rates were between 3.6 and 4.0. In moderate frailty, also, highest < 120 mm Hg at 7.2 (95% CI 6.4 – 8.0), and > 180 mm Hg, at 8 (95% CI 7.1 – 8.9), an in-between 6.1 and 6.5. In severe frailty, a J-shaped association was more evident, with rates highest < 120 mm Hg, 11.2 (95% CI 8.5 – 14.5), lowest at 120 – 129 mm Hg, 7.9 (95% CI 6.1 – 10.1), rising with sBP there upward.

Figure 4-19 Event rates with 95% confidence intervals for major adverse cardiovascular events (MACE) according to frailty status and systolic blood pressure at baseline, n=145,598

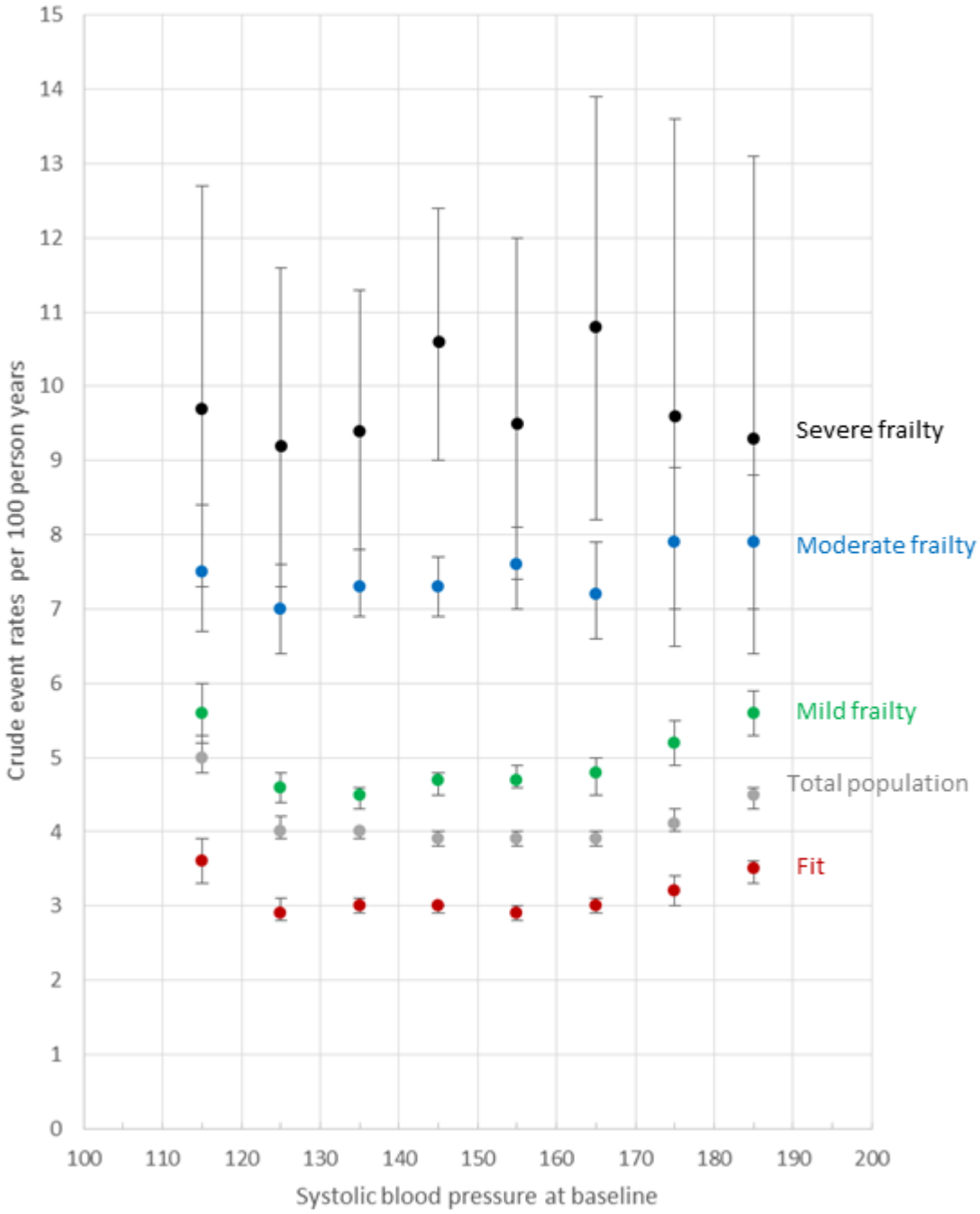


Figure 4-20 Event rates with 95% confidence intervals for all-cause mortality according to frailty status and systolic blood pressure at baseline, n=145,598

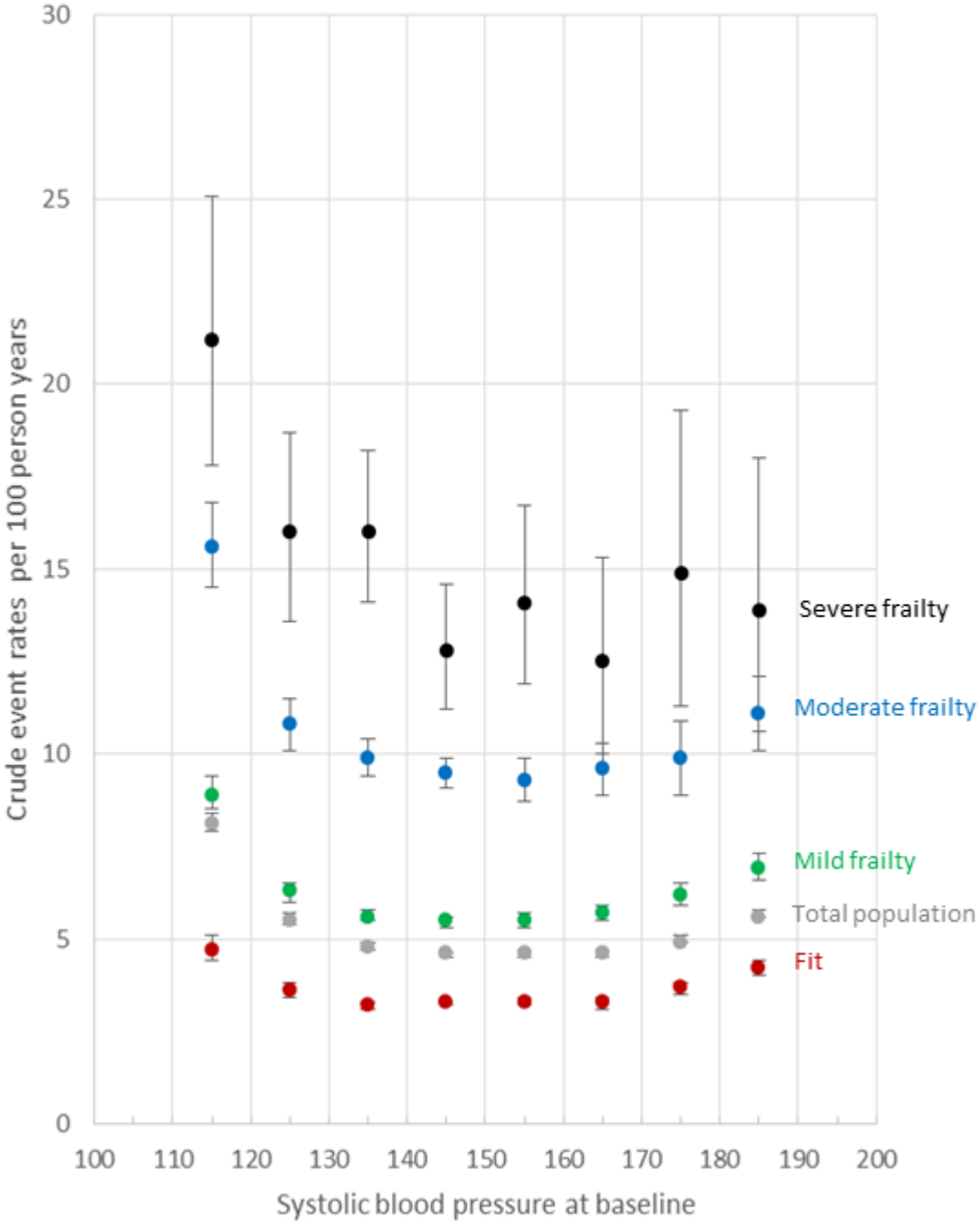
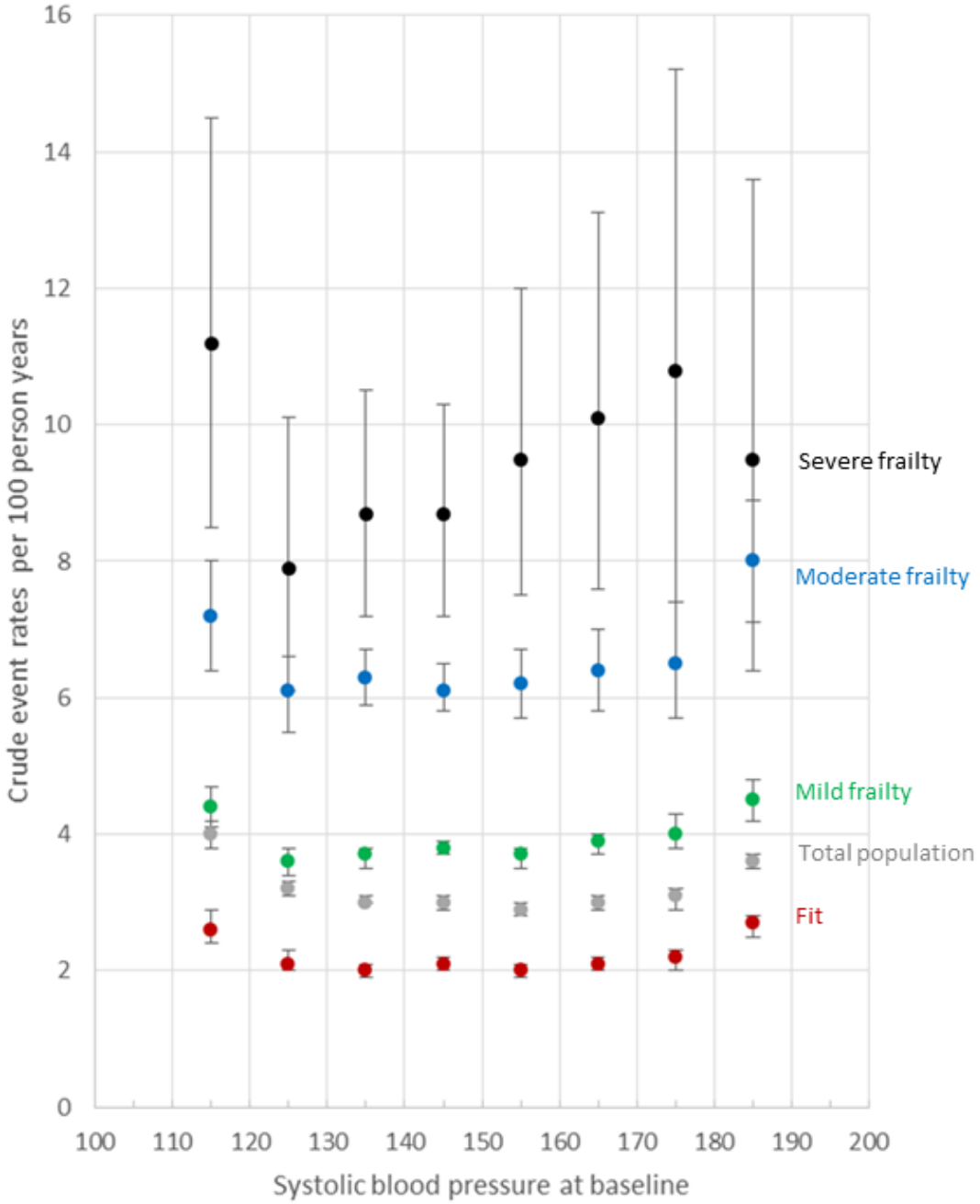


Figure 4-21 Event rates with 95% confidence intervals for injurious falls according to frailty status and systolic blood pressure at baseline, n=145,598



4.6.2 Relative risk according to systolic blood pressure in sub-populations defined by frailty

Analyses were adjusted for cardiovascular risk, BP-lowering treatment count and number of visits to the GP.

4.6.2.1 Major adverse cardiovascular events (MACE)

Overall, there was a greater relative hazard for MACE at the extremes of systolic BP (**Figure 4-22**), and this pattern was maintained in people who were fit or had mild frailty. In people who were fit, an sBP <120 mm Hg was associated with 13% higher risk of developing MACE, compared to those with sBP 130 – 139 mm Hg, HR 1.13 (95% CI 1.03, 1.23). Patients with an sBP >180 mm Hg were associated with 11% higher risk of developing MACE compared to reference range, HR 1.11 (95% CI 1.04, 1.19). In people with mild frailty, sBP < 120 mm Hg was associated with 18% increase in risk of MACE compared to reference (HR 1.18 (95% CI 1.10, 1.27), and sBP > 180 mm Hg 13% increase risk of MACE, HR 1.13 (95% CI 1.06, 1.21). In people who were fit or had mild frailty, sBPs running in-between 120 and 180 mm Hg were not associated with higher relative hazard. In people with moderate or severe frailty, there was no statistically significant difference in risk conditional on sBP.

4.6.2.2 All-cause mortality

Overall there highest risk of death from any cause was at low sBPs, and this pattern was maintained in all frailty subgroups except for severe frailty (**Figure 4-23**). For patients who were fit, compared to sBP 130 – 139 mm Hg, an sBP < 120 mm Hg was associated with 42% increased risk of death, HR 1.42 (95% CI 1.32, 1.54), an sBP 120-129 mm Hg had 13% higher risk, HR 1.13 (95% CI 1.07, 1.20), and sBP > 180 mm Hg, 12% higher risk, HR 1.12 (95% CI 1.03, 1.20). In mild frailty, sBP < 120 mm Hg was associated with a HR 1.42 (95% CI 1.35, 1.50), and, 120 – 129 mm Hg, a HR 1.10 (95% CI 1.05, 1.15). For patients with mild frailty sBP above 140 mm Hg was associated with lower risk of death up to a sBP of 170 mmHg. In moderate frailty, sBP < 120 mm Hg was associated with a HR 1.40 (95%CI 1.28, 1.52), 120 – 129 mm Hg with HR 1.10 (95%CI 1.01, 1.18). In people with severe frailty, there was no clear association that was conditional on sBP.

4.6.2.3 Injurious falls

In fit patients, hazard risk of injurious falls was highest at very low sBP and very high sBP (**Figure 4-24**). For people who were fit, compared to a reference of 130 – 139 mm Hg, the hazard risk of falling was 29% higher with an sBP < 120 mm Hg, HR 1.29 (95% CI 1.16, 1.43), 8% higher with an sBP 120-129 mm Hg, and 12 % higher with an sBP > 180 mm Hg, HR 1.12 (95%CI 1.3, 1.20). In patients with mild frailty the risk was highest only with very low sBP. Compared

to reference, in mild frailty, sBP < 120 mm Hg was associated with a 14% increase in risk of death, HR 1.14 (95%CI 1.05, 1.23). In moderate or severe frailty, there was no clear association conditional on sBP.

Figure 4-22 Associations between systolic blood pressure and major adverse cardiovascular event stratified by baseline frailty status, with 95% confidence intervals, n = 145,598

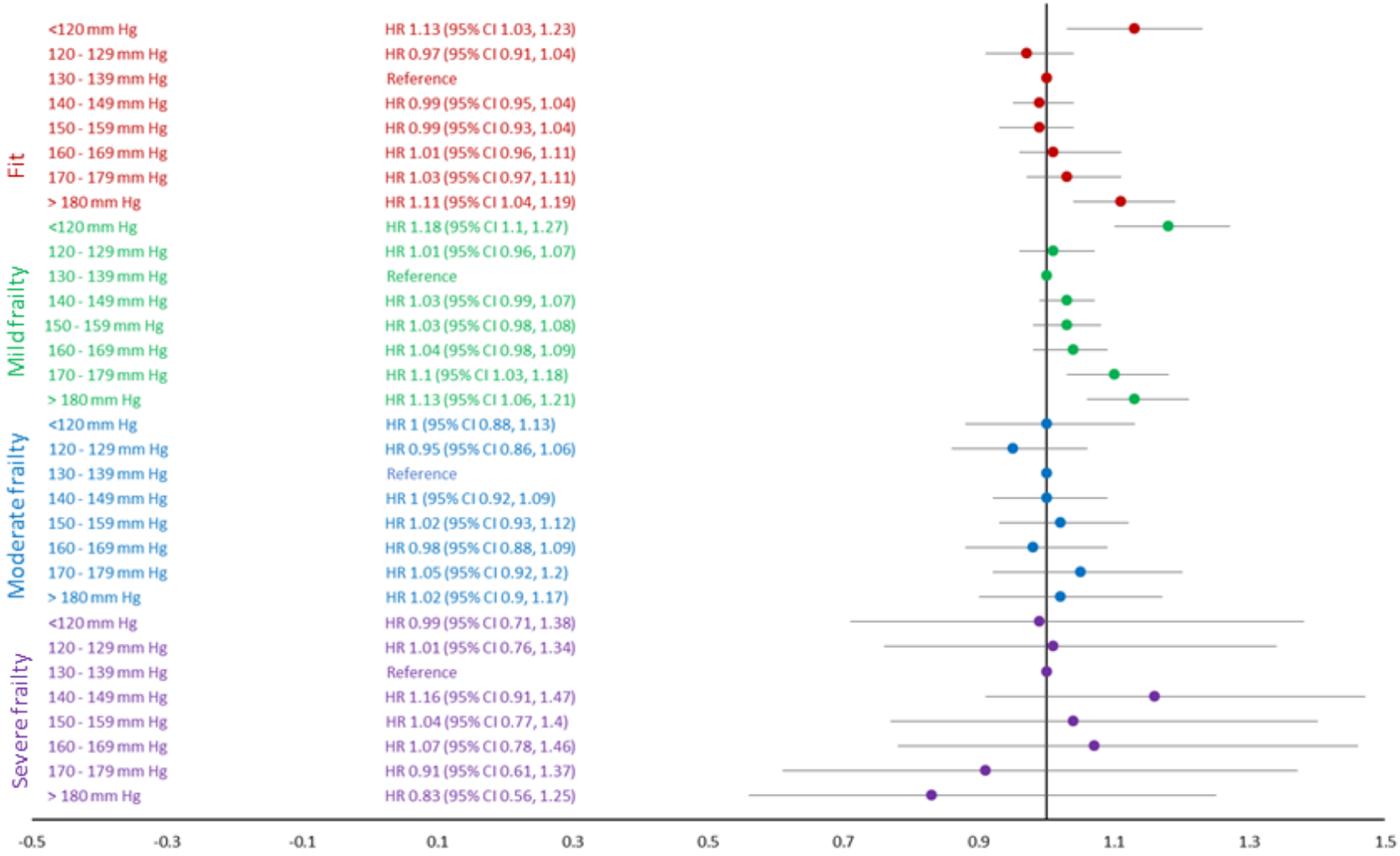


Figure 4-23 Associations between systolic blood pressure and all-cause mortality stratified by baseline frailty status, with 95% confidence intervals, n = 145,598

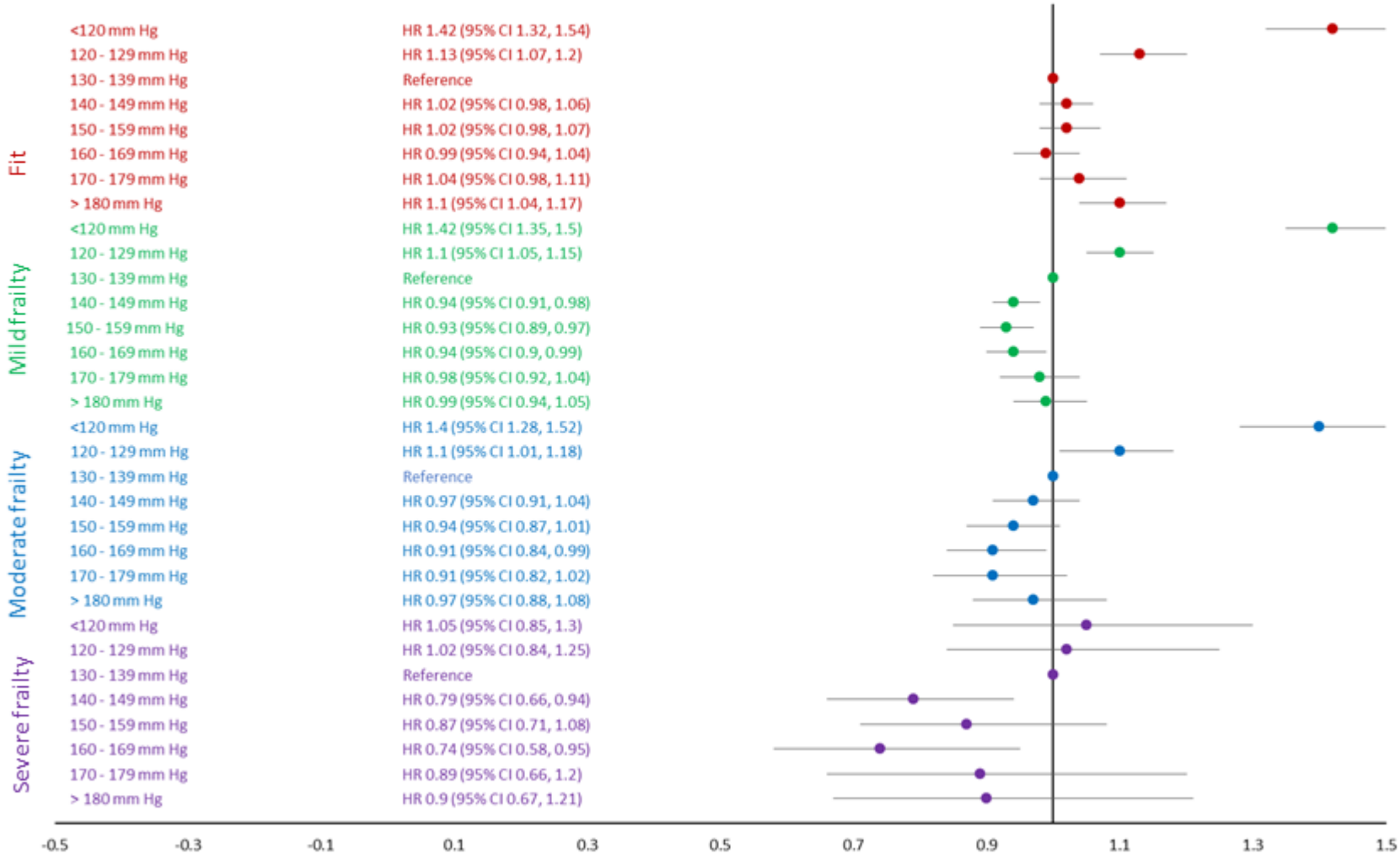
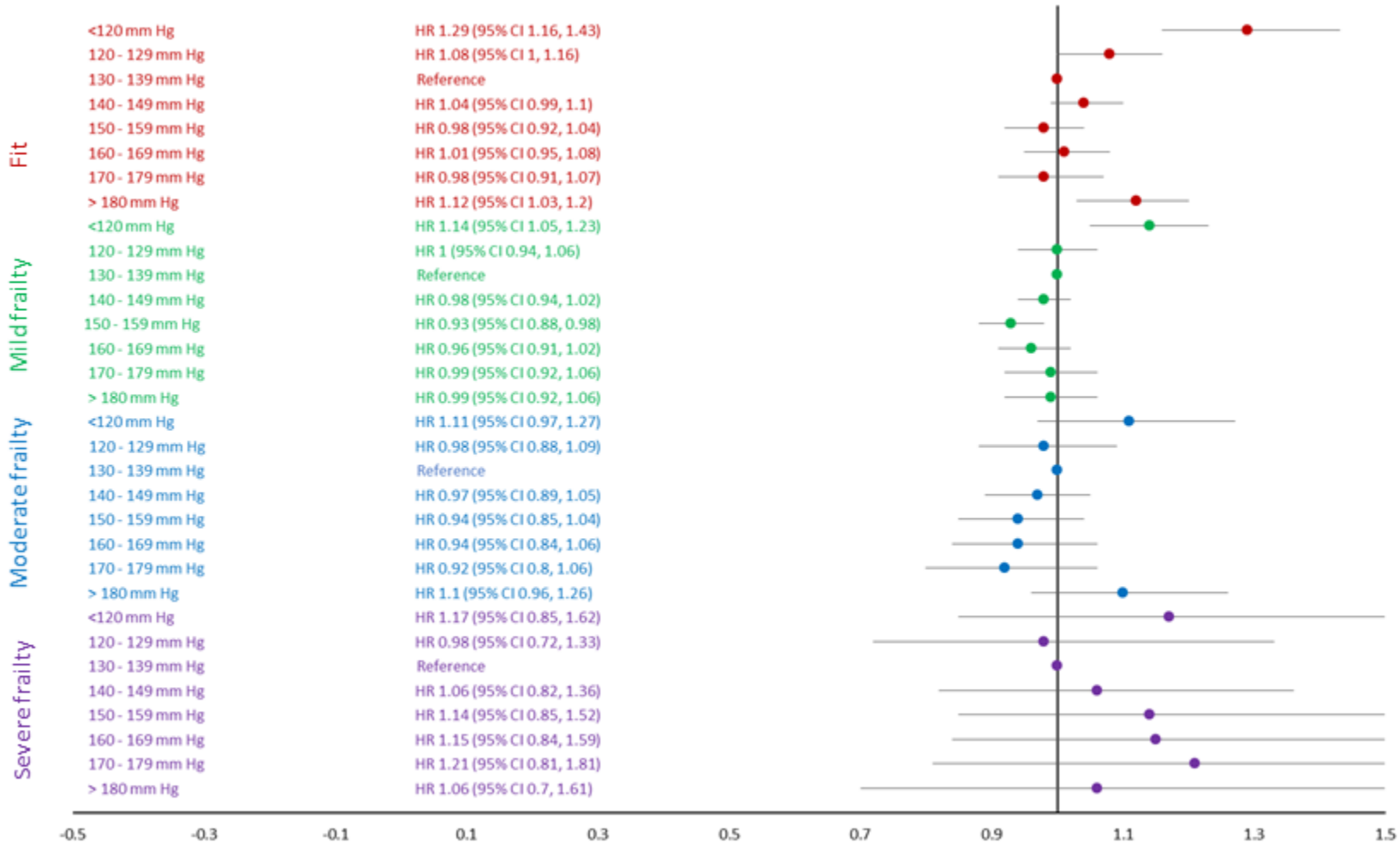


Figure 4-24Associations between systolic blood pressure and injurious falls stratified by baseline frailty status, with 95% confidence intervals, n = 145,598



4.6.3 Frailty modification of the effect of systolic blood pressure on outcomes

The model with and without an interaction term between frailty as a continuous term and sBP as a cubic spline was tested for each of the three main outcomes. The initial model was fully adjusted for cardiovascular risk, BP-lowering treatment and GP attendance.

4.6.3.1 Major adverse cardiovascular events (MACE)

The association of categorised sBP and the hazard of a MACE event was not significantly altered by the inclusion of frailty (Model 2), or an interaction between sBP and frailty (Model 3) (**Table 4-10**). The interaction term in the model itself did not have a statistically significant association with MACE (p-values for interaction with sBP splines 1 and 2: p=0.419, p=0.658). In terms of improving model fit, the addition of the interaction term (sBP with frailty) had equivocal effects on the AIC and BIC measures. The AIC of model 2 was 247,409 which reduced in model 3 to an AIC of 247,404. The BIC of model 2 was 247,579 which increased in model 3 to a BIC of 247,583. Overall then there was no evidence of effect modification by frailty of the association between sBP and MACE.

4.6.3.2 All-cause mortality

The association of categorised sBP and the hazard of death was not significantly altered by the inclusion of frailty (Model 2), or an interaction term between frailty and sBP (Model 3) (**Table 4-11**). The interaction term in the model itself did have a statistically significant association with all-cause mortality (p-values for interaction with sBP splines 1 and 2 within interaction: p<0.001, p=0.020). The AIC of model 2, for all-cause mortality was 259,252 which reduced in model 3 to an AIC of 259,241. The BIC of model 2, for all-cause mortality was 259,422 which reduced in model 3 to a BIC of 259,420. Therefore there is mixed evidence of modest improvement in model fit with the inclusion of an interaction term between frailty and sBP on all-cause mortality.

4.6.3.3 Injurious falls

The association of categorised sBP and the hazard of injurious falls was not altered by the inclusion of frailty (Model 2), or the inclusion of an interaction term between frailty and sBP (Model 3) (**Table 4-12**). The interaction term in the model did not have a statistically significant association with injurious falls (p-values for interaction with sBP splines 1 and 2 within interaction respectively: p=0.868; p=0.420). For injurious falls, the AIC of model 2 was 182,276, which reduced in model 3 to an AIC of 182,273. The BIC of model 2 was 182,446 which increased to a BIC of 182,452 in model 3. Overall then there was no evidence of effect modification by frailty of the association of sBP and injurious falls.

Table 4-10 Association between systolic blood pressure and major adverse cardiovascular events (MACE) and estimates of model fit according to pre-specified model adjustment sets

	HR associated with systolic blood pressure category								AIC	BIC
Model 1	*Adjusted for established cardiovascular risk factors & treatment*								248,829	249,023
	<120	120-129	Ref	140-149	150-159	160-169	170-179	180 <		
HR 95% CI	1.16 (1.11, 1.22)	1.01 (0.97, 1.04)		0.99 (0.96, 1.02)	0.98 (0.95, 1.02)	0.99 (0.96, 1.03)	1.03 (0.98, 1.08)	1.07 (1.02, 1.12)		
Model 2	*Model 1 + addition of frailty*								247,409	247,579
	<120	120-129	Ref	140-149	150-159	160-169	170-179	180 <		
HR 95% CI	1.12 (1.06, 1.18)	0.99 (0.95, 1.03)		1.01 (0.99, 1.04)	1.02 (0.98, 1.05)	1.03 (0.99, 1.07)	1.08 (1.03, 1.13)	1.13 (1.08, 1.18)		
Model 3	*Model 2 + addition of interaction between frailty and sBP,*								247,404	247,583
	<120	120-129	Ref	140-149	150-159	160-169	170-179	180 <		
HR 95% CI	1.10 (1.03, 1.18)	0.98 (0.94, 1.02)		1.01 (0.98, 1.05)	1.01 (0.98, 1.05)	1.03 (0.98, 1.07)	1.07 (1.01, 1.13)	1.12 (1.04, 1.19)		
Model 4	*Model 2 + addition of interaction between frailty and treatment*								247,393	247,567
	<120	120-129	Ref	140-149	150-159	160-169	170-179	180 <		
HR 95% CI	1.12 (1.06, 1.18)	0.99 (0.95, 1.03)	1	1.01 (0.98, 1.04)	1.01 (0.98, 1.05)	1.03 (0.99, 1.07)	1.07 (1.03, 1.12)	1.12 (1.07, 1.17)		

Table 4-11 Association between systolic blood pressure and all-cause mortality and estimates of model fit according to pre-specified model adjustment sets

	HR associated with systolic blood pressure category								AIC	BIC
Model 1	*Adjusted for established cardiovascular risk factors & treatment*								260,202	260,396
	<120	120-129	Ref	140-149	150-159	160-169	170-179	180 <		
HR 95% CI	1.46 (1.41, 1.52)	1.13 (1.09, 1.16)	1	0.95 (0.93, 0.97)	0.94 (0.91, 0.96)	0.92 (0.89, 0.95)	0.95 (0.92, 0.99)	0.98 (0.95, 1.02)		
Model 2	*Model 1 + addition of frailty*								259,252	259,422
	<120	120-129	Ref	140-149	150-159	160-169	170-179	180 <		
HR 95% CI	1.40 (1.34, 1.45)	1.11 (1.10, 1.15)	1	0.97 (0.95, 1.00)	0.97 (0.94, 1.00)	0.95 (0.93, 0.99)	1.00 (0.96, 1.04)	1.04 (1.01, 1.08)		
Model 3	*Model 2 + addition of interaction between frailty and sBP,*								259,241	259,420
	<120	120-129	Ref	140-149	150-159	160-169	170-179	180 <		
HR 95% CI	1.26 (1.19, 1.33)	1.07 (1.03, 1.10)	1	1.00 (0.98, 1.03)	1.02 (0.99, 1.05)	1.02 (0.98, 1.06)	1.07 (1,03, 1.13)	1.14 (1.08, 1.21)		
Model 4	*Model 2 + addition of interaction between frailty and treatment*								259,249	259,423
	<120	120-129	Ref	140-149	150-159	160-169	170-179	180 <		
HR 95% CI	1.40 (1.34, 1.45)	1.11 (1.08, 1.15)	1	0.97 (0.95, 1.00)	0.97 (0.94, 1.00)	0.96 (0.93, 0.99)	1.00 (0.96, 1.04)	1.05 (1.01, 1.08)		

Table 4-12 Association between systolic blood pressure and injurious falls and estimates of model fit according to pre-specified model adjustment sets

	HR associated with systolic blood pressure category								AIC	BIC
Model 1	*Adjusted for established cardiovascular risk factors & treatment*								184,158	184,322
	<120	120-129	Ref	140-149	150-159	160-169	170-179	180 <		
HR 95% CI	1.21 (1.15, 1.28)	1.03 (0.99, 1.07)	1	0.98 (0.95, 1.07)	0.92 (0.89, 0.96)	0.94 (0.91, 0.98)	0.93 (0.89, 0.98)	1.00 (0.95, 1.04)		
Model 2	*Model 1 + addition of frailty*								182,276	182,446
	<120	120-129	Ref	140-149	150-159	160-169	170-179	180 <		
HR 95% CI	1.16 (1.10, 1.23)	1.02 (0.97, 1.06)	1	1.00 (0.97, 1.04)	0.95 (0.92, 0.99)	0.98 (0.94, 1.02)	0.98 (0.03, 1.03)	1.06 (1.01, 1.11)		
Model 3	*Model 2 + addition of interaction between frailty and sBP,*								182,273	182,452
	<120	120-129	Ref	140-149	150-159	160-169	170-179	180 <		
HR 95% CI	1.16 (1.08, 1.26)	1.02 (0.97, 1.07)	1	1.00 (0.97, 1.04)	0.96 (0.92, 1.00)	1.00 (0.95, 1.05)	1.01 (0.95, 1.07)	1.11 (1.03,1.19)		
Model 4	*Model 2 + addition of interaction between frailty and treatment*								182,266	182,440
	<120	120-129	Ref	140-149	150-159	160-169	170-179	180 <		
HR 95% CI	1.16 (1.10, 1.23)	1.02 (0.97, 1.06)	1	1.00 (0.97, 1.04)	0.96 (0.92, 0.99)	0.99 (0.95, 1.03)	0.99 (0.94, 1.04)	1.07 (1.02, 1.12)		

4.6.4 Frailty modification of the effect of BP-lowering treatment on outcomes

The model with and without an interaction term between frailty as a continuous term and BP-lowering treatment as a continuous measure was tested for each of the three main outcomes. The initial model was fully adjusted for cardiovascular risk and GP attendance.

4.6.4.1 Major adverse cardiovascular events (MACE)

The association of categorised sBP and the hazard of a MACE event was not significantly altered by the inclusion of an interaction term involving frailty and BP-lowering treatment (Model 4) (**Table 4-10)**. The interaction term in the model itself did have a statistically significant association with MACE (p-values for interaction: $p<0.001$). With the addition of a frailty-treatment interaction term, the AIC changed from 247,409 in model 2 to 247, 393 in model 3, and BIC changed from 247,579 in model 2 to 247,567 in model 3. This reduction in AIC and BIC is consistent with evidence of effect modification by frailty of the association of BP-lowering treatment and MACE.

4.6.4.2 All-cause mortality

There was no meaningful difference in the pattern of association of sBP and all-cause mortality in the presence of another interaction term between BP-

lowering treatment and frailty (Model 4) (**Table 4-11**).The interaction term in the model itself did have a statistically significant association with all-cause mortality (p=0.020). The AIC in model 2 was 259,252, which reduced in model 3 to an AIC of 259,249. The BIC in model 2 was 259,442 which increased in model 3 to a BIC of 259,423. Therefore there is no clear evidence of effect modification by frailty on the association of BP-lowering treatment and all-cause mortality.

4.6.4.3 Injurious falls

There was no clear difference in the pattern of association of sBP and injurious falls in the presence of an interaction term between frailty and BP-lowering treatment (Model 4) (**Table 4-12**). The interaction term in the model itself did have a statistically significant association with injurious fall events (p=0.001). The addition of this interaction term changed the AIC of 182,276 in model 2 to an AIC of 182,266 in model 3 and BIC of 182,446 in model 2 to a BIC of 182,440 in model 3. This demonstrates that frailty may modify the effect of BP-lowering treatment on the risk of injurious falls.

4.7 Sensitivity analyses

Sensitivity analyses were undertaken to determine whether there was a difference conditional on sex in the association between systolic BP and major cardiovascular events (see **Table 4-13** and **Table 4-14**). Models adjusted for cardiovascular risk, BP-lowering medication, and GP attendance; with the

addition of frailty and with the addition of an interaction term between frailty and systolic blood pressure. There were no significant differences in the associations between systolic BP and MACE in these models.

Table 4-13 Association between systolic blood pressure and major adverse cardiovascular events (MACE) in men, n=55,545

	HR associated with systolic blood pressure category							
Model 1	*Adjusted for established cardiovascular risk factors & treatment*							
	<120	120-129	Ref	140-149	150-159	160-169	170-179	180 <
HR 95% CI	1.23 (1.14, 1.33)	1.00 (0.94, 1.06)	1	1.00 (0.95,1.04)	1.01 (0.96, 1.06)	1.01 0.96, 1.07)	1.06 (0.99, 1.14)	1.10 (1.02, 1.18)
Model 2	*Model 1 + addition of frailty*							
	<120	120-129	Ref	140-149	150-159	160-169	170-179	180 <
HR 95% CI	1.18 (1.09, 1.28)	0.98 (0.92, 1.04)	1	1.02 (0.97, 1.06)	1.04 (0.99, 1.10)	1.05 (0.99, 1.11)	1.11 (1.03, 1.19)	1.16 (1.08, 1.25)
Model 3	*Model 2 + addition of interaction between frailty and sBP,*							
	<120	120-129	Ref	140-149	150-159	160-169	170-179	180 <
HR 95% CI	1.14 (1.02, 1.28)	0.97 (0.91, 1.04)	1	1.02 (0.97, 1.07)	1.03 (0.97, 1.09)	1.02 (0.95, 1.09)	1.05 (0.96, 1.15)	1.05 (0.94, 1.18)

Table 4-14 Association between systolic blood pressure and major adverse cardiovascular events (MACE) in women, n=90,053

	HR associated with systolic blood pressure category							
Model 1	*Adjusted for established cardiovascular risk factors & treatment*							
	<120	120-129	Ref	140-149	150-159	160-169	170-179	180 <
HR 95% CI	1.12 (1.05, 1.20)	1.01 (0.96, 1.07)	1	0.99 (0.05, 1.02)	0.96 (0.92, 1.01)	0.98 (0.96, 1.07)	1.01 (0.96, 1.07)	1.05 (1.00, 1.11)
Model 2	*Model 1 + addition of frailty*							
	<120	120-129	Ref	140-149	150-159	160-169	170-179	180 <
HR 95% CI	1.08 (1.01, 1.15)	0.99 (0.95, 1.05)	1	1.01 (0.97, 1.05)	1.00 (0.95, 1.04)	1.02 (0.97, 1.07)	1.06 (1.00, 1.12)	1.11 (1.05, 1.17)
Model 3	*Model 2 + addition of interaction between frailty and sBP,*							
	<120	120-129	Ref	140-149	150-159	160-169	170-179	180 <
HR 95% CI	1.07 (0.97, 1.17)	0.99 (0.94, 1.05)	1	1.01 (0.97, 1.06)	1.01 (0.96, 1.06)	1.04 (0.98, 1.10)	1.09 (1.02, 1.17)	1.17 (1.07, 1.27)

4.8 Conclusion

The associations of systolic blood pressure with a range of cardiovascular and non-cardiovascular outcomes were modest and non-linear. Highest risk of adverse outcomes was associated with lowest systolic blood pressure. Findings presented in this chapter provide the first population-based evidence of frailty as a useful prognostic factor in a cohort of patients with hypertension for treatment as primary prevention of cardiovascular outcomes through the use of routine primary care data linked to routinely collected inpatient data and mortality data. The associations between systolic blood pressure and outcomes were not evident in sub-populations defined by moderate and severe frailty. This study found no clear evidence of effect modification by frailty of associations of systolic blood pressure with primary and secondary outcomes. However, findings demonstrate evidence of possible effect modification by frailty on the effect of BP-lowering treatment.

Chapter 5 Biographical interviews

5.1 Summary

This chapter presents the methods and findings of ten biographical interviews. Here I will address the final objective of this PhD which is to explore the patient's perspective using a series of narrative interviews to reveal how the concept of frailty can inform shared decision making in older people with hypertension. This study was undertaken to complement the interpretation of routine data findings presented in Chapter 4 with the perspective of those who live with hypertension and frailty. Three themes emanated from the analysis: how ageing is conceived; what is valued in life now; and, how hypertension is perceived.

5.2 Introduction

In the context of the uncertainty of how current evidence applies to older people with frailty, international guidelines recommend a more personalised approach to the management of hypertension in later life by using shared-decision making. Guidelines specifically recommend that the clinician considers: a person's competing health concerns (323); overall clinical condition; and, concomitant medications (322). Guidelines recommend involving the patient to identify whether the balance of benefits and risks related to BP-lowering are in that person's best interests, but do not indicate how this should be done.

To do this requires an understanding of how people make choices about different outcomes related to hypertension, as this may be different in the context of ageing and competing risks. Currently, there is a lack of evidence as to what is important to older people and whether this is different in the context of frailty. As such, there is a need to understand more about the lives of older people with hypertension, to appreciate how hypertension and the consequences of treatment / non treatment may impact them. This study explores the perspective of older adults living with frailty on what is important from their own perspective, to determine which outcomes might be prioritised in the management of hypertension.

5.3 Research Question

Is frailty a useful measure to inform management of hypertension from the perspective of patients themselves?

5.4 Objective 5

To explore the patient's perspective using a series of narrative interviews to reveal how the concept frailty can inform shared decision making in older people with hypertension.

5.5 Methods

This study will be reported according to Consolidated Criteria for Recording of Qualitative Research (COREQ) guidelines (485). Ethical approval was granted by the East Midlands Research Ethics Committee (REC) 18/WM/0011 and written consent sought from all participants.

5.5.1 Research team and reflexivity

5.5.1.1 Personal characteristics of interviewer and team

The interviewer throughout was the PhD student (OT). The interviewer is male, mixed white ethnicity, brought up in Cardiff, but had lived 2 years in the Bradford district where the interview participants lived. At the time of interviews, OT was aged in his early thirties, and a clinician with 9 years of clinical experience in London, Edinburgh, Bielefeld (Germany), and Katete (Zambia) following qualification. Currently, he was in post as a geriatrics registrar at Bradford Royal Infirmary. OT has experience of working with older people and was sensitive to those with frailty and the nature of mental capacity within this group.

OT was supervised by a qualitative methods researcher, Mary Godfrey who has significant expertise in qualitative research methods, particularly in the context of frail older people. MG has worked on multiple qualitative research studies in communities in Leeds and Bradford over the past 30 years. MG supervised

OT's interview methods and oversaw his development as an interviewer, using his experience of interviewing in clinical history-taking as a base.

5.5.1.2 Relationship with participants

5.5.1.2.1 Relationship established

All of the CARE 75+ study cohort participants who were approached gave their consent for their contact details to be provided to the researchers seeking their participation in related future studies. The researcher (OT) first made contact three to four weeks prior to the first interview with a personal letter inviting the person's participation in this study. The information sheet accompanying this letter explained who we were, together with photos of and contact details for the principle investigator (OT) and the qualitative PhD supervisor (MG). Shortly after the letters were sent, the interviewer (OT) called the participant to enquire whether the letter had been received and whether the person had any questions. All interviews were undertaken by one person (OT), who at the beginning of the first interview went through the participant consent process with each interviewee, and made an assessment of the mental capacity of the participant.

5.5.1.2.2 Participant knowledge of the interviewer

In an attempt to enable a more candid discussion of what can otherwise seem clinically prescribed concepts, OT introduced himself to participants in his current role as a researcher, rather than as a clinician. The invitation letter was

written by the interviewer who was introduced as the researcher on the Study of blood pressure: What matters in Later Life? (SWaLLow) project. The purpose of the study was described in the information sheet as research ‘to understand from a patient’s perspective what matters in later life with regards blood pressure, so we will be able to understand how to better treat blood pressure in later life’.

5.5.1.2.3 Interviewer assumptions

The interviewer had a medical training, so his occupation, interests, cohort and background will be factors which shaped his interviewing style and analysis of the data. The interviewer was motivated to include a patient voice in this PhD study to balance the weight given to routine data, and to inform how frailty may inform the clinical management of hypertension. Assumptions made early on in the conception of this study included that: outcomes of interest for older people with frailty may be different from those without frailty; and that, a person’s focus in later life may be more on the quality of life rather than longevity. It was also assumed that patients knew they had hypertension and may have had some experience of sharing decision making regarding BP-lowering treatment. Another assumption was that the language of priorities or choice of outcomes may be salient, as is the case in other patient groups.

5.5.2 Study design

5.5.2.1 Methodological approach

This study took an exploratory qualitative approach, employing interviews to elicit narratives and undertaking open biographical interviews, supported by a broad topic guide, among community-dwelling older participants. The choice of biographical approach was based on the following considerations:

1. Experience of older age is shaped by structural and relational factors formed across the course of one's life and therefore not something that can be considered separately from what has gone before.
2. Lives, relationships and experiences change through time as does the way in which participants frame values and their sense of self. Within this there are cohort and cumulative dimensions to consider. The times a person has lived through as well as their chronological age will contribute to a person's perceptions and values.
3. Frailty and hypertension may appear medicalised concepts, so eliciting stories represents a means of empowering the narrator to speak on their own terms and represents a socially normative way of navigating subjects that may be intimate or sensitive such as ageing and death. Narratives are often rehearsed over time, reflecting enduring values, and can represent a means of communication that is still accessible for those developing cognitive impairment.
4. Story-telling is a culturally normative means of communicating between older and younger people. Their currency may well help develop a rapport, despite differences in life experience between the interviewer

and the interviewee. The potential for humour and metaphor in stories may give the potential space for safe exploration of difficult topics.

5.5.2.2 Patient Representative

Mrs Dorothy Jones (DJ) was recruited as a patient representative. DJ is also older than 75 years old, has hypertension and has clinical features of frailty: having experienced multiple falls over the year prior to the study. A pilot interview was conducted with her to refine the topic guide. Mrs Jones also reviewed the invitation letter and information sheet for readability.

5.5.2.3 Participant selection

5.5.2.3.1 Sampling method

A purposive sampling approach was adopted. Purposive sampling is a method of sampling that is common in qualitative research (486). This sampling method seeks to identify and select informative cases (487) by identifying and selecting groups who are willing to engage, and can communicate these experiences in a reflective manner (488).

The aim of the study was to better understand the impact of one's experience of ageing on hypertension management. Many characteristics are known to shape the ageing experience. The purposive sampling strategy in this study was based on key factors involved in ageing which are measurable: age; sex; level of frailty; and, whether prospective participants were living alone, with a partner, or with family.

5.5.2.3.2 Sample size

The aim was to recruit ten people. The sample size was chosen a priori, to achieve enough data for the purpose of this research which was:

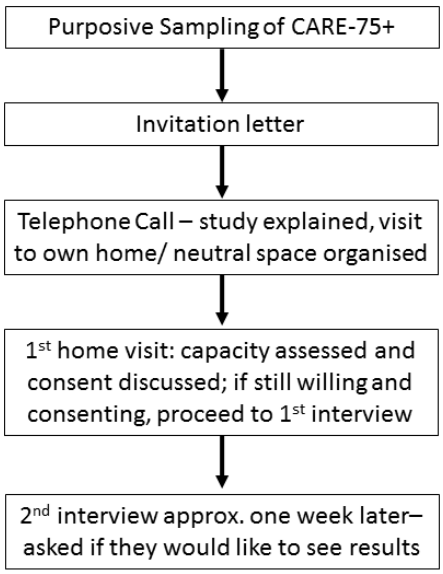
1. To explore a patient's voice to complement a large routine data study which had a more generalisable study sample;
2. To get as full a picture as possible within the limitations of this study, this being part of a research training fellowship whose dual aim was to introduce and train the investigator in qualitative research methods.

This was planned as a small study which of itself was not intended to be representative of the whole population nor definitive in its findings. A sample size of ten patients was felt to be appropriate for the methodological approach employed, the purpose of which was to discover meaning, and to explore what is said and unsaid in sufficient depth and detail (489). The choice of sample size was also informed by other studies using a narrative approach in sociological literature.

5.5.2.3.3 Recruitment

The recruitment process is presented in (**Figure 5-1**). Participants were recruited from the Community Ageing Research (CARE75+) cohort study (1,106 participants recruited nationally at that time). CARE75+ participants are community dwelling older people aged ≥75 years. Care home residents, people living at home who were bedbound, and people in the terminal stage of life were excluded from the study (490). The CARE 75+ cohort has been profiled in published literature where cohort inclusion and exclusion criteria are also detailed (490). 86% of the CARE 75+ study cohort have given consent for their contact details to be provided to researchers seeking their participation in related future studies. Only those who had volunteered to be contacted to take part in future research studies were approached. Of these participants, the CARE 75+ cohort Project Manager was asked to provide a list of potential participants meeting all the inclusion criteria to the study researcher.

Figure 5-1 Recruitment process flow diagram



Inclusion criteria:

All participants of this study were required to be:

1. Participants of the CARE 75+ cohort study who have consented to be contacted about future studies;
2. People identified as having frailty according to both the phenotype model and the electronic frailty index (both of which are defined in **Section 1.7.1**).
3. People with a diagnosis of hypertension on their GP record.
4. People living in the Bradford district.

Exclusion criteria:

This study excluded:

1. People who are deemed to lack mental capacity and cannot consent to participating in this study;
2. People who are not fluent in the English language.

Participants with cognitive impairment who had capacity to consent were not excluded. An open invitation was made for a friend or close relative to attend, particularly where there were concerns from the investigator or family member that whilst the patient had capacity to consent, because of cognitive impairment, mental capacity may fluctuate over the course of the interviews.

Given that the study was funded as a research training fellowship, interviews were undertaken in the interviewer's first language only. As a result, participation in the study was limited to those who could understand verbal or written English.

The researcher (OT) sent a letter inviting participation in the study by post to the identified potential participants. An information sheet accompanied this, explaining the study. This information sheet was co-written with the patient representative (DJ) to include contact details and photos of both the study investigator (OT) and supervisor (MG). The information sheet detailed: the study purpose; why the person had been approached; what taking part would involve; possible benefits and disadvantages of participation; and, what would happen to the results of the study. The letter clearly stated the plan to follow up with a telephone call to discuss the study in more detail. Those who did not want to discuss participation could call the team directly (i.e. an opt out process).

To provide ample time to read the information sheets, the researcher telephoned potential participants a minimum of 5 days after sending the invitation letter and the information sheet. If the participant was eligible and interested in taking part, the researcher organised a time and place to meet.

During the visit, the researcher first discussed and answered any questions about the study. It was made clear that the choice of whether to participate in this study would not affect the services and standard of care they receive in any

way. If the person was willing and had capacity to consent, they were asked to complete the study consent form, and proceed to the initial interview.

Capacity to consent was assessed by the researcher using the framework of the Mental Capacity Act (491). This assessment continued over the course of the telephone conversations and during the initial visit to explain the study, and also when going through the Consent Form. A copy of the consent form was given to the participants, and the original is stored centrally at the Academic Unit of Ageing and Stroke Research (ASR) at the Bradford Institute for Health Research.

If consent was not given, the researcher left without conducting data collection, and any information held about the person by the research team was confidentially destroyed. The right of potential participants to refuse consent without giving reasons was respected. Participants who gave consent were free to withdraw from the study at any time without giving reasons, but the data recorded until that point were retained and this was explained both at the time of consent and time of withdrawal.

For those who were unable to read but had capacity to consent, large print information sheets and consent forms were provided. Consent was also audio-recorded. For those with hearing impairment, corrective devices were sought, where they were not available, we had the use of amplification equipment.

5.5.2.3.4 Non-participation

The data manager of the CARE75+ study (490) provided a list of 42 participants who met the inclusion criteria for the study. Participants were approached in two waves to allow a period of time for people to decline and allow purposive sampling. A flow chart describes participation and reasons for rejection at each stage (**Figure 5-2**). The first patient was recruited on 9th April 2018, and the last patient was recruited on 18th May 2018. All patient recruitment was recorded using the NHS Edge research management software (492).

Figure 5-2 Participant Flow Chart

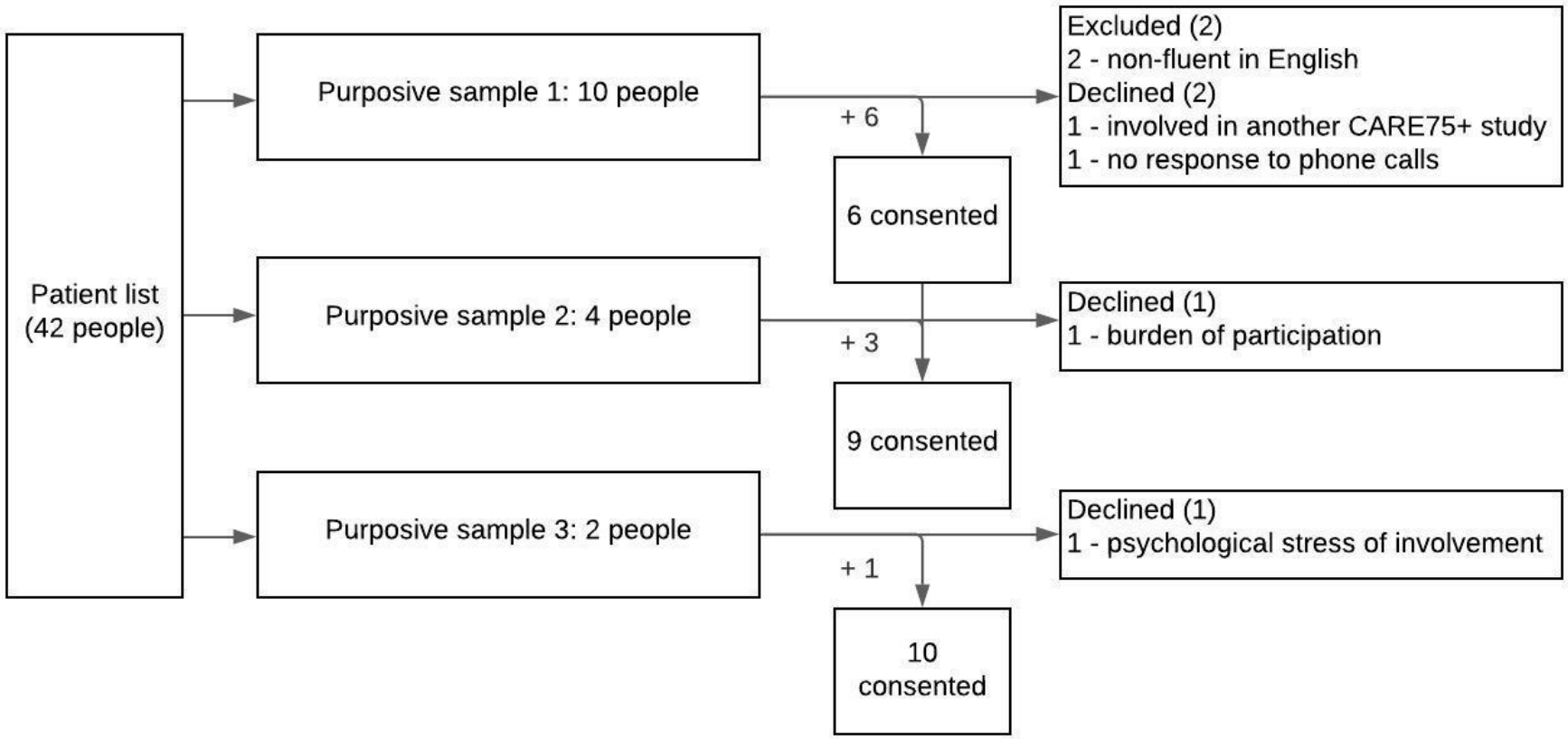


Figure description: The patient list provided by the CARE75+ data manager was an encrypted list, which was purposively sampled in successive waves across a period of two months, according to the sequence in the figure.

5.5.2.4 Setting

5.5.2.4.1 Setting of interviews

Once the consent form had been obtained and signed the researcher proceeded with the initial interview. Interviews took place at a time and location convenient for the participants and their carers, preferably at their own home. Participants were invited to have a member of their family, friend or carer present during the interview. The accompanying person was not actively involved in the interview. The interview was carried out in two parts, approximately one week apart.

5.5.2.4.2 Sample characteristics

The sample was balanced on age, sex, frailty score and living circumstances (see **Table 5-1**).

Table 5-1 Study sample according to pre-specified characteristics

Patient characteristic	Category	Proportion
Sex	Women	50%
Age	75 – 80y	30%
	81 – 85y	20%
	86 – 90y	20%
	91 - 95y	30%
Electronic frailty index	Quartile 1 (0.25<0.28)	20%
	Quartile 2 (0.29<0.36)	20%
	Quartile 3 (0.36<0.42)	20%
	Quartile 4 (0.42<0.56)	20%
Fried frailty score	3	50%
	4	30%
	5	20%
Living circumstances	Lives alone	70%
	Lives with partner/spouse	20%
	Lives with family	10%

5.5.2.4.3 Pseudonyms

Participants were allocated a pseudonym in the data analysis. The choice of a pseudonym over a study number was a purposeful decision. Although both are of equivalent anonymity, the use of pseudonym may be more appropriate for a study using qualitative methods that aims at understanding the person in their social and biographical context. From a research practice perspective, assigning a pseudonym from the outset means that the researcher maintains a picture of the interviewee in terms of their pseudonym. It avoids the reductionism implicit in using a study number and for this type of study represents a more personalised approach whilst retaining anonymity.

5.5.2.5 Data collection

5.5.2.5.1 Interview design

A two stage interview sequence was chosen to: lessen interviewee fatigue; give time to develop rapport; allow reflection by both interviewer and interviewee upon the issues discussed; and, for the interviewer to use the second interview to test out developing theories and explore emerging topics not covered in sufficient depth in the initial interview.

Interviews were semi-structured, and based on a topic guide (see **Appendix E**). The first interview focused on the person's identity, who they were, who they had become and what was important in defining a good life. The second interview was set in the context of what shaped the person over time, to explore more direct questions about: the process and meaning of older age; the concepts of frailty; hypertension; their own priorities; and, the concept of sharing decision making in the management of hypertension.

5.5.2.5.2 Development of topic guide

The interviewer used open methods of inquiry to invite the interviewee to tell their story. Prompted initially by the SWaLLow study topic guide, the interview was adapted to the needs of the individual participant. The topic guide was informed by a review of the evidence presented in **Chapter 1** and **Chapter 2**, and was developed together with the patient representative DJ. The topic guide was devised drawing on the existing literature on three general themes:

1) Life events - health and illness experience, quality of life and wellbeing:

- Briefly explore the person's own biography – place of birth and growing up, family and occupation
- Focus on any recent experience of changing health and illness, transition points, times of crisis and improvement ('good days, bad days')

2) High blood pressure - personal experience of its diagnosis, treatment, and consequences:

- Understanding of the diagnosis and implications of high blood pressure
- Perception of blood pressure monitoring as a burden or an opportunity

3) What is important for a good life - priorities in later life:

- What it is important to them in terms of quality of life and wellbeing
    - Main fears and anxieties day to day
- Priorities with respect to balancing short and long term goals.
    - Does perception change with changing overall health?

5.5.2.5.3 Data recording

Basic demographic data were extracted from the CARE75+ records. Interviews were audio-recoded and professionally transcribed in full. Field notes documented characteristics of the interviewee and home situation, reflective observations and impressions at the time. Key events in each person's biography were drawn out as timelines.

5.5.2.5.4 Duration

Interviews were planned to last approximately 45 minutes.

5.5.2.5.5 Data saturation

Once evolving concepts were fully accounted for across the data, the variability between concepts and participants was explained and relations between concepts were tested so that a theory emerged, and at this stage it could be verified that data saturation was attained (493). Data saturation is a concept where planned methods of analysis draw from a grounded theoretical approach, as did the comparative methods detailed below, where the aim was to develop an explanation of social processes in the context in which they take place (494, 495).

5.5.3 Data analysis

5.5.3.1 Analytic techniques

Narrative techniques of interviewing shaped the character of the data that emerged. A variety of techniques were explored to find meaning and to develop themes including narrative analysis and constant comparison (from grounded theory). Time-lines, matrices and coding were used to support the application of the analytic techniques.

Transcripts were revisited to establish a person's narrative or story. In particular, focus was given to how descriptions of self-identity might relate to changing experience of symptoms of ill-health over time and impact on current well-being. Both content and form were considered, and methods of inductive analysis were used, working from a reflexive stance.

Key points of the analysis included the following:

1. I sought to identify an individual's trajectory over time by drawing timelines to identify correlation between changes in health status alongside major landmark life events.
2. The data were analysed in an open manner.
3. Stories were identified and each of them assessed with regards to structure (i.e. how the story is developed, conducted and told), and content (what the story means(496)). In particular, I looked for coherence: of the story within itself; of the story with other stories (497) and, of the story within an individual's world (498). Matrices were developed that combined patterns of themes, relationships and trajectories over time around the three concepts introduced in the topic guide: ageing, high blood pressure and priorities in later life.
4. I wanted to assess in what light the person presents themselves in the context of friends, family, and society (499, 500). A reflexive diary (501) was recorded to analyse findings in the context of the standpoint as an observer, and to iterate the method of inquiry and questioning.
5. Constant comparative methods from grounded theory (494) were

applied to identify broad themes as well as the manner of their telling, the attitudes that they expressed, what was said and what was left unsaid. Incidents that are conceptually similar were grouped together (502). Areas of dissonance were explored as representing potential uncertainty (503). Interviews were compared and contrasted and critically assessed for key themes.

Coding software was not used in the analysis of transcripts.

5.5.3.2 Participant checking

Emerging findings were discussed with the Study Management Group, with the lay researcher (DJ), and with Patient and Public Involvement representatives on the Frailty Oversight Group which oversees projects involving the CARE 75+ study. At the end of the study, the findings were presented at an event to thank participants and their carers for their involvement, and feedback was sought from participants on the emerging themes identified. Findings were also presented to the Halifax Rugby Union Club Men United group and a discussion followed to determine whether the themes evolving from analyses were salient among them also.

5.5.3.3 Trustworthiness

Standard approaches to demonstrating trustworthiness and quality in qualitative research were used, including: clear documentation of the research process (methods, analysis, any problems encountered and solutions found); transparency of the development of interview topic guides; documentation of the contextual features in which the research was carried out; the exploration of deviant cases and alternative explanations; discussions of emerging findings among the research team; and, the researcher kept in a reflexive diary.

5.6 Results

Twenty interviews with ten participants took place between March and May 2018 (**Table 5-1**), lasting an average of 52 minutes (range 38 to 80 minutes). Six interviews involved family members. Participant mean age was 86 years (range 77 to 94). Half were women; half were men. The average frailty index in the cohort was 0.364 which is the equivalent of severe frailty, with a median phenotype frailty score of 3.5. Seven lived alone, two with their spouses, one with family. Hypertension had been diagnosed at different points in the life course: 2 during pregnancy, 3 following a stroke, 1 following a fall, 3 on screening.

In terms of their biography, they were mostly born to large families, but had smaller families of their own (**Table 5-2**). Most had experienced upward social mobility. Half remembered regularly going hungry as children, now seven out of ten owned their own homes.

Stories about biography focused on: overcoming constraints of the time (**Table 5-3**) about the times they lived through; and, their relationships with others. The major and minor findings are grouped in three themes: how ageing is conceived; what is valued in life now; and; how hypertension is perceived.

Figure 5-3 Study flow diagram

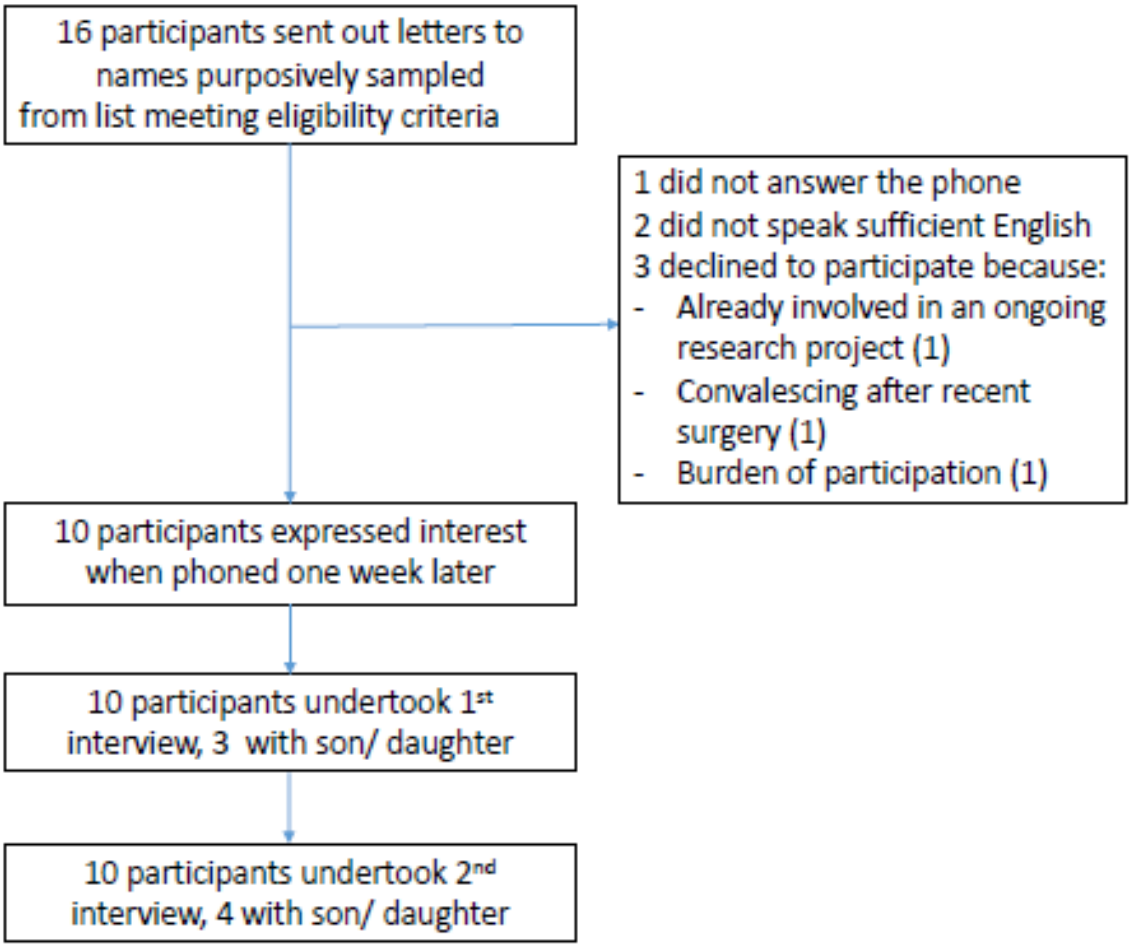


Table 5-2 Profile of study cohort according to demographics across the life-course

Childhood		
Place of Birth		Bradford (6); London(1); Northumberland (1); Sheffield (1); Pakistan (1)
Family size (of origin) mean (range)		4 (1 – 7)
School exit	<15 years	5/10 directly to work (Mills (2) Shop (3))
	>15 years	Grammar school (2); Technical school (3: mechanical engineering, nursing, secretarial); University (0)
Early adulthood		
Met spouse		Work (1); Church (2); Family (2); Social clubs/ dancing (5)
Family size (of own) mean (range)		3 (1 – 5); 9 had their own; 1 adopted
Marital status	Women	Widowed 5/5
	Men	Widowed (2); Spouse in care home (1); living with spouse (2); With family (1)
Late life		
Living Circumstances		7/10 owned own home; 3/10 lived in council accommodation (2 in sheltered living)
Hospital < last year		2/10
Mobility	Dependent	8/10
	Independent	2/10
Driving car		4 (2 men, 2 women)

Table 5-3 Characteristics of participants according to subjects of narrative across the life-course

	Early life	Mid-life	Later life
Ali	*Origin* Pakistan; parents both in business *Work* Emigrated at 18, factory work	*Family* married; 2 children *Work* moving for factory work, nearer to family	Widow, Lives with family. Council house, drives *Constraints* (physical) weakness from stroke, walking stick
Gertrude	*Origin* Sheffield; father steelworker *Training* Nursing	*Family* married, 2 children; *Work* vegetable garden; husband's police work	Widow, alone; own bungalow *Constraints* (physical) walks supported by furniture, at high risk of falls
Ron *	*Origin* Bradford; father shopkeeper; 1 sister *Training* Electrical engineer	*Family* married and adopted 3 children. *Work* electrical engineer and woodcraft as hobby	Widow, alone; own house; son & carers visit daily *Constraints* (cognitive) deficits, (physical) falls, walking stick
Betty *	*Origin* Bradford; father window cleaner; 6 siblings *Work* Shop from 14 then mill work	*Family* married, 1 daughter; *Work* in mill with husband and daughter	Widow, alone, Sheltered housing; daughter visits daily *Constraints* (cognitive) deficits, (physical) wheelchair
Patricia	*Origin* Bradford; father tended railway horses *Work* book-keeper	*Family* married, 2 children; *Work* set up own flowershop business	Widow, alone, own home; drives *Constraints* (physical) risk of falls
Trevor	*Origin* Bradford; father electrician, mother cleaner; 1 brother *Training* Civil service training, national service	*Family* married, 2 children; *Work* Council director	Married, own home; 4 carers, *Constraints* (physical) blind; wheelchair-bound, hoist-transfers
Margaret *	*Origin* Northumberland; father chip shop; 3 siblings *Work* Millwork from 14	*Family* married 3 children; *Work* shop	Widow, Own home; daughter-in-law visits daily; drives *Constraints* (cognitive) recent delirium (physical) walking stick
Charlie *	*Origin* London; father bus conductor; 4 siblings *Work* Paperboy, golf-caddy, army cook in WW2	*Family* married; 4 daughters. *Work* bus driver and handyman for kids	Married, Own house, Wheelchair bound; four carers/day *Constraints* (cognitive) deficits (physical) help with transfers.
Glen	*Origin* Keighley; father farm work; 1 brother *Training* Motor mechanic	*Family* married, 2 children; *Work* self-taught farmer.	Married, Own house – farm; no impairments, drives *Constraints* (physical) risk of falls
Mary	*Origin* Bradford; father mill-worker; 4 siblings *Training* Secretarial school	*Family* married, 5 children. *Work* secretarial work, bringing up children, allotment,	Widow, Council sheltered housing *Constraints* (physical) zimmer frame

Key: * = dyadic interview - family member present; NH: nursing home; TB: tuberculosis; TV: television; T/L: timeline; WW: world war

5.6.1 How is ageing conceived?

5.6.1.1 Points of agreement

There were several overarching themes in defining what ageing looked like in terms of the older people themselves. Ageing was often described as a gradual process made evident by external events, illnesses, or in other terms personal to that individual. Ageing was more visible in others than in oneself. Most did not identify as frail and described the term in negative and value laden terms.

In their stories, participants used different markers to identify transitions across the life-course. Most often these markers represented changes of role, rather than age, and variably used children's birthdays, a new job, moving house, one's own illness, or more often, the illness of others. Several interviewees recalled childhoods in the inter-war years moving house or city in search of work, and went on to describe periods of their life by where they lived. Betty called the sheltered housing she moved into after her husband's death "God's waiting rooms". Women including Margaret and Mary used the birthdays of children and grandchildren to charter their timelines. Men including Glen, Trevor, and Charlie referred to jobs, or associations with clubs.

Ageing was variably described by it's associated limitations, with the struggle to overcome these limitations, and with loss. For Betty, it was the limitations imposed by illness, she said "*I walk slowly now*", "*I think I'm tired, I must be tired at 94*", "*I'm breathless all the time*". For Margaret it was a struggle that was personal and that characterised later life : *I'm frail, I know I am*" "*I struggle. I do*

most things for myself but I do struggle. I don't always tell [my Daughter in Law, present]". Indeed at each of Margaret's losses: her husband's death, her developing breathlessness, her delirium, she described how she had to find a new way to adjust and now life was "*in slow motion. I mean I can't shower every day else I'd never be out of it. I have to prepare me self every step of the way that I'm doing because it takes me so long to do everything*". Since her experience of post-operative delirium, Margaret felt more insecure about her memory, and she had taken measures to keep records, lists and plan the following day beforehand: she said, that now "*there are a lot more things to remember*".

Ron, engineer by profession, and do-it-yourself man in retirement, similarly characterised himself by his adaptations to overcome the effects of ageing. When Ron was asked whether he identified himself as frail, his son who was present, refined the question:

Son: "*A jar opened and it was really stiff, that's a sign of frailty if you're not able to twist the jar open, or something like that…"*

Ron: "*Well, I've got a gadget…"*

5.6.1.2 Points of divergence

There were differences in how people characterised their attitude to ageing and how much the ageing process was perceived to be in one's own hands. On one hand, for many, there was an explicit acceptance that life would not go on for ever. Trevor described his mother, who he esteemed highly, and for whom he

had become a carer in her later years. Her attitude to old age was "*I've had my life, get off home lad*". On the other hand, 'keeping doing' was a major theme, and a strong identity as 'survivors' was expressed by various interviewees. Patricia, herself a soroptimist and strong believer in the importance of education, spoke of how the role of the older person had changed, and how people were themselves agents of that change. Patricia described ageing as a state of mind: "*age is just a number isn't it*" and, "*there's no point just sitting in the corner with a shawl around your shoulders is there?*"

This related in part to where someone was on their own trajectory of ageing. For some, particularly where time had elapsed since, acute health events were associated with a permanent loss that had changed their landscape. This was the case both for illnesses of their own, and (more often), illnesses affecting their spouse. Ali said that "*since my wife got cancer, then, I changed myself.. a lot of things happened"*, he became much more focused on his faith and maintaining a healthy lifestyle.

In others, one could sense a current tension, as their recognition of themselves ageing, seemed to be in transition. For Gertrude whose situation was changing, the effects of ageing were characterised as a (hopefully) temporary phenomenon. Gertrude said of the changes of aging *"you just ignore them don't you"*, and seemed aware that her current way of life was under threat from increasing instability and falls, but pointed to different hobbies and tasks about the house, even hanging the washing on the line during the second interview. Gertrude said "*Well I'm catching up with all that's been left and I've got a pile of*

work in that corner as you see there, there's probably a thousand or two stamps there".

5.6.1.3 Frailty

Most did not identify as frail and there was a resistance to accept the label for oneself. Ali said "*I think I didn't want.. to say I was frail, no, but weak … Sometimes weak, you know, I mean but it's very rare I feel frail*". Frailty was often characterised in others rather than oneself. Frailty was differently defined but perceived generally in negative terms, and as something to avoid.

Falls or rather the fear of falls defined frailty for Trevor who characterised frailty by decribing a relative: "*she's perfectly capable of walking but she's frightened of falling again so she can't walk unaided*". Patricia said of her own fear "*I didn't trust meself*", "*a matter of not being stupid, not doing something stupid to bring about [a fall]".* For others it was physical weakness. Mary described someone she had met at a community group *"a lady there who was on crutches and she can't come anymore because she can't get out of her house, she must've twisted her ankle",* or another with memory problems: *"she didn't know where the heck she were, I know she couldn't help it and it was pitiful".*

For Charlie the image of frailty was of death itself, an image he had from a childhood memory when he was delivering papers "*I went back to the shop and I said, "She's not in," "She is, get on and see, she takes a long while to get to the door", "so I go down again, shoves the door, never seen… never seen in all*

me life, like a bloody skeleton, face were all eyeballs, you know, all there". Margaret described frailty as complete dependence – as a pitiable state: "*just a weakling and needing other people, needing help*".

The fear of loneliness was profound. For Charlie, himself a soldier in world war 2, survivorship came to him as much as a sense of duty as a matter of choice – he was "*on the last bit*" and it could be a "*very lonely life in't it, same with the watching telly like, and that's bloody rubbish*".

5.6.2 What is valued in life now?

5.6.2.1 Points of agreement

Narratives were focused on maintaining identity and finding meaning. Stories championed: survivorship in the face of adversity; inter-relatedness; and, keeping going. In contrast, giving up or being given up on characterised chief fears.

Participants presented themselves as survivors, with an emphasis on defiance in the face of adversity. Participants were born between 1924 and 1941, so early life was characterised by living with the effects of world war one (WW1), the depression and world war two (WW2). Stories of ageing and disability were not confined to later life. Stories of youth, particularly for women, commonly involved caring for prematurely ill fathers: three of whom returned disabled from fighting in WW1; and two of whom ultimately died from occupational injury.

Identity was forged through experience of hardship and disability. After the death of Betty's father whilst she was still a child, her mother and six siblings were left in poverty, "*but she always fed us, you know, we never went hungry, [despite] being very poor*".

'Keeping going', whatever the circumstance was a means of dealing with challenges of old age too. In later life, Glen, who had two jobs and kept working a 14 hour day until he was 75 said, "*you're better keeping work because once you stop you lose it and you can't do it and if you stop you're up the creek*". Surviving against the odds was esteemed in others. Betty revered her neighbour: "*He'll be 86 this time, I'm sure he is, he wants to see 100. But, there isn't a lot like [him], is there, I mean, I see how he walks, he goes, he lives downstairs and he walks round"*.

Giving up the will or being given up on was a fear expressed in stories comparing themselves to peers. Glen described his younger neighbour who was ageing before his time as if a moral failure: *"I know there's a chap up [the road, and when I last visited, I asked] 'Where's Len?', I said 'It's dinner time, where's Len, I've been looking for him?', [his wife replied] 'Oh, he hasn't got out of his bed yet', I said, 'It's bloody one o'clock', 'Oh, well he doesn't get up if he's nowt to get up for'".*

How people justified themselves as not being frail also revealed values important to them. Charlie's daughter identified his being able to enjoy drinks

and dinner, and, being able to shave himself. These were functions he had previously lost whilst sick in hospital.

Daughter: "*He isn't frail if he can do that is he, he isn't frail if he can sit and have his drinks and have his dinner, no, I think you're doing alright dad".*

Charlie: "*I'm not going to say 'owt about that love".*

[Both laughed]

Betty resisted that she was frail because she is still going out, even if it was just once a week. Betty asked her daughter whether she was frail:

Betty: "Am I frail love?"

Daughter: "You're frail now, yeah"

Betty: "Yes, I am frail, yeah. "But I go out, we go out you see, a lot"

Engaging with others was valued highly. Patricia described her friend talking about another from church *"You're the oldest of the lot of us", she says, "and you're organising us all!". She got that straight, to keep going and want to be the organiser. So [...] it's only a matter of a number on a book isn't it, you know, age, it's as you feel" .*

5.6.2.2 Points of divergence

Differences in values were expressed in how they related to the individual, to family, or, to the community. Women often valued family and community more explicitly in the stories they told.

Stories characterised their narrators by group identity, whether that was: as a couple; as a family; or, in their local community. Early in life, Betty developed tuberculosis for which she was moved to a sanatorium for more than a year, and her mother was left to bring up her new-born child. Explaining how this worked, Betty said "*we got by, stuck together*".

The post-war years were associated with a celebration of communal spirit, Margaret recollected the street parties in Keighley at the end of WW 2. Gertrude described in vivid detail the kindness of strangers who, 50 years ago, looked after her other children when she had to accompany her eldest daughter to hospital.

In later life, inter-dependence emerged as a means of dealing with sickness. All five women married older men. When describing her husband suffering three life-threatening illnesses, and each time going to intensive care, Patricia spoke as if she and her husband went through it together. Patricia said "*we went through intensive care and we got him through absolutely fine*".

Sharing the burdens of family did not abate with age, even in the context of significant personal limitations. In spite of being housebound through illness of

her own, Mary organised a family holiday for her son who had cancer, and was busy supporting her daughter through a difficult divorce.

Existing without one's family could be difficult to imagine. About the future, Ali said regarding his niece who planned to move out of their shared house "*I think when she will go out [moves out], God knows what happen[s then]*".

The role of inter-dependence in identity appeared particularly prominent for those for whom memory loss was a problem. This was evident in the exchanges enabled by the dyadic interviews (listed with * in **Table 5-2**). The interviewee seemed more comfortable in the presence of the son/ daughter. In different ways the son/ daughter helped craft a scaffold for which the interviewee's fledgling memory could transmit a fuller sense of themselves. For example, in an exchange between Betty and her daughter, they describe Betty's excitement about pension day, which is celebrated with tea at the supermarket:

Daughter: *"Every day she'll say 'Is it Thursday?', No, it's not pension day, mum"*

Betty: *laughs*

Daughter: *"It's Saturday. She'll say "What day is it? Oh, I thought it was Thursday"*

Betty: *Is it Thursday today?* "

Daughter: *"No, it isn't Thursday today, no. And when it's Thursday, it's "Is it Monday?"*

Betty: "*No, I think that's it, I think you're right there"*

The daughter recounts the significance of Thursdays for her mother as a celebratory event, but the exchange does not suggest embarassement at her mother always asking ‘is it Thursday?’. This exchange reveals the manner in which Betty’s daughter supports her recall without challenging her competence, reinforcing her sense of self.

5.6.3 How is hypertension perceived?

5.6.3.1 Points of agreement

Hypertension was a peripheral matter, abstract, medicalised and difficult to relate to in its impact on one's day to day life. This contrasted with discussions among participants about other health matters, falls for example. Hypertension was difficult to characterise as having an impact in a way that one could tell stories about. Margaret said "*I've never had high blood pressure before, till that last time they said I had it!*". The relevance of hypertension to participants lives was evident by what was not said about hypertension. Glen said "*I wouldn't know that I've got blood pressure except they tell me*". Gertrude said of her hypertension: "*Yes, it did worry me but it didn't alter me*". However, there was more of a sense of the dangers of high blood pressure, than the dangers of low blood pressure. Trevor said his BP varied a lot: "*it can vary from reasonable to oh my God I'm glad to know I'm still here, so*".

There was a sense that hypertension is something for which care could be delegated to others, not only doctors. Patricia was not worried about her own hypertension but when describing a visit to her friend in hospital, she said she asked the nurse "*have you checked [his BP]... and [the nurse] showed me the chart… I said, 'that's better than mine'*". Similarly Glen said of his own hypertension: "*it's made no difference to me, you know, that's why I said I can't really tell you much about blood [pressure], because it hasn't actually affected me. Now, me wife has blood pressure,..".*

5.6.3.2 Points of divergence

There was variation in the degree to which participants were engaged with the concept of hypertension, and how much they were actively involved in shared decision making regarding its management.

Hypertension mattered where it's outcomes were tangible, such as in pregnancy. Gertrude said "*I knew more about it then than I do now really, but there was not as much you could do about it*". Or, after Ali's stroke "*but after the stroke I worried about it, yeah, after the stroke, everything went wrong with it anyway*". Ali remained clearly aware of blood pressure targets. Ali: "*so I hope that [my BP] will come down again, you know? Hope it's 140 at least, or 145. So I was thinking you will take the blood pressure"*.

Hypertension management decisions were contested by those who were more able to engage with their GPs. Trevor, who knew his GP socially, told him *" 'I haven't had one of your bloody pills for a month'. So [GP] said 'you could have killed yourself; and I said ' well that would be my choice not yours".*

Others experienced blood pressure management as outside of their control, particularly in how treatment changed over time. Charlie said *"Some of them [tablets] have changed, you know, they [doctors] know you better*". Gertrude said "*different doctors have different rules*". It was unclear how much this was

influenced by the importance that their own doctor had placed on their hypertension. Mary was aware of the uncertainty of the interpretation of BP measurement: "*my blood pressure was always high there [at one GP], ..I finished up taking about seven different tablets, ..and as soon as I came over.., it was normal on the pump up one [sphygmomanometer]…we stopped them all. Apart from three*."

5.6.4 Reflexive analysis

Using narrative empowered the participants to take the floor, to speak on their terms. Narrative as a means of communication was something the participants felt at ease with and enjoyed. With it they used humour to navigate topics that were intimate including uncertainty about the future, their fears and threats to health. Narratives provided a rich picture of the complexity of ageing and it's multifaceted aspects. Stories also communicated a person's identity as more than their current condition, and the sum of all they were across their life-course.

A motivation for this study was to understand how people described their ageing trajectories and how priorities may change over time. Trajectories were difficult to discern because each person sees themselves as they are now and it is difficult to separate oneself from that to think about yourself in younger years.

These stories revealed ageing on a person's own terms. It became evident that just as not all people of the same chronological age are the same, not all

cohorts of older people are the same. The social, economic and cultural context in which a cohort has grown up in forms who they are and what they value. The people interviewed in this study are part of a generation that are trail-blazers – ahead of the curve of a demographic shift to an ageing society, and the first generation for whom living to advanced old age is normal. They had defied odds that would have applied to earlier generations. Similarly, some of them lived through two world wars, tuberculosis, many illnesses that the past half century has found cures for. So they have experience of living with uncertainty that is beyond what someone in a much younger generation could understand. Perhaps related to this, the language of choices, priorities or outcomes do not translate well to this group. Similarly, sharing decision making may be a difficult concept for a generation for whom the same family doctor may have looked after people from ‘cradle to grave’, and social class was less transferable making doctors separate beings to be treated differently.

One’s sense of age was a subject of tension in the stories. Ageing was estimated differently in others to oneself, and sometimes was presented in moral terms. Grounding approaches to shared decision making on an external measure of someone’s biological age may therefore prove challenging, particularly where it diverges from a person’s own sense of their age.

The impression gained was that the way the doctor thought about their hypertension may have influenced how the patient thinks about hypertension. The way clinicians talk about medical problems influences the way the patient thinks about them. The outcome quoted in terms of risk may be less important

than the manner and attitude respected to a person's blood pressure. If BP is checked routinely, and seen to be interpreted in a varied manner, it could be interpreted as indifference, and this could be projected onto patients.

Experience as a doctor motivated the original research enquiry, and formed the basis of the heuristic technique of medical history taking which I was able to develop into a method of qualitative interviewing. However medical experience also will have shaped my interpretation of the data. Hypertension was not focal to these people, as I had expected it to be. Indeed medical conditions were not focal to their description of themselves. The personhood that emerged from these stories dwarfed the patient identity that electronic health records could ever capture, and witnessing this was rich and enlightening. From these stories emerged a person redefined not only as an individual but also in terms of their spouse and their community, with a high degree of interdependence.

Frailty has social meaning separate from its academic definition. Language in society is not determined by academic health papers, denial of which could lead to harm, because current terminology has the potential to appear nihilistic or pejorative.

Finally, from an ethical standpoint there are categorical imperative and utilitarian duties of a doctor. Blood pressure management is generally considered a matter of public health. On an individual level, population risk is difficult to translate. The language of shared decision making then in interventions of public health may risk conflating the two roles. Interviewees, at least of this

cohort, recognised the role of the doctor in balancing these risks, and that this was something that it would be difficult to do objectively themselves.

5.7 Discussion

5.7.1 Key findings

1. Summary of key results according to objectives

This study set out to explore what older people with frailty value and to determine whether or not frailty may be a useful measure to guide management of hypertension for patients on their own terms. Emerging from these interviews are three key factors impacting on shared decision making in the management of hypertension: their sense of ageing; ‘what matters’; and, hypertension itself.

First, in relation to ageing, narratives revealed the agency of older people to adapt to maintain a good life despite the constraints of increasing disability and illness. The interviewees did not define themselves as frail, but rather by who they were in spite of their frailty. Frailty was characterised in reference to physical or cognitive impairments, or to the sense of ‘giving up’, and frailty was described generally in negative and value laden terms.

Second, with regards to what matters, keeping going and maintaining identity were strongly valued. The prospect of giving up or being given up on were

feared. The role of the spouse, family and community were important to maintaining identity, as a scaffold for what matters, especially where a person's identity was under threat, e.g. with cognitive impairment.

Third, participants were engaged with the concept of hypertension where the outcomes were tangible (i.e. in secondary prevention) and the impact was evident in their everyday lives. In the absence of these factors, and in contrast with competing problems such as falls and obstacles to getting around, hypertension seemed abstract and peripheral to what matters.

5.7.2 Limitations

The individuals interviewed all lived in the Bradford district, they had grown up and lived with the shared social and cultural influences of a particular period of time; and only one of the ten was born outside the UK. This cohort had experienced a particular world in their upbringing which will have defined who they were. They held values such as keeping going and resilience and respected the social status given to doctors. These factors may have influenced how a person approaches shared decision making, and may not generalise: to other older people from younger cohorts; to those in different cultural settings across the UK; or, to those of different ethnic origin.

The life course methods chosen in this study enabled a rich exploration of the topics relevant to the research question. Maybe as a result of the choice of biographical methods, the interviews were strongly participant led and this was

the intention of the study design. Limitations included the primary assumption on which this study was based, i.e. what matters to someone is evident in the stories they tell, but there are likely to be additional implicit values that are not easy to articulate in narrative. How one presents oneself in an interview does not necessarily represent how one sees oneself, although this gap may have been addressed in small part by returning for a second interview.

Participants were not forthcoming on the topic of hypertension. It seems possible that while clinical aspects of hypertension are more difficult to tell stories about, hypertension is not necessarily less pertinent to a person. In this study sample there was a minority of people who seemed to have engaged with sharing decision making on hypertension management, the majority had not. Subsequent presentation of the findings to a Patient and Public Involvement group (PPI) revealed a much more engaged approach to hypertension management among panel members. The purposive selection of older people with more active engagement in their hypertension management may provide a useful extension of the study to explore more divergent views.

5.7.3 Cautious interpretation of results

1. Concept of the ageing process and utility of frailty

A rich picture emerged of ageing across the life course, of cohort effects, and of the role of spouse and community. The life course approach highlighted stories of agency, in the face of adversity, be that: war and poverty; the consequences of illness and ageing of others in their family and communities; or, illness and

ageing of their own. Frailty was defined by its impairments and by the negative stereotypes which may represent stereotypes of ageing itself. However, frailty did open up conversations about what matters, and it facilitated discussions on how social and psychological factors may impact upon people's lives.

2. Hypertension and shared decision making

Agency was a key theme in the stories that described ageing, and in values in later life. Shared decision making is of course an exercise in empowering a patient to be an agent in their medical care. However, to have meaning, shared decision making must engage issues that are tangible or salient with the person. For a minority of those interviewed, this may include hypertension. For example for Ali, for whom hypertension was diagnosed after a life changing stroke, and the management of hypertension was in the secondary prevention of a future recurrent stroke. For others, where hypertension was less pertinent, shared decision making might better focus on matters that are salient. For many, falls or ability to move around were highly relevant to their day to day. The management of BP and its impact maybe relevant then in the context of these goals, rather than to manage hypertension per se.

Therefore, rather than focus on greater guidance for shared decision making in hypertension, tools for discussing BP lowering should be applicable to a range of contexts including falls, mobility, and activities of daily living.

5.7.4 Generalisability - considering the literature

In the qualitative literature, there are two major themes in research involving the concept of frailty. Firstly, those with frailty do not regard themselves as frail, and they tend to distance themselves from the label of frailty. Secondly, people who have frailty, and may not consider themselves to be frail, are very resilient and highly adaptive in managing to adapt to changes brought on by frailty in ways that may not be evident if seeing them only through a medical lens.

With regard to the first, it was apparent from these interviews, that people with frailty had a different perception of frailty to how clinicians may perceive people with frailty, which may also be different to the clinical concept of frailty (504, 505). Negative outcomes or fears or being ‘given up on’ or ‘giving up’ oneself (506), were revealed through techniques of ‘othering’ of frailty (507). Othering describes a process taken by individuals to identify those who are classified in a negative way and distinct from oneself. Othering can reveal the biomedical and cultural notions of what it means to have frailty. Warmoth et al describe the resistance to the label of frailty as representing an identity that can be stigmatising and disempowering (504). Nicholson described frailty as perceived by patients, as assuming a moral character or denoting a lack of agency (505).

Secondly, people who have frailty, and may not consider themselves to be frail, are very resilient and highly adaptive in managing to adapt to changes brought on by frailty. This is evident in the narratives in this study which describe clearly

the limitations on these people's lives that are brought upon by ageing as affected by loss, disability, and illness. However, as Ron described when he could not open a jar by himself, but he could with the aid of a gadget, not being able to do things, forced people to do things differently. This adaptive capacity is described elsewhere and may represent the features of successful ageing (508); ageing characterised not by the absence of health problems but by the adjustment to health problems – and in that adjustment a sense of self growth through loss.

The value of maintaining identity in spite of illness, described in these stories, correlates with the description of 'work as illness' (509). Corbin and Strauss describe the trajectory of living with illness, as a combination of the physiological unfolding of disease, medical treatments given, and the inter-related work of both the person who is ill and those around them, to live, adapt to, and manage illness.

The work of illness was not evident with respect to hypertension as much as it was in relation to other problems such as falls or mobility. However, this is perhaps unsurprising because for most individuals interviewed, hypertension was not evident in their narratives. Hypertension hadn't caused disruption in their biographies. The BP-lowering medication routine did not stand out as being particularly meaningful or unusual for any of the interviewees. The side effects or burden of medications did not, as far as they were aware, threaten their identity. This may relate to limitations of the methodological approach, aspects of the sample, or indeed demonstrate that the management of

hypertension, particularly as primary prevention is not a salient issue among this cohort. This may relate to the lack of association with impact on their daily life, or relate to a perceived lack of importance placed on hypertension by their clinicians.

The utility of frailty given the different understandings of the term between clinicians and patients pose questions for the use of ‘frailty’ in prompting shared decision making in hypertension. On reflection, the narratives around frailty in these interviews themselves framed discussions about coping strategies and what matters to an individual. As a clinical concept, frailty does at least open up the impact of social and psychological factors (510, 511) and aspects of agency (512) upon the ageing process. These discussions, sometimes enabled by the presence of a care-giver or family member, may help to reveal the sense of a person through a non-medical lens – out with their identity as a patient. This was evident from the exchanges between Betty and her daughter which was full of humour, that their relationship was bidirectional, each gained from the another, and they were inter-dependent (513).

5.8 Conclusions

The conception of frailty emerging from the perspectives of patients with hypertension is different to how clinicians may routinely consider the concept of frailty. Understanding how a person conceives of frailty offer a means to understand that person on their terms: how they identify themselves, what they

value and what they fear. Shared decision making in hypertension was engaged in where the outcomes relating to treatment were tangible and relevant. Therefore, guides and tools for shared decision making about BP-lowering should have application to a range of patient concerns. Involving a close family member or friend can help empower a person in sharing decision making.

Chapter 6 Discussion

6.1 Introduction

Cardiovascular disease is the leading cause of death worldwide (514) and hypertension is its most common risk factor (5). Hypertension is the most frequent lifelong condition (9), and its prevalence increases steadily with age (23). However, guidelines for the management of hypertension for older people remain based on expert opinion (320, 322, 323) due to the absence of a good quality evidence base.

This study set out to address an important knowledge gap in the current understanding of the association of BP with outcomes for older people with frailty. The research was motivated by new advances in the field of vascular ageing and the aim of this work was to ascertain the application of knowledge gained through ‘bench’ science to ‘bedside’ clinical hypertension care.

The research presented in this thesis is a thorough investigation of BP and outcomes in older people according to their frailty status. This is the first study of its kind to do so in a large scale generalisable population which has direct application to a specific clinical setting, namely those with hypertension that is managed for primary prevention of cardiovascular risk in primary care. This study is novel in distinguishing distinct questions of prognosis and causal inference in relation to BP and outcomes whilst also advancing on previous

research by applying more rigorous statistical methods to account for the complexity of this real world data. These methods included the use of parametric models to address non-proportional hazards; adjustment for the most up-to-date profile of established cardiovascular risk (QRISK-3); investigation of non-cardiovascular and non-fatal outcomes; and, data imputation to mitigate bias resulting from missing data. Moreover, the research presented in this thesis pioneers the use of mixed methods to explore the perspectives of patients in the interpretation of data findings; and in the use of narrative methods to understand the perspectives of older people on priorities in hypertension management.

The empirical and novel findings which have arisen from this thesis are summarised below. A synthesis and a detailed discussion of these results are given in **Section 6.2.1**, **Section 6.2.2**, **Section 6.2.3** and **Section 6.3**. All findings are placed in the context of an up to date literature review assessing a broad set of relevant prior research. Strengths and limitations of the methodological approaches used throughout the PhD research study are discussed. This will be followed by an examination of various sources of potential bias which may impact on the interpretation of findings. The chapter concludes with a comprehensive set of study implications, recommendations for clinical management, healthcare policy and future research before reaching an overall conclusion.

The empirical and novel findings arising from this thesis are as follows:

1. In the systematic review and meta-analysis, I summarised evidence from traditional cohort studies, identifying that lower systolic BP is associated with reduced all-cause mortality in those without frailty, but that there is no association in those with frailty.

2. In the large routine data study, I identified that frailty represents an important prognostic factor for cardiovascular and non-cardiovascular outcomes, in addition to measures of established cardiovascular risk.

3. In the large routine data study, I found no evidence that the effect of systolic BP on outcomes is different in older people according their frailty status. However, I did find evidence that the effect of BP-lowering treatment on outcomes was different in older people according to their frailty status.

4. My interviews with people living with frailty and hypertension reveal that engaging patients in the management of their hypertension is possible when the outcomes relating to treatment are tangible and relevant to that person. Identifying how a person conceives frailty may itself offer a means to understand that person on their terms: how they identify themselves; what they value; and, what they fear.

6.2 Summary of key findings

6.2.1 Systematic review and meta-analysis

Evidence from existing observational studies found no statistical difference in risk of all-cause mortality for older people with frailty whose systolic BP is <140 mm Hg, compared to those with a systolic BP >140 mm Hg.

In these nine studies, there were both general limitations due to the use of traditional cohort studies, and specific limitations relating to the design of these particular cohort studies. A key constraint of the use of traditional cohort studies in comparison to routine data is the lack of external validity (as discussed in **Section 3.5.3.1**). Concerning the particular design of the nine included studies: the study numbers were small; BP was categorised according to various classifications that do not relate to hypertension guideline categorisations; cardiovascular risk was measured without using established cardiovascular risk scores, and frailty without using frailty measures that are commonly used in clinical practice. More specifically, none of the included studies distinguished between older people in their study sample who had hypertension and those without hypertension, or hypertension management for primary prevention with that for secondary prevention. Only five out of the nine included studies reported the overall risk of outcomes in the study population as a whole before stratifying by frailty (318, 351, 354-356). In all of these five studies, risk of outcome was decreased in association with higher BPs.

The methods and designs of these studies were not distinguished as either prognostic, or causal inference studies, although doing so would have also aided the interpretation of their results. The absence of methods to address missing data may have further biased findings. For all of these reasons, findings

were therefore difficult to extrapolate to a particular clinical setting, with limited ability therefore to impact upon clinical practice.

6.2.2 Association between systolic BP and outcomes in 145,598 people over the age of 65 years

The analysis of primary healthcare records of people older than 65 years who had hypertension but no previous history of cardiovascular disease, revealed that there was a higher risk of outcomes associated with low systolic BP over 10 year follow-up. Findings indicate that despite adjustment, the risk of death from any cause is 46% higher in those with a systolic BP < 120 mm Hg compared to a systolic BP between 130-139 mm Hg; injurious falls are 21% higher, and MACE 16% higher. Risk of high BP was only evident with respect to MACE at a systolic BP > 180 mm Hg which is associated with a 7% increased risk of MACE compared to a systolic BP between 130-139 mm Hg (see **Section 4.4.2**).

6.2.3 Investigation of frailty as a prognostic factor in the management of hypertension

Older people with higher degrees of frailty had lower average systolic and diastolic BP recordings and variability of systolic BP increased. Despite adjustment for known cardiovascular risk factors, patients were at higher risk of MACE with advancing frailty. Compared to those who were fit, mild frailty was associated with a 38% increased risk of MACE; moderate frailty; 84% increased risk; and, severe frailty, 117% increased risk (see **Section 4.5.2**). Greater baseline frailty was similarly associated with increased risk of all-cause mortality

and sustaining injurious falls. The addition of frailty improved model fit significantly above that using cardiovascular risk factors alone (see **Section 4.5.3**). This is evidence that frailty is a useful prognostic factor for cardiovascular and non-cardiovascular adverse events in the context of hypertension management.

6.2.4 Epidemiological investigation of associations between BP and outcomes in the context of frailty

The findings of the PhD study indicate that extremes of low and high systolic BP are associated with higher risk of cardiovascular and non-cardiovascular outcomes in older people without frailty, and in people with mild frailty. However, in people with moderate and severe frailty, the results indicate no difference conditional on systolic BP with respect to cardiovascular and non-cardiovascular outcomes measured (see **Section 4.6.2**).

The association of systolic BP and outcomes was not different in the context of frailty. Specifically, three pre-specified tests of effect modification returned equivocal results. This indicates that the effect of systolic BP on outcomes was not meaningfully different on condition of baseline frailty (see **Section 4.6.3**). However, the PhD study did find evidence of a differential effect of BP-lowering medication on outcomes in the context of frailty (**see Section 4.6.4**). This may suggest that the modifying effect of frailty in the context of hypertension management, is in the degree to which someone sustains benefit or suffers

adverse effects of BP-lowering treatment. This is an important finding and one deserving of further investigation.

6.2.5 Personal perspectives of older people treated for hypertension

The personal perspectives of people who are in receipt of care for hypertension, and have features of frailty was informative. In the stories reported in Chapter 5, ageing was presented in terms that challenged established negative stereotypes of ageing. Stories championed the concept of agency, as defined as the capacity of an individual to act independently and make free choices (515). In the context of this more holistic depiction of an older person's life, hypertension management appeared abstract, medicalised and peripheral to what mattered to the people interviewed. Only a minority recalled being engaged with the management of their hypertension. For this minority, this engagement was in a context where outcomes were tangible, personal and salient to them. Although this study was small and exploratory in nature, it may inform the interpretation of the data findings to clinical care and future research.

6.3 Data findings in the context of previous research

6.3.1 Investigation of associations of systolic BP and outcomes

First, the association between systolic BP and outcomes was non-linear and the increase in cardiovascular risk associated with systolic BP was modest.

The PhD study finding of a U-shaped association between systolic BP and outcomes is consistent with the findings of many small traditional cohort studies which were presented in **Table 1.4**. In addition, the PhD findings are consistent with those five studies included in the meta-analysis which reported BP-outcome associations in their study populations overall (318, 351, 354-356). Other studies also investigating associations of BP and outcome in the context of frailty, using routine data from primary care records, did not report overall population associations before stratifying by frailty (365, 366).

However, the findings of the PhD study are inconsistent with data from trials which, despite the caveats discussed in **Section 1.6.1**, demonstrate evidence of a positive dose-response relationship between systolic BP and outcomes. The associations demonstrated between BP and outcomes in the PhD study are also inconsistent with the findings of other large epidemiological research studies that demonstrate a linear association between BP and cardiovascular outcomes. The Prospective Studies Collaborative (PSC) undertook an individual patient data (IPD) meta-analysis, including 958,074 participants in 61 studies in America, Asia, and Europe published in 2001 (367). This large meta-analysis demonstrated that above a systolic BP of 115 mm Hg, there is a continuous association between systolic BP and cardiovascular risk (367).

The finding of the PhD study, that the association between BP and outcomes was only modestly increased with higher BP is also contrary to the findings of the Prospective Studies Collaborative (PSC). In the PSC meta-analysis, a 20 mm Hg lowering of systolic BP was associated with stroke reduction: in those

aged 60 – 69 years, by 57% (HR 0.43 (95% CI 0.41 – 0.45); in those aged 70-79 years, by 50% (HR 0.50 (95% CI 0.48 – 0.52); and in those aged 80- 89 years, by 33% (HR 0.67 (95% CI 0.63 – 0.71) (367). Risk reduction for incident ischaemic heart disease and other vascular events were similarly marked, and remained significant in older age groups.

There are two major differences in study design between the PhD study and both the PSC meta-analysis and the trial data: in relation to disease burden in the study population; and, in relation to the method of BP measurement. I will discuss each in turn.

Firstly, considering study population, the PhD study involved a relatively current and broadly generalisable population representative of clinical practice, i.e. a cohort with a disease burden representative of older people with hypertension. Of the whole PhD study cohort, 1.4% were care home residents. The median number of co-morbidities in this study population was three (inclusive of hypertension), and 67.5% had multi-morbidity (defined as two or more long-term conditions), which is consistent with proportions reported in a recent large scale community UK cohort study (340). In contrast, trial populations represented selective, healthy populations, as discussed in **Section 1.6.1**(277).

Examining the studies included in Lewington's PSC meta-analysis, whilst they included people of older age, these participants had a low burden of non-cardiovascular disease. The study cohorts included in the pooled analysis had an average publication date of 1973 (range 1949 to 1990). Hypertension

management changes with time (516) and will have been markedly different in the time of the PSC study period compared to the PhD study period. Also, the population of older people at that time had a lower level of chronic disease than the population of older people in 2007, as the prevalence of living with chronic disability has been increasing over time in the UK (517). Fewer people at the time of the PSC study would have been on BP-lowering treatment. Indeed adjustment in the synthesis was made for age and sex only, not for BP-lowering treatment or other cardiovascular risk factors. Furthermore, there was no analysis of the risk of bias in included studies or of the representativeness of study populations.

Secondly, a major difference between the PhD study, relevant trials such as SPRINT (275) and HYVET (267), and epidemiological studies such as included in the PSC meta-analysis (367), is in the method of BP measurement. BP measurement in a trial setting is typically more precise and time consuming, and for those reasons maybe closer to a person's true BP than BPs measured in routine clinical practice (518). In the PSC study, whilst the practice of BP measurement was not necessarily more precise, methods of correction of time-dependent regression dilution used sequential BPs to address the imprecision of single BP measures. Bias because of regression dilution will be discussed in greater detail in **Section 6.6.4**.

The more modest point estimate of cardiovascular risk associated with systolic BP in the PhD is consistent with other recent studies in the UK that also use routine data, in which adjustment has also been made for cardiovascular risk

and BP-lowering treatment. In the development of the QRISK-3 cardiovascular score using the QRESEARCH database (profiled in **Table 3-1**), a 1 mm Hg increase in systolic BP was associated with an 0.5% increase in cardiovascular outcomes, HR 1.005 (95% CI 1.004 – 1.005) (446). Like SAIL, QRESEARCH, is representative of clinical practice where high BPs are treated and therefore their associated clinical risk is mitigated.

Another study also using routine data with single BP measures is work published by Rapsomaniki et al in 2014 using UK primary care data from CPRD (also profiled in **Table 3-1**) to examine the association between systolic BP and 12 cardiovascular outcomes in a population of 1,258,006 adults over the age of 30 years (519). The Rapsomaniki study found associations between BP and 12 cardiovascular outcomes in the age group 60 – 79 years remained linear. However, the authors reported that associations were more modest in the oldest age sub-population (>80 years), and that the association of increased outcomes with increasing BP was not significantly different for unstable angina, stroke or abdominal aortic aneurysm. For incidence of myocardial infarction, new diagnosis of heart failure, peripheral arterial disease and stable angina, risk with increased systolic BP was only evident above a systolic BP of 160 mm Hg. Associations were U-shaped only for those with unheralded coronary death and cardiac arrest, but in these cases, systolic BP hazard ratios were not statistically different at any systolic BP.

Important differences with the PhD study include that the study population in the Rapsomaniki study was not limited to those with hypertension. Only 34% of the

CPRD study cohort had BP > 140/90 mm Hg, and only 21% were prescribed BP-lowering drugs at baseline. This is in contrast with the PhD study in which all of the patients had either a diagnosis of hypertension or a BP measure which was above NICE guideline diagnostic criteria for hypertension, and 87% of whom were on BP-lowering drugs at baseline. Adjustment of the CPRD data was made for age and sex only, rather than the full profile of cardiovascular risk and BP-lowering treatment.

In a similarly large prospective cohort study involving 512,891 adults living in China who were between the ages of 30 and 79 years, followed up for a median period of 9 years, Lacey et al demonstrated linear associations of systolic BP with cardiovascular outcomes (520). In this study every 10 mm Hg increase in systolic BP was associated with a 31% increase in ischaemic heart disease (HR 1.31 (95% CI 1.28 – 1.34)), and a 30% increase in stroke (HR 1.30 (95% CI 1.29 – 1.34)). However, it was estimated that in this same study population only 5% had been diagnosed with hypertension and were prescribed BP-lowering medication (521).

In summary, before discussing whether there is a differential association between systolic BP and outcomes relative to levels of frailty, it has been important to examine the generalisability of BP-outcome associations in the PhD study compared to other major studies in the field. The findings of current evidence are conflicting: with some studies demonstrating a U-shaped or J–shaped non-linear association between systolic BP and outcomes, and others demonstrating a linear association. In this thesis, it is proposed that the

variation in the existing evidence base may relate not so much to study design (i.e. whether a study is interventional or epidemiological) as to the burden of disease in the population studied (and related to this, the level of BP-lowering treatment), and the precision of the methods of BP and outcome measurement employed.

6.3.2 Investigation of frailty as a prognostic factor in the management of hypertension

This study has found that advancing frailty is associated with increased variability in systolic BP and that average systolic and diastolic BP fall with advancing frailty. However, there was no difference in pulse pressure conditional on frailty. The finding that systolic BP variability increases with increasing arterial stiffness was demonstrated by early studies of the elasticity of the human aorta (66). Falling BP in the 20 years ahead of death has also been shown in another large population study using CPRD data (32).

The finding of the PhD study, that the measurement of frailty has prognostic utility in hypertension, is a confirmation of findings of other studies. The role of frailty alongside other measures of traditional cardiovascular risk factors for cardiovascular outcomes has been investigated in a Canadian health records data set (522). This comparatively small study analysed population-based medical records with a ten year follow up where the outcomes included coronary heart disease (CHD) hospitalisation and coronary heart disease (CHD) mortality in a study population with an average age of 47 years. None of the participants in the Canadian study were care home residents and none had a history of coronary heart disease. Those with missing data were excluded. The study investigated the value of non-traditional risk factors for the prediction of cardiovascular events. Only 8% of the population went on to sustain a cardiovascular event. The study found non-traditional risk factors were associated with increased risk of future cardiovascular events despite adjustment for known cardiovascular risk factors. The association between non-

traditional cardiovascular risk factors and incident CHD events was also significant after controlling for all of the traditional cardiovascular risk factors (adjusted HR=1.31, 95% CI 1.14 – 1.51, p=0.001), and the estimate associated with a frailty index that combined cardiovascular and non-cardiovascular risk factors was further from the null. (adj. HR=1.61, 95% CI 1.40 – 1.85) (522).

The findings of the PhD also are consistent with a recent post-hoc analysis of 13 randomised control trial populations involving a variety of cardiovascular interventions (including the HOPE-3 trial (276) profiled in **Table 1-2**) (523). In a total population of 154,696 individuals, frailty (defined as an FI > 0.21) added prognostic value to a Framingham cardiovascular risk model in predicting cardiovascular morbidity and mortality (C statistic improved from 0.58 to 0.60). The PhD builds on the work of Farooqi: by using a measure of frailty that is gradable rather than dichotomised; to extend the role of frailty to a particular application in the management of hypertension for primary prevention; and to a study population which has greater external validity that trial populations can afford.

6.3.3 Epidemiological investigation of associations between systolic BP and outcomes in the context of frailty

The findings of the PhD routine data study are in parts both consistent and inconsistent with the pooled synthesis of the meta-analysis presented in **Chapter 2**. Consistent with the meta-analysis, the PhD routine data study found that in the absence of frailty, the risk of all-cause mortality is conditional on a

person's systolic BP, but in the presence of frailty, there is no association between systolic BP and all-cause mortality. The routine data study extended this finding to a broader range of outcomes to include major adverse cardiovascular events and injurious falls.

In contrast with the findings of the meta-analysis, the PhD routine data study demonstrates systolic BP < 120 mm Hg was associated with a higher risk of all outcomes in participants who were fit or had mild frailty. Results of the meta-analysis demonstrated that in participants without frailty, systolic BP < 140 mm Hg was associated with lower mortality. However, as discussed in **Section 6.3.1**, it seems plausible that these differences relate to variation in population characteristics or in the method of BP measurement between the PhD data study and the traditional cohort studies included in the meta-analysis.

6.3.3.1 No evidence that frailty causes an effect modification of the association between systolic BP and outcomes

The PhD routine data study found no evidence that frailty causes an effect modification of the association between systolic BP and outcomes. This is in keeping with five of the six cohort studies included in the meta-analysis that tested for an interaction term between BP and outcome in an adjusted model (351, 354-357), as discussed in **Section 2.4.7**. In the single study reporting a significant role of frailty as effect modifier of the association of systolic BP with outcomes (318), frailty was measured using a phenotype measure of frailty whereas the PhD study used a cumulative deficit model to measure frailty.

Other differences included: the population ethnicity (Lv study was located in China); and the proportion of the population prescribed BP-lowering treatment (59% in Lv et al study; 87% in the PhD study). Furthermore, it was unclear in the Lv study's reporting whether the interaction term had been tested within a model already adjusted for cardiovascular risk. The method of testing for the interaction term was not detailed in the Lv study. Finally, the interaction term with frailty was one of eight interaction terms tested in the Lv study, raising the risk that multiple testing may have led to a false positive finding (524).

6.3.3.2 Evidence frailty causes effect modification of the association between BP-lowering treatment and outcomes

This study found evidence that frailty modified the effect of BP-lowering treatment on outcomes. The number of BP-lowering treatments was not different conditional on frailty in this study population, so it seems less plausible that the effect modification represents different prescribing practice. This may suggest that the modifying effect of frailty in the context of hypertension management, is in the degree to which someone suffers adverse effects or gains benefit from BP-lowering treatment. This is an important finding, as it may be consistent with the evidence that older people with frailty are more at risk of adverse effects from treatment (**Section 1.6.2.2.1**). From this study alone, given its observational nature, it is not possible to infer any causal relationship from the interaction between BP-lowering treatment and frailty on outcomes.

Importantly, this observation, of the association of BP-lowering treatment exposure on outcomes was exploratory in nature: it was not pre-specified in the protocol; and, the size of effect was not measured. The interaction between measured BP and outcomes stratified by frailty and treatment has previously been investigated in electronic health records (365), but in this study, like the pre-specified analysis of this PhD, the exposure was BP not BP-lowering treatment.

These exploratory findings are inconsistent with both analyses of randomised control trials in the management of hypertension that have been retrospectively analysed with a post-hoc frailty index (359, 362). Both analyses demonstrated no evidence of effect modification by frailty on the effect of treatment on cardiovascular outcomes. As discussed in **Section 2.5.2.1**, there were particular limitations about the retrospective measurement of frailty, the over-representation of cardiovascular risk factors in those frailty indices and the lack of statistical power of these analyses for them to be definitive.

The exploratory findings are consistent with those of the Predictive Values of BP and Arterial Stiffness in Institutionalised Very Aged Population (PARTAGE) study undertaken among 1,127 nursing home residents over the age of 80 years in France and Italy with 2 year follow up (525). The PARTAGE study demonstrated that those with a systolic BP of less than 130 mm Hg, on > 2 BP-lowering medications had a higher risk of all-cause mortality (HR 1.78, 95% CI 1.34 - 2.37) compared to other patients. This finding remained fit in three sensitivity analyses which adjusted separately for: propensity score matching;

cardiovascular risk; and, the authors also tested their findings by repeating analyses limited only to those people who had a diagnosis of hypertension and were prescribed BP-lowering medication.

The PhD study findings are also consistent with one of the few studies examining the association between BP and falls. The Tinetti study in the USA included 4,961 Medicare participants enrolled between 2004-2007 who were over the age of 70 years old. The study followed up participants for 3 years to record serious fall injuries including hip and other major fractures, traumatic brain injuries and joint dislocations. 85.9% of study participants were prescribed BP-lowering medications. BP-lowering medications were categorised as low, moderate or high intensity corresponding to the patient's defined daily dose of relevant classes of BP-lowering medication. The adjusted risk of a fall with serious injury was HR 1.4 (95% CI 1.03 – 1.90) in moderate intensity, and HR 1.29 (95% CI 0.91 – 1.80) in the high intensity groups (526).

The rates of descriptive outcomes in the PhD study were too low to enable a more granular investigation of drug side effects which may underlie the association between low BP and higher all-cause mortality. Relevant are the findings from another CPRD study which included 570,445 adults of all ages, with records on the database between 1997 and 2014 and a mean follow up of 4.1 years. The primary outcome was acute kidney injury. The exposure was time on treatment where treatment was an Angiotensin-converting enzyme inhibitor (ACEi) or an Angiotensin Receptor Blocker (ARB) and time without these treatments. Compared to time without, time on an ACE/ARB was

associated with a higher risk of acute kidney injury (HR 1.12, 95% CI 1.07 - 1.17). Risk of acute kidney injury varied per patient: those at highest absolute risk of acute kidney injury experienced little relative risk difference on or off an ACE/ ARB. On the other hand, those at low absolute risk of acute kidney injury experienced statistically significant difference in the relative risk on and off ACE/ ARB (527). These findings are consistent with the PhD study findings of significant associations of systolic BP and outcome in people with low levels of frailty, but insignificant associations of systolic BP and outcomes in the context of high levels of frailty.

6.4 Data findings in the context of the patient perspective

Major hypertension guidelines recommend considering a person's frailty in shared decision making around hypertension management (**Table 1-5**). The PhD study has shown that frailty predicts an increased risk of cardiovascular and non-cardiovascular outcomes in hypertension management in the routine data. However, participants in the narrative interviews (**Section 5.7.1**) did not define themselves as frail but rather by how they faced or managed frailty. The agency demonstrated in the stories told challenged the stereotypes of frailty/ageing which are often passive and dependent. The tensions around the concept of frailty are perhaps inevitable of any measure of ageing. As a prognostic factor, frailty may usefully identify a sub-population of older adults who are at higher risk of cardiovascular and non-cardiovascular outcomes, for whom it may be necessary to take a different clinical approach to managing their disease.

The outcomes measured in the routine data study (**Section 3.8.4**) were not mentioned in the stories told in **Chapter 5**, except among participants for whom hypertension was diagnosed in the context of a stroke. Medical conditions generally received little mention in the narratives. Instead, stories focused on everyday challenges: getting up; moving around; dressing; washing oneself; and, being able to get out and about. These aspects of life are not measured or recorded well in routine healthcare records, preventing their inclusion in the analysis. Physical function, disability or cognitive function are clearly important in their impact on quality of life, but they are not recorded or are under-recorded in routine data. However, there are moves towards developing core outcome sets relevant to older people with frailty designed in conjunction with older patients themselves (528). There is also recent progress in developing patient reported outcomes for older people (529, 530) that could be recorded in routine data. In the more immediate future, including a broader range of outcomes in trials and epidemiological studies is important to better understand the relative risks of treatment in the context of an individual patient.

Self-management and shared decision making (SDM) in the management of hypertension have been studied predominantly in populations whose primary and single problem is hypertension(531). A recent review highlighted a lack of research in how to undertake SDM in hypertension in a wider context(531). Ways of empowering patients in making choices need to start by including and directly involving patients in the research informing this.

It is plausible that clinical equipoise experienced by clinicians in the context of frailty is reflected in the overall indifference expressed by participants in the narrative interviews to the concept of hypertension. Indeed a recent survey of clinicians (which I co-authored) demonstrates significant uncertainty among practitioners who manage hypertension around BP targets and at which target BP a new trial is needed (532). Alternatively the lack of relevance attributed to hypertension may simply reflect that older people place less emphasis on medical problems than healthcare professionals think they do.

6.5 Strengths and limitations

Strengths and limitations of the PhD study will be considered with respect to various aspects of the study design: in relation to routine data in general; in relation to the SAIL data set; and, in relation to the methods adopted.

6.5.1 Study population

The study population included in the PhD study appears to be broadly representative of older people in the UK. In terms of frailty, the distribution in the PhD study cohort was categorised as: 50% fit, 40% with mild frailty, 9% with moderate frailty, and, 1% with severe frailty. These proportions are subtly different from those reported in ResearchOne and THIN data sets (50% fit; 35% mild frailty; 12% moderate frailty; 3% severe frailty) (341) and in other extracts from the SAIL data set (52% fit; 33% mild frailty; 12% moderate frailty; 3% severe frailty) (407). Those with moderate and severe frailty are marginally less

well represented in the PhD study cohort. This may relate to the exclusion of participants with established cardiovascular disease from the study population.

The proportion of the PhD study population who reside in care homes at study baseline was 1.5% of the total study population. This is likely to be an underestimation of the true care home population in Wales in 2007. In the UK overall a survey has shown that 4% of people over the age of 65 lived in a care home in 2018 (533). This does not account for differences across the devolved nations which may be present. However, there are limitations in identifying care home residence in the SAIL data. The care home registry available to identify care homes within the SAIL databank was created using a list of care homes defined by the Care Inspectorate Wales (408). This care home list was created in 2018 and is therefore not contemporaneous to the time of study start in 2007. This is a limitation as care homes will have opened and closed over time, resulting in the list being incomplete between 2007 and 2018 which represented the duration of follow-up in the PhD study.

The geographic representation of a whole UK nation is unique to SAIL, in comparison to other UK routine data sets that have been established (the exception being SPIRE in Scotland which is still in development). In England, there is a clustering of ‘research’ GP practices in the South of England. This is largely as a result of changes in market share of the companies responsible for the respective computer systems. The Vision primary care electronic health record system is the source of the main routine primary care data sets (CPRD-Gold, THIN) that have supported published research in the past 10 years.

However, the geographical coverage of Vision is concentrated in only three urban conurbations throughout England, and in the south of England (385). Cross sectional analysis of the spatial distributions of primary care clinical computer systems in 2016 also revealed that SystmOne (the system underlying ResearchOne) does not include the North West, West Midlands, London and South East. In contrast, QRESEARCH which is relatively under-represented in published research literature, is the most nationally representative single database across England (385).

Although representative of the Welsh population, the study population's ethnic diversity was not generalisable to many other UK settings. Across England and Wales, the ethnic mix of the population over the age of 65 years was: 95.5% White; 2.6% Asian/ Asian British; 1.3% Black; 0.4% Mixed; 0.3% Other (534). In Wales alone the population over 65 years is 98.9% White, 0.5% Asian; 0.3% Mixed; 0.17% Black ethnicity (535).

In the study cohort, non-White ethnicity represented 1.8% of the SAIL cohort, which is higher than that reported (1.1%) in the Census data for Wales. The ethnicity data in the PhD study data set were extracted from hospital data because primary care ethnicity data were not available in SAIL at the time of extraction. Ethnicity data were only present for 26.2% of the PhD study's participants. Other primary care data bases have similar levels of completeness of ethnicity data (CPRD – 29.3%, QRESEARCH – 33.5%, THIN – 23.1%) (536). As for SAIL hospital ethnicity, GP coded ethnicity also seems to be broadly representative of the ethnicity proportions of the overall population (536).

It is planned for ethnicity data recorded in the Welsh Demographic Service Data (WDSD) sets to be uploaded to SAIL within the next year to address this lack of comprehensive ethnicity data. Secondly, ethnicity coding has been incentivised by the Quality Outcomes Framework in 2006/2007 and 2011/2012, and ethnicity coding in general practice has been shown to improve since (536, 537).

Deprivation measures, according to Townsend quintiles were broadly representative of the overall UK population although proportionally the most deprived were less well represented (16.8% were in the poorest quintile). Evidence from the King's Fund using ResearchOne data demonstrated that people living in high deprivation areas were more likely to attend medical services (538). Frequency of attendance to general practice was not measured in the PhD study data, only the attendances when BP was measured. It is not possible therefore, to infer whether the differences in deprivation profile relate to those who are poor accessing GP services less often for hypertension management, or that, despite accessing services, those who are poor are less likely to have their BP checked by their GP as frequently. This is a research question that requires further investigation.

6.5.2 Study design

There was a balance to be struck in the design of this study, between what is precise and is true of the underlying biology described in **Chapter 1**, and what is measurable and generalisable to UK general practice. The value of BPs

measured in a research setting have been criticised for not being generalisable to clinical practice (539), although they are likely to be more representative of that person's true resting BP. On the other hand, clinical BP measures, whilst more likely to be representative of clinical practice, are less likely to be indicate a person's true BP, and therefore any association with the true biology may be diluted (235). An office reading is not a good representation of a person's true BP because it may instead represent masked or white coat hypertension.

Informed by the qualitative study, it is evident the context in which a BP is measured is important. A significant unknown in this study is the context in which each BP was measured in primary care, whether it was undertaken as: an opportunistic screening measure; because of concern a person's BP was too low; because the patient was unwell, and may need to attend hospital; or, whether it was to inform titration of BP-lowering therapy. In the future, contextual information should be extracted alongside a BP measure to indicate the purpose of the recording, such as by using hypertension review codes. Even if this contextual information is only available for a minority of BP measures, a sensitivity analysis comparing the use of these codes with BP codes more generally could reveal potential bias in the main analysis.

6.5.3 Choice of exposure

Blood pressure was chosen as the primary exposure for this study, informed by the biological considerations outlined in **Chapter 1**, and the uncertainty arising from conflicting clinical guidelines on the target maintenance BP in managing

hypertension in older people. An alternative exposure would have been BP-lowering therapy, and this was highlighted in the exploratory analysis (**Section 6.3.3.2**). The choice of BP-lowering treatment as exposure has advantages: treatment represents the reversible factor and an interventional study could determine whether this is causal; and, treatment is easier to measure than BP. However, the prescription data available in electronic health records does not represent what the patient actually takes; and important information on dose was not available in the SAIL data set during the study time period chosen.

6.5.4 Definition of BP

In considering the measurement of BP in this study, there is the potential for bias at various points: at the point of measurement; at data entry; at data cleaning; at data analysis; and at the point of model development.

At BP measurement, there are multiple reasons to question the accuracy of a single reading to be a true representation of a person's BP. From a biological perspective, BP will vary, in an individual: within seconds to minutes, conditional on activity and psychological stress; and, within hours, according to a circadian pattern (see **Section 1.5.5**). In addition, measurement error exists in the recording device and the method of taking a person's BP. Unlike in trials, there is no quality control undertaken on how BP is measured in routine data. The challenges involved in the extraction of systolic BP < 100 mm Hg from 7 digit rather than 8 digit strings (see **Section 3.9.2.1**) may have unequally affected low systolic recordings causing bias to the overall study findings.

At the start point of the PhD study, in 2007, it is likely there were many manual sphygmomanometers still in use when readings were often rounded to the nearest 5 or 10 mm Hg (540). As such, a greater tendency to round up or round down may have led to bias of BP entry. However, the histogram of BP results shows that the three patterns of BP results are more or less in keeping with one another which is partly reassuring (**Figure 4-2**).

Data entry in electronic health records is undertaken at the time of the clinical care interaction or is entered subsequently from medical notes. The primary focus of the person inputting the data will be to record the clinical encounter and the delivery of care as opposed to recording data for research purposes. The data from all GP practices are included in SAIL. This is not the case in other data sets, for example, in CPRD, data is extracted only from practices that meet data quality criteria (395). In SAIL the processes assuring quality of data entry and maintenance are less clear.

There is evidence GPs generally follow hypertension guidelines (**Section 1.6.3**) – they record the first reading where this is normal, and when it is too high they then record the lowest reading (541). This recording bias may dilute the effect of BP on outcomes as described in greater detail in **Section 6.6.4**.

During data cleaning certain assumptions were made to determine which readings were likely to be outliers, to exclude a small minority of anomalous or false readings from the data analysis (**Section 3.9.2**). These were subjective

decisions that may have influenced the data entered, although the transparent presentation of the decisions made do subject them to scrutiny.

When carrying out data analysis, the minimum BP recorded on a particular day was used. This measure was chosen to represent BP because it is this measure that is recommended in the guidelines used to inform treatment (320). This method has particular application to the prognostic factor study (addressing **Objective 3**). However it is conceivable that for the causal inference research question (addressing **Objective 4**), one of the alternative methods presented in **Table 3-5** would have provided greater precision in estimates of a person's true BP and therefore greater precision in detecting the true relationship between BP and outcomes.

There are significant discrepancies in a person's BP measured at home and in the clinic or practice. In this study, we have used BP recorded by GPs, without specifying whether they were home, office or ambulatory measures. It is likely therefore that a proportion of the BP measurements are not true readings for those individuals and will include both white coat effect, and masked hypertension (**Section 1.6.1**). Home BP measurements were not specified in the NICE guidelines in 2006 (**Table 3-8**), at the time of study start, and therefore it was not possible to undertake a sensitivity analysis to determine whether the association with home readings was different to those with clinic readings. Since 2011, NICE guidelines have increasingly recommended the use of home BP readings for the diagnosis and follow-up of BP. Sensitivity analyses using home or ambulatory BP readings only are recommended for future research.

There is evidence from electronic health records that BP decreases more steeply towards the end of life in the context of frailty (32). The inclusion of BP trajectories as a covariate was not undertaken in the prognostic study whose aim was to investigate the role of frailty in addition to current hypertension management; the measurement of BP trajectories is not part of current hypertension management. Indeed, the inclusion of BP trajectories as a covariate in the epidemiological study may have better characterised the true relationship between BP and outcomes. However, the inclusion of a frailty index as a covariate would be methodologically challenging. The measurement of the frailty index would have to be prior to the series of BP readings or else the eFI could represent a mediator of the association of BP and outcomes, thereby introducing collider bias (**Section 6.6.1**). This may be possible using joint longitudinal modelling techniques. Whilst these methods are outside of the scope of this PhD, they may represent a potential avenue for future research (**Section 6.7.3**).

During model development- BP recordings were ultimately categorised to allow for the non-linear association with outcomes observed elsewhere. However, methods more closely aligned to the true association would have been more ideal. For example, rather than superimpose guideline BP categories, cubic splines or fractional polynomials could have been employed (519), or categories informed by the data distribution around the median value (542). Such methods, that are led by the distribution of BP in the data, would have improved both the

power and precision of the analysis. These methods were outside the scope of the PhD but ones that are important for future investigation.

6.5.5 Definition of frailty

Frailty in this study was measured using a method accessible to the majority of general practitioners in the UK (543), and this improves the external validity of PhD study findings. However, whilst the frailty phenotype and frailty index (FI) measures often indicate similar proportions of a population as having frailty, they do not correlate exactly (544). Previous research using the CARE75 cohort from which the narrative interview study recruited patients (**Section 5.5.2.3.3**), reported that the electronic frailty index (eFI) has a correlation coefficient of 0.68 (95% CI 0.62 - 0.74) with a research standard FI in the same population (545). When comparison is made between the eFI and the phenotype model of frailty the Spearman's coefficient, was lower still, - ρ = 0.59 (95% CI 0.49–0.65) (545). As the authors discuss, this may be because functional deficits are not as well coded in routine primary care data as is the case in an epidemiological cohort study (545). Whilst these coefficients represent moderate-to-good agreement in terms of test coefficients, the degree of discordance would have significant impact on an individual's classification as frail or not frail (546).

With hindsight, it is evident from the findings of this PhD that the concept of frailty may be too broad to be helpful in personalising hypertension management for older people. The global measure of frailty combines patients with heavy cardiovascular disease burden and patients without cardiovascular

disease, but at high risk of falls. Whilst the former group may conceivably benefit from low BP, the latter may be at risk of harm from low BP. However, dissecting the different parts of the frailty index would jeopardise the clinical utility of the frailty measure as a whole. Instead, an alternative potential approach for future research would be to investigate from first principles, which are risk factors for harm from BP-lowering treatment in older people.

6.5.6 Choice of covariates

The choice of covariates to be included in this study was made to represent the optimal prognostic model currently in clinical use, so as to best investigate the additive value of frailty. The decision to use QRISK-3 as a measure of cardiovascular risk was made because of its recommended and widespread use in UK primary care, and thus is in line with the aim of the PhD to be generalisable to current practice. However, there are limitations to the choice of QRISK-3. The QRISK-3 used was not developed at the time of the study, so it has been calculated retrospectively. Clinical practice guidelines stipulate a measure of cardiovascular risk should be measured in the management of hypertension, but this is at the time of diagnosis of hypertension. Given the focus of this study was the long-term management of hypertension, and most patients were not captured at the time of hypertension diagnosis, this may explain the high proportion of missing data on cardiovascular risk factors for the majority of included patients. Hence, the PhD study does not fully mimic clinical decisions made in 2007. The analysis followed the pre-analytic protocol, and the choice of covariates was not reduced in the face of the high amount of

missing data on cardiovascular risk. This means that whilst confounding bias has been minimised, the risk of bias from missing data is likely to be high, although this is difficult to estimate. In future research investigating important predictors involved in hypertension management at follow up, the choice of confounders should be more targeted specifically to the context of follow up and based on theoretical grounds.

Furthermore there are limitations specific to the QRISK score itself. The QRISK-3 Score is not validated over the age of 84 years and the algorithm applies a ceiling of risk at this age limit. QRISK-3 was not developed to account for competing risks, and so the cardiovascular risk prediction for this group may theoretically have been over-inflated.

There are multiple cardiovascular prediction models (319). The majority have been developed for adults in middle age and there is evidence these have poor predictive value in adults who are older (547). Several studies have demonstrated that the association between traditional cardiovascular risk factors and cardiovascular outcomes weakens with age (548), and other risk factors may become important, for example, measures of inflammation (549), apathy (550), and polypharmacy. A minority of cardiovascular risk models have recently been developed specifically for older people (551, 552). One of these uses a competing risks framework, in a post-hoc analysis of data from 1,811 participants of the Prevention of Dementia – Intensive Vascular care (Pre-DIVA) trial undertaken in Holland (553). However, these prediction models are not yet

in common use in UK primary care or recommended in clinical guidelines (320). This is an area requiring future research.

Despite these caveats, using the algorithm to calculate the QRISK in those with complete observational data in the PhD study estimated a 10 year cardiovascular risk of 29.3% which compared to the observed cardiovascular event rate of 28.5% suggests good calibration in this cohort. It is also important to note that in the survival model used to test frailty as a prognostic factor, cardiovascular risk was defined by variables included in the QRISK-3 but not the QRISK-3 algorithm itself. Separately, the QRISK-3 algorithm, as a complete score, was run in a minority of patients for whom the component data were complete. In this minority of the study population, the QRISK-3 prediction of 10 year cardiovascular risk was highly consistent with the observed associations with cardiovascular disease in the whole data set, and the predictive ability of QRISK-3 was maintained in sub-groups defined by frailty (see **Section 4.3.4**).

6.5.7 Definition of treatment

Adjustment for the treatment effect in this research may have been insufficient. Treatment was measured by the number of BP-lowering medications by class recorded in a patient record whereas number of prescribed medications, drug adherence and frequency of prescription all influence the degree to which a person's BP is treated. Furthermore, a far greater degree of granularity may have been necessary given the central role of treatment in influencing any effect associated with BP. This is all the more important because a clinical encounter

was chosen as the PhD study's start date, and the BP recorded will have directly informed treatment and therefore future risk of outcomes.

6.5.8 Outcomes

Outcomes are typically less well recorded in routine data compared with registry data, and there is evidence that the lack of linking to registry data may lead to missed outcome records (554). Code lists for disease phenotypes that are widely accessible and developed by consensus were used where they were available, that is for cardiovascular disease. However, equivalent code lists were not available for outcomes which relate more closely to the diseases of ageing. These limitations exists because these phenotype code lists have not been developed, but also because diseases of ageing are not well coded in routine primary and secondary care data.

Mortality rates reported in the PhD study are consistent with other routine data studies. In the PhD study 39.2% of participants died during 10 year follow up. This rate was higher than: the Masoli study population who were over 75 years and had a mortality rate overall of 33% (366); and the Ravindrarajah study population who were over the age of 80 years and had a mortality rate of 36% (365). Differences in mortality rates between this study and the other two may relate to: the PhD study's selection of people with hypertension in whom mortality is known to be higher; and PhD study's use of ONS linked data records which represents a more robust method of death identification than methods using primary care records alone.

The choice of MACE as the primary outcome was justified in the study design by its use as a primary outcome in trials and observational data in hypertension research. The choice of MACE as primary outcome was pre-specified and informed the sample size calculation in Chapter 3. The crude rates per 100 person years varied between the individual MACE outcomes. Greater depth of analysis may have revealed variation between individual MACE outcomes in their associations with BP and frailty. However, these analyses were not pre-specified and therefore not undertaken. The qualitative study highlighted the importance of specific outcomes to patients and their day-to-day lives. Composite outcomes may therefore be of unclear relevance to patient-centred or shared decision making. Future research would be better powered to investigate individual outcomes and involve patients in their study design.

The PhD study data set benefited from linkage to hospital record data in the ascertainment of outcomes, and this is particularly evident in the descriptive outcomes. Proportions admitted to hospital with symptoms that may represent side effects of BP-lowering treatment ranged between 7.9% for electrolyte disturbances to 15.6% for hypotension over the 10 year follow up period. However, ageing related conditions including urinary incontinence and delirium were uncommonly reported. The rate of delirium was 1.5% over 10 years for a population 67.1% of whom was admitted to hospital in that same time period. This suggests significant under-reporting of delirium in this study sample given that prevalence of delirium is estimated between 10-31% of inpatients over the age of 65 years (555). An exception to the under-reporting of ageing related

diseases was the incidence of dementia. Incidence rates of dementia over the age of 65 years in the PhD study were calculated using records from primary and secondary care and incidence was estimated at 15 per 1,000 person years, which is consistent with rates reported in a definitive cohort study characterising dementia – the Cognitive Function and Ageing Study (CFAS) where it was reported as 20.0 (95% CI: 16.9–23.8) per 1,000 person years in CFAS I, and 17.7 (95% CI: 15.2–20.9) in the CFAS II study (556).

The difficulty recording ageing related problems, such as delirium and urinary incontinence in not unique to SAIL, it is true of all routine data sets. Electronic health records only include data items relevant to the particular clinical or administrative process, rather than what is relevant to an individual research question. The loss of higher-order function (cognition, mobility or continence) featured heavily in the narratives told in **Chapter 5**. In routine data, these higher function losses are most often represented by codes for the easiest attributable cause (e.g. urinary tract infection instead of delirium), whether accurate or not. Indeed the use of codes in recording symptoms may be insufficient to represent the complex interaction of multiple pre-disposing and precipitating factors involved in a geriatric syndrome. Where the dominant symptom is the only one recorded, the accompanying symptoms are missing. In such cases, the content of free text may be informative. The analysis of narrative text using Artificial Intelligence (AI) techniques, such as natural language processing algorithms is an emerging area in ageing research.

Arising from the PhD I have established, together with other researchers across the UK, an Ageing Data Research Collaborative (@geridata) with the support of the British Geriatrics Society (BGS) (557). This community has been developed to foster peer support among researchers and encourage sharing of pre-analytic protocols, code lists for conditions relevant to geriatric medicine and gerontology, methods of data cleaning and analysis.

6.5.9 Missing data

Important information was missing in this study. Data were missing in different ways. Some data were missing when they should have been recorded, such as the Cholesterol: HDL ratio and smoking status, given cardiovascular risk assessment is a necessary part of hypertension management and treatment. This was assumed to be data 'missing at random'. However, this missing data may affect some people more than others because some people will have had fewer opportunities to have their data recorded, because they used healthcare services less. On the other hand, there is the problem of informed presence bias which will be examined in more detail in **Section 6.6.2**.

Data may have also been missing because of the design of routine data records. Routine data is produced by positive recording, so: the absence of a recording of a particular diagnosis is assumed to represent the absence of diagnosis. Codes represent disease as being either present or absent. Therefore, the grade or severity of disease is difficult to account for in routine data analysis (558). Particular conditions are not routinely recorded in clinical

care or are under recorded (e.g. delirium and incontinence) and the omission or undercounting of such information could lead to spurious research findings.

6.5.10 Period of study

The availability of data on outcomes, covariates, and BP recordings is predetermined by what was measured in routine care in 2007 and in the ten years of follow up. Over the period of follow up (from 2007 until 2018) a number of guidelines for hypertension management changed significantly. NICE revised the initial 2004 guidelines in 2011 (559). Also, the NHS Health Check cardiovascular screening was launched in 2009 (560) and impacted on pay-for-performance targets for GPs, according to the Quality and Outcomes Framework (QOF) for BP in 2013 (380). These factors and other guideline changes from the American and European societies may have influenced clinical decisions made during the period of study. The PhD study could have been improved by including a longer time period of index dates and adjusting models for the year of index date.

6.6 Bias

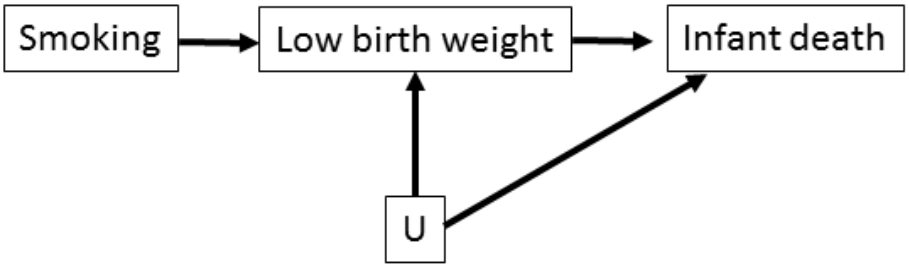
Given the observational nature of this study, no causal inference can be made from the findings. The interpretation of observational studies must account for their higher risk of reverse causality and residual confounding. There are several aspects to this study which may have caused bias to influence study findings, as discussed below.

6.6.1 Reversal paradox

A key limitation of observational research is confounding bias. Confounding is the effect on the association between an exposure and an outcome by a common cause. By conditioning on a confounder, we close off an alternative causal pathway from exposure to outcome. Methods to address conditioning include: restriction; confounder adjustment; stratification; and, matching. However, problems can arise if the variable conditioned upon is a mediator, as conditioning for a mediator may block the causal path. Conditioning on a mediator can also introduce collider bias (561). A collider represents a variable which is affected by two or more other variables in a causal path (562).

Conditioning on mediators can bias the results so much to cause a reversal of the overall effect. This has been described as the reversal paradox or Simpson's paradox (563). This was best described in the context of smoking and infant death, stratified by ethnicity and birthweight. In a series of studies analysing infant death in low birthweight infants, maternal ethnicity and smoking status were adjusted for. The surprising findings were that infant deaths in low birthweight babies were lower if the mother had smoked (564). Hernan and colleagues dissected the birth weight paradox by explaining that birthweight is a collider for unobserved causes of infant death (such as congenital disorders) and conditioning on it may well have led to a reversal of the association between smoking and infant death (**Figure 6-1**) (565).

Figure 6-1 Directed acyclic graph demonstrating Simpson's paradox



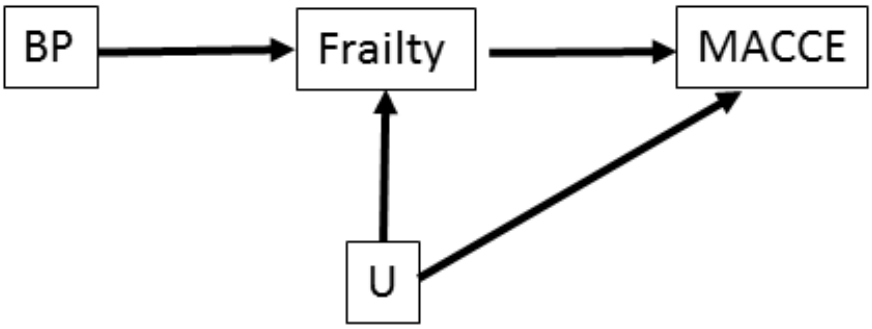
This schematic describes a simplified directed acyclic graph(566) illustrating Simpson's paradox with respect to investigations into low birthweight and infant death. This schematic is developed from discussions in Porta et al (375): low birth weight represents the collider in this graph because it is acted on by both smoking and unmeasured confounding (e.g. congenital disorders). Conditioning (e.g. adjusting or stratifying) for this collider opens up other causal pathways of unmeasured confounding **Abbreviations**: u – unmeasured confounder.

The frailty index represents a prognostic model, not a causal construct. This thesis demonstrates that frailty has a role in predicting future cardiovascular and non-cardiovascular outcomes in the context of hypertension. However, the question of how to intervene on BP differently in the context of frailty is an epidemiological question that requires causal methodology. Drawing a directed acyclic graph is a recognised method to identifying potential mediator and confounder relationships to reduce bias of the sort described by Simpson's paradox (567).

If frailty had a mediating role in the association between BP and cardiovascular outcomes this would theoretically introduce collider bias (**Figure 6-2**). In such a case, stratification on frailty sub-group, as has been undertaken in the PhD study, could lead to overall findings being influenced by un-observed factors. Measures of vascular ageing could plausibly represent such unobserved

factors, for example, endothelial dysfunction which relates both to cardiovascular risk and to frailty (see **Section 1.5.4**).

Figure 6-2 Simplified directed acyclic graph for Frailty as a mediator



This schematic describes a simplified directed acyclic graph demonstrated the potential challenges of collider bias if frailty is a mediator in the association between BP (BP) and major adverse cardiovascular events (MACE) making the findings vulnerable to the effects of unmeasured confounding (U).

As a multicomponent variable, frailty has constituent deficits, some of which may have a mediating role on the causal pathway from BP to cardiovascular outcomes, some of which may have a confounding role. The different relationships of the deficits within the eFI will vary according to the causal framework in which the eFI is being examined. This limitation is not specific to the eFI, and would similarly present a problem for the causal investigation of other measures of frailty, such as gait speed, grip strength or the Fried phenotype model, because all represent global proxy measures of an individual's overall health. Indeed, the problem is more explicit with a frailty measure that lists its constituent parts. However, dissecting frailty into mediator and confounder parts, as required by a causal inference study, would mean developing a different version of frailty from what is currently used across primary care settings in the UK. Redeveloping the eFI for the sake of

hypertension management would undermine the universality and global utility of the eFI.

6.6.2 Informed presence bias

As a consequence of using a positive recording database, inclusion in this cohort is reliant on a person's attendance to medical services. More frequent attenders will be better represented in routine data. This phenomenon is called informed presence bias (introduced in **Section 3.5.3.3**). The frailty index is highly correlated with use of healthcare services (568), so the analysis was adjusted for frequency of attendances where BP was measured to adjust for informed presence bias. Nevertheless it is likely to have been insufficient.

6.6.3 Confounding by indication

Making a causal interpretation of observational data on treatment is of limited value because treatments have not been randomised. The level of treatment in an effective healthcare system, will relate to the indication for treatment. Applied to BP, the more persistent someone presents with high BP whilst adhering to prescribed therapy, the more that person will be in receipt of treatment. This describes the concept of confounding by indication, where the comparison of medication users to medication non-users may lead to bias or difficulty in interpreting findings (569). There is a variety of methods to address this, all share the aim of emulating a clinical trial using observational data (570). These include propensity score matching (369). Where there are repeated events (as in the case of prescriptions for BP-lowering treatments), adjustment can be

made for the estimate of the outcome during a prior treatment-free window (571). This is called the ‘difference-in-differences’ approach (572).

6.6.4 Regression dilution

Regression dilution may also have contributed to a more modest association between BP and cardiovascular outcomes in the PhD study and in QRESEARCH data (368). Regression dilution illustrates bias as a result of the factors which make the single measure of BP as an exposure unreliable. These factors are described with regard to BP measurement in **Section 6.5.3**. An alternative approach could have been to take an average of serial measures, but as presented in **Table 3-5** this method also has the disadvantage that it leads to a regression to the mean. Another possibility would have been to use a method of time-dependent correction for regression dilution (367) whereby repeat BP measures during follow up time are used to correct for random measurement and short-term BP variability (368). This method was not used because the chief aim when designing this study was to imitate the clinical encounter a GP faces. As a result, residual bias of regression dilution may well have acted to underestimate the strength of association between BP and outcomes.

6.6.5 Unmeasured confounding

In retrospective analyses of routine data, the choice of confounders is determined by what is available rather that what the investigator considers

biologically relevant (572). As a consequence, unmeasured confounding may have significant consequences on study findings. In the PhD study, these unobserved factors may include GP practitioner effects, i.e. the degree to which clinicians varied in the way they managed a person's BP, and the degree to which treatment was not sufficiently accounted for.

The E-value represents a method of assessing the impact of unmeasured confounding. It is a measure of the minimum strength of association that unmeasured confounding needs to have to explain the exposure- outcome relationship (573). A sensitivity analysis or E-value estimate of the impact of potential unmeasured confounding is a recommended means of estimating the robustness of the effect size if it is determined without information on these factors.

For the prognostic factor study, the adjusted hazard ratio (HR) of MACE associated with mild frailty compared to those who were fit was reported as HR 1.38 (95% CI 1.35 to 1.41) (see **Section 4.5.2**). Using an E-value calculator, an adjusted HR of 1.38 could be explained by an unmeasured confounder that was associated with both frailty and the cardiovascular outcome by a risk ratio of 1.81-fold each, above and beyond the measured confounders. An unmeasured confounding effect of this magnitude may therefore be conceivable, and the estimated effect size reported in association with mild frailty may purely represent residual confounding.

Measurement error was a key concern in this analysis. Many of the continuous variables included in my analyses will have been associated with measurement error. One way of addressing this is to take repeated measures, to ensure that the variability can be accounted for, as was undertaken by including a measure of standard deviation of BP recordings. However the same was not undertaken for other continuous variables, including the eFI. Where variation is large (e.g. in severe frailty), prognostic factor effects may be too conservative (closer to 1) or too precise (having narrow confidence intervals), when measurement error is not accounted for (574).

6.6.6 Misclassification bias

Whilst an attempt was made to use best methods to measure outcomes in a way that is robust and valid, particularly for non-cardiovascular outcomes, where there are no consensus code lists available, outcome recording may have been misclassified or missed. Code lists have been included (**Appendix C** and **Appendix D**), as recommended by RECORD guidelines (575), to improve transparency. However, in an ideal scenario the CTV codes used for this study would have included code phenotypes for all outcomes and covariates, which have been validated against data from other sources to reduce the risk of bias at the level of code entry (see **Section 3.6.5**) Where code phenotypes are not developed (i.e. in non-cardiovascular disease) code lists were relied upon which were drawn from other published studies which reported disease prevalence consistent with other literature.

In future, work involving diseases of ageing needs to develop code phenotypes to combine EHR information from a variety of complementary sources (primary and secondary care) to improve case detection. There is a validated process of creating EHR phenotypes that has been undertaken in cardiovascular diseases (576), which could be pursued for conditions of ageing also. This process involves the assembly of terms through research and consensus work, implementation and validation procedures to ensure that these phenotypes are reproducible (577).

In routine data, patients may be misclassified as having a disease when they previously had a disease which has since resolved with treatment, cancer for example. This is relevant to the measurement of frailty where the frailty index includes symptoms and disabilities which may resolve with treatment or therapy. Whilst levels of frailty and comorbidity in the PhD study population are consistent with studies of similar cohorts, it is conceivable that the average comorbidity count, frailty and past medical history were inflated. Methods to address this include running sensitivity analyses :

- using code lists for conditions that prioritise specificity over sensitivity of diagnostic capture.
- using codes with allied information, for example, not include AF in the context of a concurrent illness, where the AF may therefore be reasonably assumed to have a reversible cause.
- Using codes for conditions that include temporal parameters –e.g. diabetic review entry in the past year’.

6.7 Interpretation

My interpretation of the key findings in the PhD are as follows:

1. **Frailty does not identify a population of older people with hypertension in whom the associations of BP and outcomes are meaningfully different**

   The PhD study was designed primarily to test the hypothesis that frailty may usefully distinguish a population in whom the association of BP and outcomes is non-linear as distinct from a population in whom the association of BP and outcomes is linear. This study has found no evidence to support this hypothesis and this is an important negative finding of the PhD.

   Furthermore this negative finding is evidenced by the lack of significant interaction between frailty and BP and outcomes. As discussed in this chapter there are aspects of the study design which may have influenced distorted these findings. Considered in the context of the wider literature, it is proposed that the difference in populations in whom the association of BP and outcomes is non-linear to populations in whom the association is linear may instead relate to two factors:

   a. the degree of cardiovascular disease burden and/ level of BP-lowering treatment, and
   b. the precision of BP and outcome measurement.

2. Frailty has a mediating role in the association between BP and outcomes

The PhD found clear evidence that frailty is a prognostic factor which is relevant to the prediction of cardiovascular outcomes in addition to established cardiovascular risk factors. The finding that frailty improves model fit in addition to the components of QRISK-3, and that separately, the QRISK-3 model when run in its entirety, has a high level of accuracy in predicting cardiovascular risk in this population, are together suggestive that frailty has a mediating role in the cardiovascular risk measured by the QRISK-3 algorithm.

Frailty as a mediator in the association between BP and outcomes would also be consistent with another key finding of the PhD. The associations between systolic BP and outcomes were not evident in sub-populations defined by more advanced frailty. By conditioning on the mediator (frailty), the association between BP and outcomes is no longer evident. This is in keeping with the concept of the reversal paradox, and having conditioned on a mediator in this analysis, unobserved confounding has been allowed to influence the findings.

The implications of considering frailty as a mediator of cardiovascular risk are manifold. They include the need to consider frailty as a prognostic factor in prognostic models to predict cardiovascular risk in relation to hypertension. In parallel, this finding indicates that interventions targeting

ageing processes should also be tested on cardiovascular events. A similarly less parochial approach to prediction and intervention in cardiovascular disease in the context of ageing, has been proposed in relation to heart failure with preserved ejection fraction (578).

3. Frailty modifies the association of BP-lowering treatment and outcomes in older people with hypertension

The PhD found evidence that frailty modified the effect of BP-lowering treatment on cardiovascular and non-cardiovascular outcomes. There at least three possible explanations for this, which will be considered in turn:

1. Frailty alters the benefit from BP-lowering treatment. This explanation would be consistent with evidence presented in **Chapter 1** indicating that ageing is central to the aetiology of hypertension in old age, and that therefore the targets and the effectiveness of BP-lowering treatment could conceivably be altered in the context of ageing.

2. The modifying effect of frailty in the context of hypertension management, is in the degree to which someone suffers adverse effects from BP-lowering treatment. This explanation would be consistent with clinical conception of frailty as increasing vulnerability to adverse effects of medication, and the research findings elsewhere associating BP-lowering treatment: at low BP with higher mortality risk (525); and, with increased risk of falls (526).

3. Frailty alters prescription of BP-lowering medications in older people. Whilst the GP at the index encounter in 2007 would not have had access to an eFI of the patient, it is likely that if the eFI suggests frailty the GP would have been aware of the patient's frailty through other clinical features, such as multi-morbidity or disability. However, the number of treatment (by BP-lowering class) was the same in all frailty sub-groups. Another possibility is that adherence to BP-lowering therapy is different in the context of frailty. For example, adherence may be higher in people who have carers every morning attending to give medications, either visiting their home or within a care home setting.

6.7.1 Implications for clinical practice

The clinical implications of the PhD findings are:

1. Precision of BP measurement in older people is important, and where possible office readings should not direct BP-lowering treatment. The PhD study findings demonstrated increased variability of systolic BP with advancing frailty. The use of home readings or 24 h ambulatory readings have been shown to be more accurate in their representation of a person's true BP, and can better predict cardiovascular risk in comparison to office BP readings (579).

2. Frailty as measured by the eFI can identify people who are at high cardiovascular risk and high risk of non-cardiovascular outcomes related to hypertension management including death and injurious falls. Frailty can identify a sub-population of older people for whom a different approach to treatment may be necessary.

3. This study found no evidence that justifies the use of an eFI in clinical practice, to identify an alternative BP for an older person with hypertension.

4. The PhD findings indicate a possible modifying effect of frailty in the context of hypertension management, in the degree to which someone suffers adverse effects from BP-lowering treatment. In this context, potential side effects related to BP-lowering medication should be kept under regular review in older people with frailty who have hypertension.

6.7.2 Implications for policy

The findings of the PhD routine data study support international consensus hypertension guidelines which recommend the measurement of frailty in old age (320, 322) to inform approach to hypertension management. The exploration of the patient's perspective highlighted the necessity for shared decision making to address what matters to the individual in terms of outcomes that are tangible and salient to them.

Shared decision making strategies may need to be varied according to whether hypertension management is in the context of either primary or secondary prevention of cardiovascular disease. Consideration to whether this decision making is best placed in the context of hypertension review, or as part of a comprehensive geriatric assessment that involves anticipatory planning around frailty. This needs serious consideration with patient representatives. In the future, investigations into different methods of SDM could inform a step-by-step approach to guide clinicians on how to do this effectively and in a patient centred way.

A more holistic approach to hypertension treatment review in the context of frailty may be enabled by a more integrated approach from national guidelines. There are calls to better adapt UK single disease guidelines to the care of patients multi-morbidity by cross-referencing guidelines which are applicable to the same patient (580). In the case of NICE hypertension guidelines for older people with frailty, this could involve NICE guidelines on multi-morbidity (581) and the ‘Fit for Frailty’ guideline on the identification and management of frailty (582).

6.7.3 Future research

There are two particular lines of potential future enquiry emerging from the PhD:

1. **Which risk factors predict adverse effects of BP-lowering treatment in older people?**

   The primary exposure would be BP lowering treatment given this is the potentially reversible factor which a trial could proceed to investigate. The choice of covariates would be informed by systematic review of risk factors relating to ageing that do interact with BP treatment to cause different associations with outcomes. Consideration would be given to characterising BP in greater granularity, including:

   1. Between visit BP variability, short and long term;
   2. BP trajectory, using join modelling techniques;
   3. Home or ambulatory BP readings.

   Prognostic models would be developed in a competing risks framework, according to PROGRESS-III consensus methods of prognostic model development (374). Prediction scores for treatment harm on a range of outcomes could inform shared decision making with patients and identify populations of older people who may be candidates for a BP-lowering treatment de-escalation trial.

2. **Randomised control trial to investigate the role of BP-lowering treatment withdrawal in patients who are at high risk of adverse outcomes.**

To adequately address the limitations identified with confounding and other sources or bias, a randomised control trial is required. Using a prognostic model developed from the study above, a trial would target a population of older adults at high risk from treatment harm. Two levels of treatment arms would potentially align with different treatment strategies as set out by international guideline systolic BP treatment thresholds, e.g. American Family Physicians (AFP) target of <150 mm Hg; European Society of Cardiology (ESC) target of < 140 mm Hg, and > 130 mm Hg. Precise measurement of BP will be necessary in this trial, using methods that are replicable in routine daily care such as ambulatory or home BP measurement. A range of cardiovascular and non-cardiovascular outcomes would be measured, and patient representatives would need to be involved early in the development of trial design.

6.8 Conclusions

The research presented in this thesis is a thorough investigation of BP and outcomes in older people according to their frailty status. This is the first study in a population which has direct application to a specific clinical setting, namely those with hypertension managed for primary cardiovascular prevention. This is the first study to use mixed methods to explore the perspectives of patients in the interpretation of data findings. The study population was over 65 years old, large in scale (145,598), and generalizable to routine clinical care: 67.5% had multi-morbidity, and, 87% were prescribed BP-lowering treatment. The study used linked data sets to ascertain primary and secondary outcomes including 57,157(39.2%) deaths from any cause.

There is strong evidence frailty is a prognostic factor that identifies older people who are at high risk of cardiovascular and non-cardiovascular outcomes in the management of hypertension. Frailty may therefore identify patients for whom a different approach to shared decision making is indicated. From a patient's perspective, this could include understanding how a person conceives of frailty as a means to understand what they value to engage them in shared decision making regarding BP-lowering treatment. The finding of a significant interaction between frailty and BP-lowering treatment may suggest that the modifying effect of frailty in the context of hypertension management, is in the degree to which someone suffers adverse effects of BP lowering treatment. This finding needs to be tested in

an epidemiological study using more precise measures of BP and BP-lowering treatment. Ultimately a randomised control trial is needed to investigate whether the effect of treatment is the same across frailty states.

List of References

1. Lloyd-Jones, D. General Population and Global Cardiovascular Risk Prediction. In: Bakris, G.S., M; ed. *Hypertension: A companion to Braunwald's Heart Disease*. 3rd ed. Philadelphia, USA: Elsevier, 2018.
2. Rose, G. Epidemiology. In: Marshall, A.B., DW; ed. *The Hypertensive Patient*. Kent, UK: Pittman Medical, 1980, pp.1-21.
3. Collaborators, G.B.D.R.F. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet.* 2016, **388**(10053), pp.1659-1724.
4. Ferrucci, L., Guralnik, J.M., Pahor, M., Corti, M.C. and Havlik, R.J. Hospital diagnoses, Medicare charges, and nursing home admissions in the year when older persons become severely disabled. *JAMA.* 1997, **277**(9), pp.728-734.
5. Lozano, R., Naghavi, M., Foreman, K., Lim, S., Shibuya, K., Aboyans, V., Abraham, J., Adair, T., Aggarwal, R., Ahn, S.Y., Alvarado, M., Anderson, H.R., Anderson, L.M., Andrews, K.G., Atkinson, C., Baddour, L.M., Barker-Collo, S., Bartels, D.H., Bell, M.L., Benjamin, E.J., Bennett, D., Bhalla, K., Bikbov, B., Bin Abdulhak, A., Birbeck, G., Blyth, F., Bolliger, I., Boufous, S., Bucello, C., Burch, M., Burney, P., Carapetis, J., Chen, H., Chou, D., Chugh, S.S., Coffeng, L.E., Colan, S.D., Colquhoun, S., Colson, K.E., Condon, J., Connor, M.D., Cooper, L.T., Corriere, M., Cortinovis, M., de Vaccaro, K.C., Couser, W., Cowie, B.C., Criqui, M.H., Cross, M., Dabhadkar, K.C., Dahodwala, N., De Leo, D., Degenhardt, L., Delossantos, A., Denenberg, J., Des Jarlais, D.C., Dharmaratne, S.D., Dorsey, E.R., Driscoll, T., Duber, H., Ebel, B., Erwin, P.J., Espindola, P., Ezzati, M., Feigin, V., Flaxman, A.D., Forouzanfar, M.H., Fowkes, F.G., Franklin, R., Fransen, M., Freeman, M.K., Gabriel, S.E., Gakidou, E., Gaspari, F., Gillum, R.F., Gonzalez-Medina, D., Halasa, Y.A., Haring, D., Harrison, J.E., Havmoeller, R., Hay, R.J., Hoen, B., Hotez, P.J., Hoy, D., Jacobsen, K.H., James, S.L., Jasrasaria, R., Jayaraman, S., Johns, N., Karthikeyan, G., Kassebaum, N., Keren, A., Khoo, J.P., Knowlton, L.M., Kobusingye, O., Koranteng, A., Krishnamurthi, R., Lipnick, M., Lipshultz, S.E., Ohno, S.L., Mabweijano, J., MacIntyre, M.F., Mallinger, L., March, L., Marks, G.B., Marks, R., Matsumori, A., Matzopoulos, R., Mayosi, B.M., McAnulty, J.H., McDermott, M.M., McGrath, J., Mensah, G.A., Merriman, T.R., Michaud, C., Miller, M., Miller, T.R., Mock, C., Mocumbi, A.O., Mokdad, A.A., Moran, A., Mulholland, K., Nair, M.N., Naldi, L., Narayan, K.M., Nasseri, K., Norman, P., O'Donnell, M., Omer, S.B., Ortblad, K., Osborne, R., Ozgediz, D., Pahari, B., Pandian, J.D., Rivero, A.P., Padilla, R.P., Perez-Ruiz, F., Perico, N., Phillips, D., Pierce, K., Pope, C.A., 3rd, Porrini, E., Pourmalek, F., Raju, M., Ranganathan, D., Rehm, J.T., Rein, D.B., Remuzzi, G., Rivara, F.P., Roberts, T., De Leon, F.R., Rosenfeld, L.C., Rushton, L., Sacco, R.L., Salomon, J.A., Sampson,

U., Sanman, E., Schwebel, D.C., Segui-Gomez, M., Shepard, D.S., Singh, D., Singleton, J., Sliwa, K., Smith, E., Steer, A., Taylor, J.A., Thomas, B., Tleyjeh, I.M., Towbin, J.A., Truelsen, T., Undurraga, E.A., Venketasubramanian, N., Vijayakumar, L., Vos, T., Wagner, G.R., Wang, M., Wang, W., Watt, K., Weinstock, M.A., Weintraub, R., Wilkinson, J.D., Woolf, A.D., Wulf, S., Yeh, P.H., Yip, P., Zabetian, A., Zheng, Z.J., Lopez, A.D., Murray, C.J., AlMazroa, M.A. and Memish, Z.A. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012, **380**(9859), pp.2095-2128.

6. Collaborators, G.B.D.R.F. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet.* 2017, **390**(10100), pp.1345-1422.
7. Division, U.D.o.E.a.S.A.P. *World Population Prospects: the 2019 Revision DVD edition.* 2019.
8. Scholes, S. *Health Survey for England 2018: Adult Health.* [Online]. 2019. [Accessed 20.09.2020].
9. Benjamin, E.J., Blaha, M.J., Chiuve, S.E., Cushman, M., Das, S.R., Deo, R., de Ferranti, S.D., Floyd, J., Fornage, M., Gillespie, C., Isasi, C.R., Jimenez, M.C., Jordan, L.C., Judd, S.E., Lackland, D., Lichtman, J.H., Lisabeth, L., Liu, S., Longenecker, C.T., Mackey, R.H., Matsushita, K., Mozaffarian, D., Mussolino, M.E., Nasir, K., Neumar, R.W., Palaniappan, L., Pandey, D.K., Thiagarajan, R.R., Reeves, M.J., Ritchey, M., Rodriguez, C.J., Roth, G.A., Rosamond, W.D., Sasson, C., Towfighi, A., Tsao, C.W., Turner, M.B., Virani, S.S., Voeks, J.H., Willey, J.Z., Wilkins, J.T., Wu, J.H., Alger, H.M., Wong, S.S., Muntner, P., American Heart Association Statistics, C. and Stroke Statistics, S. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation.* 2017, **135**(10), pp.e146-e603.
10. Finley, C.R., Chan, D.S., Garrison, S., Korownyk, C., Kolber, M.R., Campbell, S., Eurich, D.T., Lindblad, A.J., Vandermeer, B. and Allan, G.M. What are the most common conditions in primary care? Systematic review. *Can Fam Physician.* 2018, **64**(11), pp.832-840.
11. Violan, C., Foguet-Boreu, Q., Roso-Llorach, A., Rodriguez-Blanco, T., Pons-Vigues, M., Pujol-Ribera, E., Munoz-Perez, M.A. and Valderas, J.M. Burden of multimorbidity, socioeconomic status and use of health services across stages of life in urban areas: a cross-sectional study. *BMC Public Health.* 2014, **14**, p.530.
12. Board;, B.P.S.L. *New figures show high blood pressure costs NHS billions each year.* [Online]. 2014. [Accessed 21.09.2020]. Available from: https://www.gov.uk/government/news/new-figures-show-high-blood-pressure-costs-nhs-billions-each-year
13. Collaboration, N.C.D.R.F. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet.* 2017, **389**(10064), pp.37-55.

14. Kearney, P.M., Whelton, M., Reynolds, K., Muntner, P., Whelton, P.K. and He, J. Global burden of hypertension: analysis of worldwide data. *Lancet.* 2005, **365**(9455), pp.217-223.
15. Danaei, G., Finucane, M.M., Lin, J.K., Singh, G.M., Paciorek, C.J., Cowan, M.J., Farzadfar, F., Stevens, G.A., Lim, S.S., Riley, L.M., Ezzati, M. and Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating, G. National, regional, and global trends in systolic blood pressure since 1980: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5.4 million participants. *Lancet.* 2011, **377**(9765), pp.568-577.
16. Geldsetzer, P., Manne-Goehler, J., Marcus, M.E., Ebert, C., Zhumadilov, Z., Wesseh, C.S., Tsabedze, L., Supiyev, A., Sturua, L., Bahendeka, S.K., Sibai, A.M., Quesnel-Crooks, S., Norov, B., Mwangi, K.J., Mwalim, O., Wong-McClure, R., Mayige, M.T., Martins, J.S., Lunet, N., Labadarios, D., Karki, K.B., Kagaruki, G.B., Jorgensen, J.M.A., Hwalla, N.C., Houinato, D., Houehanou, C., Msaidie, M., Guwatudde, D., Gurung, M.S., Gathecha, G., Dorobantu, M., Damasceno, A., Bovet, P., Bicaba, B.W., Aryal, K.K., Andall-Brereton, G., Agoudavi, K., Stokes, A., Davies, J.I., Barnighausen, T., Atun, R., Vollmer, S. and Jaacks, L.M. The state of hypertension care in 44 low-income and middle-income countries: a cross-sectional study of nationally representative individual-level data from 1.1 million adults. *Lancet.* 2019, **394**(10199), pp.652-662.
17. Rode, A. and Shephard, R.J. Physiological consequences of acculturation: a 20-year study of fitness in an Inuit community. *Eur J Appl Physiol Occup Physiol.* 1994, **69**(6), pp.516-524.
18. Yoon, S.S.F., C.D. ; Carroll, M.D. . *Hypertension prevalence and control among adults: United States, 2011-2014.* Hyattsville, MD: National Center for Health Statistics, 2015.
19. Cornoni-Huntley, J., LaCroix, A.Z. and Havlik, R.J. Race and sex differentials in the impact of hypertension in the United States. The National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. *Arch Intern Med.* 1989, **149**(4), pp.780-788.
20. Lackland, D.T. Racial differences in hypertension: implications for high blood pressure management. *Am J Med Sci.* 2014, **348**(2), pp.135-138.
21. Shaper, A.G., Ashby, D. and Pocock, S.J. Blood pressure and hypertension in middle-aged British men. *J Hypertens.* 1988, **6**(5), pp.367-374.
22. Foster, H.M.E., Celis-Morales, C.A., Nicholl, B.I., Petermann-Rocha, F., Pell, J.P., Gill, J.M.R., O'Donnell, C.A. and Mair, F.S. The effect of socioeconomic deprivation on the association between an extended measurement of unhealthy lifestyle factors and health outcomes: a prospective analysis of the UK Biobank cohort. *Lancet Public Health.* 2018, **3**(12), pp.e576-e585.
23. Wills, A.K., Lawlor, D.A., Matthews, F.E., Sayer, A.A., Bakra, E., Ben-Shlomo, Y., Benzeval, M., Brunner, E., Cooper, R., Kivimaki, M., Kuh, D., Muniz-Terrera, G. and Hardy, R. Life course trajectories of systolic blood pressure using longitudinal data from eight UK cohorts. *PLoS Med.* 2011, **8**(6), p.e1000440.

24. Akahoshi, M., Soda, M., Carter, R.L., Nakashima, E., Shimaoka, K., Seto, S. and Yano, K. Correlation between systolic blood pressure and physical development in adolescence. *Am J Epidemiol.* 1996, **144**(1), pp.51-58.
25. Benetos, A., Petrovic, M. and Strandberg, T. Hypertension Management in Older and Frail Older Patients. *Circ Res.* 2019, **124**(7), pp.1045-1060.
26. Franklin, S.S., Jacobs, M.J., Wong, N.D., L'Italien, G.J. and Lapuerta, P. Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives: analysis based on National Health and Nutrition Examination Survey (NHANES) III. *Hypertension.* 2001, **37**(3), pp.869-874.
27. Franklin, S.S., Pio, J.R., Wong, N.D., Larson, M.G., Leip, E.P., Vasan, R.S. and Levy, D. Predictors of new-onset diastolic and systolic hypertension: the Framingham Heart Study. *Circulation.* 2005, **111**(9), pp.1121-1127.
28. Vasan, R.S., Beiser, A., Seshadri, S., Larson, M.G., Kannel, W.B., D'Agostino, R.B. and Levy, D. Residual lifetime risk for developing hypertension in middle-aged women and men: The Framingham Heart Study. *JAMA.* 2002, **287**(8), pp.1003-1010.
29. Lloyd-Jones, D., Adams, R., Carnethon, M., De Simone, G., Ferguson, T.B., Flegal, K., Ford, E., Furie, K., Go, A., Greenlund, K., Haase, N., Hailpern, S., Ho, M., Howard, V., Kissela, B., Kittner, S., Lackland, D., Lisabeth, L., Marelli, A., McDermott, M., Meigs, J., Mozaffarian, D., Nichol, G., O'Donnell, C., Roger, V., Rosamond, W., Sacco, R., Sorlie, P., Stafford, R., Steinberger, J., Thom, T., Wasserthiel-Smoller, S., Wong, N., Wylie-Rosett, J., Hong, Y., American Heart Association Statistics, C. and Stroke Statistics, S. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2009, **119**(3), pp.e21-181.
30. Satish, S., Zhang, D.D. and Goodwin, J.S. Clinical significance of falling blood pressure among older adults. *J Clin Epidemiol.* 2001, **54**(9), pp.961-967.
31. Rogers, M.A., Ward, K., Gure, T.R., Choe, H.M., Lee, P.G., Bernstein, S.J. and Blaum, C.S. Blood pressure trajectories prior to death in patients with diabetes. *Diabetes Care.* 2011, **34**(7), pp.1534-1539.
32. Delgado, J., Bowman, K., Ble, A., Masoli, J., Han, Y., Henley, W., Welsh, S., Kuchel, G.A., Ferrucci, L. and Melzer, D. Blood Pressure Trajectories in the 20 Years Before Death. *JAMA Intern Med.* 2018, **178**(1), pp.93-99.
33. Gurven, M., Blackwell, A.D., Rodriguez, D.E., Stieglitz, J. and Kaplan, H. Does blood pressure inevitably rise with age?: longitudinal evidence among forager-horticulturalists. *Hypertension.* 2012, **60**(1), pp.25-33.
34. Bell, J. *Redefining disease.* Royal College of Physicians, 2010.
35. Page, I.H. Pathogenesis of arterial hypertension. *J Am Med Assoc.* 1949, **140**(5), pp.451-458.
36. Harrison, D.G. The mosaic theory revisited: common molecular mechanisms coordinating diverse organ and cellular events in hypertension. *J Am Soc Hypertens.* 2013, **7**(1), pp.68-74.

37. Oparil, S., Acelajado, M.C., Bakris, G.L., Berlowitz, D.R., Cifkova, R., Dominiczak, A.F., Grassi, G., Jordan, J., Poulter, N.R., Rodgers, A. and Whelton, P.K. Hypertension. *Nat Rev Dis Primers.* 2018, **4**, p.18014.
38. Chau, N.P., Coleman, T.G., London, G.M. and Safar, M.E. Meaning of the cardiac output-blood volume relationship in essential hypertension. *Am J Physiol.* 1982, **243**(3), pp.R318-328.
39. Sabir, I.U.-S.J. *A thinking approach to Physiology.* London, UK: World Scientific, 2008.
40. Safar, M.E., Levy, B.I. and Struijker-Boudier, H. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. *Circulation.* 2003, **107**(22), pp.2864-2869.
41. Marchais, S.J., Guerin, A.P., Pannier, B., Delavaud, G. and London, G.M. Arterial compliance and blood pressure. *Drugs.* 1993, **46 Suppl 2**, pp.82-87.
42. Nichols, W.O.R., MF; Vlachopoulos, C;. *McDonald's Blood Flow in Arteries.* Florida, USA: CRC Press, 2011.
43. Safar, M.O.R., ME. Arterial Stiffness in Hypertension. In: 1st ed. Amsterdam, NL: Elsevier, 2006, pp.3–62. 75–136, 459–501.
44. Kozakova, M.S.-T., A;. Age-Induced Endothelial Dysfunction and Intima-Media Thickening. In: Nilsson PM, O.M., Laurent S ed. *Early Vascular Aging (EVA): New Directions in Cardiovascular Protection*. London, UK: Academic Press, 2015, pp.137-145.
45. Glagov, S. Hemodynamic risk factors: mechanical stress, mural architecture, medial nutrition and vulnerability of arteries to atherosclerosis. In: Wissler, R.G., JC; ed. *The Pathogenesis of Atherosclerosis*. Baltimore, Maryland: Williams and Wilkins, 1972, pp.164-199.
46. Rosenquist, T.H., Beall, A.C., Modis, L. and Fishman, R. Impaired elastic matrix development in the great arteries after ablation of the cardiac neural crest. *Anat Rec.* 1990, **226**(3), pp.347-359.
47. Greenwald, S.E. Ageing of the conduit arteries. *J Pathol.* 2007, **211**(2), pp.157-172.
48. Kung, C.F. and Luscher, T.F. Different mechanisms of endothelial dysfunction with aging and hypertension in rat aorta. *Hypertension.* 1995, **25**(2), pp.194-200.
49. Laurent, S., Cockcroft, J., Van Bortel, L., Boutouyrie, P., Giannattasio, C., Hayoz, D., Pannier, B., Vlachopoulos, C., Wilkinson, I., Struijker-Boudier, H. and European Network for Non-invasive Investigation of Large, A. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J.* 2006, **27**(21), pp.2588-2605.
50. Safar, M.E., Blacher, J., Mourad, J.J. and London, G.M. Stiffness of carotid artery wall material and blood pressure in humans: application to antihypertensive therapy and stroke prevention. *Stroke.* 2000, **31**(3), pp.782-790.
51. Safar, M.E. The arterial system in human hypertension. In: Swales, J. ed. *Textbook of Hypertension*. London, UK: Blackwell Scientific, 1994.
52. Virmani, R., Avolio, A.P., Mergner, W.J., Robinowitz, M., Herderick, E.E., Cornhill, J.F., Guo, S.Y., Liu, T.H., Ou, D.Y. and O'Rourke, M.

Effect of aging on aortic morphology in populations with high and low prevalence of hypertension and atherosclerosis. Comparison between occidental and Chinese communities. *Am J Pathol.* 1991, **139**(5), pp.1119-1129.

53. Nagai, Y., Metter, E.J., Earley, C.J., Kemper, M.K., Becker, L.C., Lakatta, E.G. and Fleg, J.L. Increased carotid artery intimal-medial thickness in asymptomatic older subjects with exercise-induced myocardial ischemia. *Circulation.* 1998, **98**(15), pp.1504-1509.
54. Lakatta, E.G., Wang, M. and Najjar, S.S. Arterial aging and subclinical arterial disease are fundamentally intertwined at macroscopic and molecular levels. *Med Clin North Am.* 2009, **93**(3), pp.583-604, Table of Contents.
55. Davis, E.C. Stability of elastin in the developing mouse aorta: a quantitative radioautographic study. *Histochemistry.* 1993, **100**(1), pp.17-26.
56. van Varik, B.J., Rennenberg, R.J., Reutelingsperger, C.P., Kroon, A.A., de Leeuw, P.W. and Schurgers, L.J. Mechanisms of arterial remodeling: lessons from genetic diseases. *Front Genet.* 2012, **3**, p.290.
57. Lakatta, E.G. and Levy, D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part II: the aging heart in health: links to heart disease. *Circulation.* 2003, **107**(2), pp.346-354.
58. Orlandi, A., Marcellini, M. and Spagnoli, L.G. Aging influences development and progression of early aortic atherosclerotic lesions in cholesterol-fed rabbits. *Arterioscler Thromb Vasc Biol.* 2000, **20**(4), pp.1123-1136.
59. Lakatta, E.G. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part III: cellular and molecular clues to heart and arterial aging. *Circulation.* 2003, **107**(3), pp.490-497.
60. Semba, R.D., Nicklett, E.J. and Ferrucci, L. Does accumulation of advanced glycation end products contribute to the aging phenotype? *J Gerontol A Biol Sci Med Sci.* 2010, **65**(9), pp.963-975.
61. Larsson, A., Peng, S., Persson, H., Rosenbloom, J., Abrams, W.R., Wassberg, E., Thelin, S., Sletten, K., Gerwins, P. and Westermark, P. Lactadherin binds to elastin--a starting point for medin amyloid formation? *Amyloid.* 2006, **13**(2), pp.78-85.
62. Mucchiano, G., Cornwell, G.G., 3rd and Westermark, P. Senile aortic amyloid. Evidence for two distinct forms of localized deposits. *Am J Pathol.* 1992, **140**(4), pp.871-877.
63. Haggqvist, B., Naslund, J., Sletten, K., Westermark, G.T., Mucchiano, G., Tjernberg, L.O., Nordstedt, C., Engstrom, U. and Westermark, P. Medin: an integral fragment of aortic smooth muscle cell-produced lactadherin forms the most common human amyloid. *Proc Natl Acad Sci U S A.* 1999, **96**(15), pp.8669-8674.
64. Lacolley P, C.P., Regnault V, Lakatta EG, Wang M. Cellular and Molecular Determinants of Arterial Aging. In: Nilsson PM, O.M., Laurent S ed. *Early Vascular Aging: New Directions in Cardiovascular protection*. London: Academic Press, 2015, pp.7 - 16.

65. Thompson, R.C., Allam, A.H., Lombardi, G.P., Wann, L.S., Sutherland, M.L., Sutherland, J.D., Soliman, M.A., Frohlich, B., Mininberg, D.T., Monge, J.M., Vallodolid, C.M., Cox, S.L., Abd el-Maksoud, G., Badr, I., Miyamoto, M.I., el-Halim Nur el-Din, A., Narula, J., Finch, C.E. and Thomas, G.S. Atherosclerosis across 4000 years of human history: the Horus study of four ancient populations. *Lancet.* 2013, **381**(9873), pp.1211-1222.
66. Hallock, P. and Benson, I.C. Studies on the Elastic Properties of Human Isolated Aorta. *J Clin Invest.* 1937, **16**(4), pp.595-602.
67. Imura, T., Yamamoto, K., Kanamori, K., Mikami, T. and Yasuda, H. Non-invasive ultrasonic measurement of the elastic properties of the human abdominal aorta. *Cardiovasc Res.* 1986, **20**(3), pp.208-214.
68. Hall, J.E. *Guyton and Hall Textbook of Medical Physiology.* 12th ed. Philadelphia: Saunders Elsevier, 2011.
69. Aggarwal, S.G., C.M.; Porcelli, R.J.; Black, S.M. Pulmonary Hemodynamics. In: Parent, R. ed. *Comparative Biology of the Normal Lung*. 2nd ed. London, UK: Academic Press, 2015, pp.205-243.
70. De Leeuw, P. Isolated Systolic Hypertension. In: Bakris, G.L.S.M.J. ed. *Hypertension: A Companion to Braunwald's Heart Disease*. Philadelphia, USA: Elsevier, 2018.
71. Safar, M.P., G.E.; London, G.M.;. Vascular compliance and blood volume in essential hypertension. In: Laragh J, B.B. ed. *Hypertension: Pathophysiology, diagnosis, and management*. New York: Raven Press, 1995, pp.377–388.
72. Westerhof, N., Lankhaar, J.W. and Westerhof, B.E. The arterial Windkessel. *Med Biol Eng Comput.* 2009, **47**(2), pp.131-141.
73. Mitchell, G.F. Arterial stiffness and wave reflection in hypertension: pathophysiologic and therapeutic implications. *Curr Hypertens Rep.* 2004, **6**(6), pp.436-441.
74. Mulvany, M.J. and Aalkjaer, C. Structure and function of small arteries. *Physiol Rev.* 1990, **70**(4), pp.921-961.
75. Levy, B.I., Ambrosio, G., Pries, A.R. and Struijker-Boudier, H.A. Microcirculation in hypertension: a new target for treatment? *Circulation.* 2001, **104**(6), pp.735-740.
76. London, G.M., Guerin, A.P., Pannier, B., Marchais, S.J. and Stimpel, M. Influence of sex on arterial hemodynamics and blood pressure. Role of body height. *Hypertension.* 1995, **26**(3), pp.514-519.
77. Klabunde, R. *Cardiovascular Physiology Concepts.* [Online]. 2016. [Accessed 25.06.2020]. Available from: https://www.cvphysiology.com/Blood%20Pressure/BP006
78. Kroeker, E.J. and Wood, E.H. Comparison of simultaneously recorded central and peripheral arterial pressure pulses during rest, exercise and tilted position in man. *Circ Res.* 1955, **3**(6), pp.623-632.
79. Safar, M. Arterial stiffness: A Simplified Overview in Vascular Medicine. In: Safar, M.E.F., E.D.; ed. *Atherosclerosis, Large Arteries and Cardiovascular Risk*. Basel, Switzerland: Karger, 2007, pp.1-18.
80. Strait, J.B. and Lakatta, E.G. Aging-associated cardiovascular changes and their relationship to heart failure. *Heart Fail Clin.* 2012, **8**(1), pp.143-164.

81. Grewal, J., McCully, R.B., Kane, G.C., Lam, C. and Pellikka, P.A. Left ventricular function and exercise capacity. *JAMA.* 2009, **301**(3), pp.286-294.
82. DeLoach, S.S. and Townsend, R.R. Vascular stiffness: its measurement and significance for epidemiologic and outcome studies. *Clin J Am Soc Nephrol.* 2008, **3**(1), pp.184-192.
83. Mitchell, G.F., Parise, H., Benjamin, E.J., Larson, M.G., Keyes, M.J., Vita, J.A., Vasan, R.S. and Levy, D. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. *Hypertension.* 2004, **43**(6), pp.1239-1245.
84. O'Rourke, M.F. Arterial aging: pathophysiological principles. *Vasc Med.* 2007, **12**(4), pp.329-341.
85. O'Rourke, M.F. and Hashimoto, J. Mechanical factors in arterial aging: a clinical perspective. *J Am Coll Cardiol.* 2007, **50**(1), pp.1-13.
86. Madhavan, S., Ooi, W.L., Cohen, H. and Alderman, M.H. Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. *Hypertension.* 1994, **23**(3), pp.395-401.
87. Blacher, J., Guerin, A.P., Pannier, B., Marchais, S.J., Safar, M.E. and London, G.M. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation.* 1999, **99**(18), pp.2434-2439.
88. Laurent, S., Boutouyrie, P., Asmar, R., Gautier, I., Laloux, B., Guize, L., Ducimetiere, P. and Benetos, A. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension.* 2001, **37**(5), pp.1236-1241.
89. Adrian, M., Laurant, P. and Berthelot, A. Effect of magnesium on mechanical properties of pressurized mesenteric small arteries from old and adult rats. *Clin Exp Pharmacol Physiol.* 2004, **31**(5-6), pp.306-313.
90. Briones, A.M., Salaices, M. and Vila, E. Mechanisms underlying hypertrophic remodeling and increased stiffness of mesenteric resistance arteries from aged rats. *J Gerontol A Biol Sci Med Sci.* 2007, **62**(7), pp.696-706.
91. Lakatta, E.G., Mitchell, J.H., Pomerance, A. and Rowe, G.G. Human aging: changes in structure and function. *J Am Coll Cardiol.* 1987, **10**(2 Suppl A), pp.42A-47A.
92. Oakley, R. and Tharakan, B. Vascular hyperpermeability and aging. *Aging Dis.* 2014, **5**(2), pp.114-125.
93. Seals, D.R., Kaplon, R.E., Gioscia-Ryan, R.A. and LaRocca, T.J. You're only as old as your arteries: translational strategies for preserving vascular endothelial function with aging. *Physiology (Bethesda).* 2014, **29**(4), pp.250-264.
94. Franke, R.P., Grafe, M., Schnittler, H., Seiffge, D., Mittermayer, C. and Drenckhahn, D. Induction of human vascular endothelial stress fibres by fluid shear stress. *Nature.* 1984, **307**(5952), pp.648-649.
95. Spieker, L.F., AJ; Luscher TF. The Vascular Endothelium in Hypertension. In: Moncada, S.H., A; ed. *The Vascular Endothelium II*. Springer-Verlag Berlin Heidelberg, 2006, pp.249-283.
96. Serrano-Ponz, M., Rodrigo-Gasque, C., Siles, E., Martinez-Lara, E., Ochoa-Callejero, L. and Martinez, A. Temporal profiles of blood pressure, circulating nitric oxide, and adrenomedullin as predictors of

clinical outcome in acute ischemic stroke patients. *Mol Med Rep.* 2016, **13**(5), pp.3724-3734.

97. Qiu, W., Kass, D.A., Hu, Q. and Ziegelstein, R.C. Determinants of shear stress-stimulated endothelial nitric oxide production assessed in real-time by 4,5-diaminofluorescein fluorescence. *Biochem Biophys Res Commun.* 2001, **286**(2), pp.328-335.
98. Kohan, D.E. and Barton, M. Endothelin and endothelin antagonists in chronic kidney disease. *Kidney Int.* 2014, **86**(5), pp.896-904.
99. Lakatta, E.G. and Levy, D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease. *Circulation.* 2003, **107**(1), pp.139-146.
100. Sun, D., Huang, A., Yan, E.H., Wu, Z., Yan, C., Kaminski, P.M., Oury, T.D., Wolin, M.S. and Kaley, G. Reduced release of nitric oxide to shear stress in mesenteric arteries of aged rats. *Am J Physiol Heart Circ Physiol.* 2004, **286**(6), pp.H2249-2256.
101. Tschudi, M.R., Barton, M., Bersinger, N.A., Moreau, P., Cosentino, F., Noll, G., Malinski, T. and Luscher, T.F. Effect of age on kinetics of nitric oxide release in rat aorta and pulmonary artery. *J Clin Invest.* 1996, **98**(4), pp.899-905.
102. Paneni, F., Diaz Canestro, C., Libby, P., Luscher, T.F. and Camici, G.G. The Aging Cardiovascular System: Understanding It at the Cellular and Clinical Levels. *J Am Coll Cardiol.* 2017, **69**(15), pp.1952-1967.
103. Watanabe, S., Kawamoto, S., Ohtani, N. and Hara, E. Impact of senescence-associated secretory phenotype and its potential as a therapeutic target for senescence-associated diseases. *Cancer Sci.* 2017, **108**(4), pp.563-569.
104. Kleinert, H., Wallerath, T., Euchenhofer, C., Ihrig-Biedert, I., Li, H. and Forstermann, U. Estrogens increase transcription of the human endothelial NO synthase gene: analysis of the transcription factors involved. *Hypertension.* 1998, **31**(2), pp.582-588.
105. Yang, Y.M., Huang, A., Kaley, G. and Sun, D. eNOS uncoupling and endothelial dysfunction in aged vessels. *Am J Physiol Heart Circ Physiol.* 2009, **297**(5), pp.H1829-1836.
106. Berkowitz, D.E., White, R., Li, D., Minhas, K.M., Cernetich, A., Kim, S., Burke, S., Shoukas, A.A., Nyhan, D., Champion, H.C. and Hare, J.M. Arginase reciprocally regulates nitric oxide synthase activity and contributes to endothelial dysfunction in aging blood vessels. *Circulation.* 2003, **108**(16), pp.2000-2006.
107. Bohm, F. and Pernow, J. The importance of endothelin-1 for vascular dysfunction in cardiovascular disease. *Cardiovasc Res.* 2007, **76**(1), pp.8-18.
108. Westby, C.M., Weil, B.R., Greiner, J.J., Stauffer, B.L. and DeSouza, C.A. Endothelin-1 vasoconstriction and the age-related decline in endothelium-dependent vasodilatation in men. *Clin Sci (Lond).* 2011, **120**(11), pp.485-491.
109. Muller-Delp, J.M., Spier, S.A., Ramsey, M.W. and Delp, M.D. Aging impairs endothelium-dependent vasodilation in rat skeletal muscle arterioles. *Am J Physiol Heart Circ Physiol.* 2002, **283**(4), pp.H1662-1672.

110. Supiano, M.A. Hypertension. In: Halter, J.B.O., J.G.; Studenski, S.; High, K.P.; Asthana, S.; Ritchie, C.S.; Supiano, M.A. ed. *Hazzard's Geriatric Medicine and Gerontology*. McGraw-Hill Education, 2017.
111. Celermajer, D.S., Sorensen, K.E., Spiegelhalter, D.J., Georgakopoulos, D., Robinson, J. and Deanfield, J.E. Aging is associated with endothelial dysfunction in healthy men years before the age-related decline in women. *J Am Coll Cardiol.* 1994, **24**(2), pp.471-476.
112. DR;, D.A.B.A.J.K.G.L.S. Aging is Associated with Greater Nuclear NFκB, Reduced IκBα and Increased Expression of Proinflammatory Cytokines in Vascular Endothelial Cells of Healthy Humans. *Ageing Cell.* 2008, **7**(6), pp.805-812.
113. Marchesi, C., Paradis, P. and Schiffrin, E.L. Role of the renin-angiotensin system in vascular inflammation. *Trends Pharmacol Sci.* 2008, **29**(7), pp.367-374.
114. Paravicini, T.M. and Touyz, R.M. Redox signaling in hypertension. *Cardiovasc Res.* 2006, **71**(2), pp.247-258.
115. Rauscher, F.M., Goldschmidt-Clermont, P.J., Davis, B.H., Wang, T., Gregg, D., Ramaswami, P., Pippen, A.M., Annex, B.H., Dong, C. and Taylor, D.A. Aging, progenitor cell exhaustion, and atherosclerosis. *Circulation.* 2003, **108**(4), pp.457-463.
116. Shi, Y., Camici, G.G. and Luscher, T.F. Cardiovascular determinants of life span. *Pflugers Arch.* 2010, **459**(2), pp.315-324.
117. Gkaliagkousi, E., Gavriilaki, E., Triantafyllou, A. and Douma, S. Clinical Significance of Endothelial Dysfunction in Essential Hypertension. *Curr Hypertens Rep.* 2015, **17**(11), p.85.
118. Erusalimsky, J.D. Vascular endothelial senescence: from mechanisms to pathophysiology. *J Appl Physiol (1985).* 2009, **106**(1), pp.326-332.
119. Campisi, J. Cellular senescence: putting the paradoxes in perspective. *Curr Opin Genet Dev.* 2011, **21**(1), pp.107-112.
120. Guyton, A.C. and Coleman, T.G. Quantitative analysis of the pathophysiology of hypertension. *Circ Res.* 1969, **24**(5 Suppl), pp.1-19.
121. Julius, S., Krause, L., Schork, N.J., Mejia, A.D., Jones, K.A., van de Ven, C., Johnson, E.H., Sekkarie, M.A., Kjeldsen, S.E., Petrin, J. and et al. Hyperkinetic borderline hypertension in Tecumseh, Michigan. *J Hypertens.* 1991, **9**(1), pp.77-84.
122. Guyton, A.C. Physiologic regulation of arterial pressure. *Am J Cardiol.* 1961, **8**, pp.401-407.
123. Guyton, A.C. Renal function curve--a key to understanding the pathogenesis of hypertension. *Hypertension.* 1987, **10**(1), pp.1-6.
124. Ching;, N. *The Yellow Emperor's Classic of Internal Medicine.* Published between 2698 and 2598 B.C.
125. Group, I.C.R. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. . *BMJ.* 1988, **297**(6644), pp.319-328.
126. He, F.J., Li, J. and Macgregor, G.A. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. *BMJ.* 2013, **346**, p.f1325.

127. Denton, D., Weisinger, R., Mundy, N.I., Wickings, E.J., Dixson, A., Moisson, P., Pingard, A.M., Shade, R., Carey, D., Ardaillou, R. and et al. The effect of increased salt intake on blood pressure of chimpanzees. *Nat Med.* 1995, **1**(10), pp.1009-1016.
128. Karppanen, H. and Mervaala, E. Sodium intake and hypertension. *Prog Cardiovasc Dis.* 2006, **49**(2), pp.59-75.
129. Cogswell, M.E., Mugavero, K., Bowman, B.A. and Frieden, T.R. Dietary Sodium and Cardiovascular Disease Risk--Measurement Matters. *N Engl J Med.* 2016, **375**(6), pp.580-586.
130. Feng, W., Dell'Italia, L.J. and Sanders, P.W. Novel Paradigms of Salt and Hypertension. *J Am Soc Nephrol.* 2017, **28**(5), pp.1362-1369.
131. Cowley, A.W., Jr. Renal medullary oxidative stress, pressure-natriuresis, and hypertension. *Hypertension.* 2008, **52**(5), pp.777-786.
132. Kaplan NM, V.R. *Kaplan's Clinical Hypertension.* Philadelphia: Wolters Kluwer, 2015.
133. Mimran, A., Ribstein, J. and Jover, B. Aging and sodium homeostasis. *Kidney Int Suppl.* 1992, **37**, pp.S107-113.
134. Weinberger, M.H. and Fineberg, N.S. Sodium and volume sensitivity of blood pressure. Age and pressure change over time. *Hypertension.* 1991, **18**(1), pp.67-71.
135. Barker, D.J., Bull, A.R., Osmond, C. and Simmonds, S.J. Fetal and placental size and risk of hypertension in adult life. *BMJ.* 1990, **301**(6746), pp.259-262.
136. Weder, A.B. and Schork, N.J. Adaptation, allometry, and hypertension. *Hypertension.* 1994, **24**(2), pp.145-156.
137. Hall, M.E.H., J. E. Pathogenesis of Hypertension. In: Bakris, G.L.S.M. ed. *Hypertension: A Companion to Braunwald's Heart Disease*. 3rd ed. Philadelphia: Elsevier, 2018, pp.33-51.
138. Singh, A.W., G.H. *Textbook of Nephro-Endocrinology.* 2nd ed. San Diego, USA: Academic Press, 2017.
139. Zhou, Z.H. and Bubien, J.K. Nongenomic regulation of ENaC by aldosterone. *Am J Physiol Cell Physiol.* 2001, **281**(4), pp.C1118-1130.
140. Grim, C.E., Luft, F.C., Weinberger, M.H., Miller, J.Z., Rose, R.J. and Christian, J.C. Genetic, familial and racial influences on blood pressure control systems in man. *Aust N Z J Med.* 1984, **14**(4), pp.453-457.
141. O'Donnell, E., Floras, J.S. and Harvey, P.J. Estrogen status and the renin angiotensin aldosterone system. *Am J Physiol Regul Integr Comp Physiol.* 2014, **307**(5), pp.R498-500.
142. Conti, S., Cassis, P. and Benigni, A. Aging and the renin-angiotensin system. *Hypertension.* 2012, **60**(4), pp.878-883.
143. Varagic, J., Ahmad, S., Nagata, S. and Ferrario, C.M. ACE2: angiotensin II/angiotensin-(1-7) balance in cardiac and renal injury. *Curr Hypertens Rep.* 2014, **16**(3), p.420.
144. Musso, C.G. and Jauregui, J.R. Renin-angiotensin-aldosterone system and the aging kidney. *Expert Rev Endocrinol Metab.* 2014, **9**(6), pp.543-546.
145. Gilliam-Davis, S., Payne, V.S., Kasper, S.O., Tommasi, E.N., Robbins, M.E. and Diz, D.I. Long-term AT1 receptor blockade improves metabolic function and provides renoprotection in Fischer-

344 rats. *Am J Physiol Heart Circ Physiol.* 2007, **293**(3), pp.H1327-1333.
146. Wang, M., Takagi, G., Asai, K., Resuello, R.G., Natividad, F.F., Vatner, D.E., Vatner, S.F. and Lakatta, E.G. Aging increases aortic MMP-2 activity and angiotensin II in nonhuman primates. *Hypertension.* 2003, **41**(6), pp.1308-1316.
147. Wang, M., Zhang, J., Jiang, L.Q., Spinetti, G., Pintus, G., Monticone, R., Kolodgie, F.D., Virmani, R. and Lakatta, E.G. Proinflammatory profile within the grossly normal aged human aortic wall. *Hypertension.* 2007, **50**(1), pp.219-227.
148. Michel, J.B., Heudes, D., Michel, O., Poitevin, P., Philippe, M., Scalbert, E., Corman, B. and Levy, B.I. Effect of chronic ANG I-converting enzyme inhibition on aging processes. II. Large arteries. *Am J Physiol.* 1994, **267**(1 Pt 2), pp.R124-135.
149. Meade, T.W., Imeson, J.D., Gordon, D. and Peart, W.S. The epidemiology of plasma renin. *Clin Sci (Lond).* 1983, **64**(3), pp.273-280.
150. Weidmann, P., De Myttenaere-Bursztein, S., Maxwell, M.H. and de Lima, J. Effect on aging on plasma renin and aldosterone in normal man. *Kidney Int.* 1975, **8**(5), pp.325-333.
151. Ajayi, A.A., Hockings, N. and Reid, J.L. Age and the pharmacodynamics of angiotensin converting enzyme inhibitors enalapril and enalaprilat. *Br J Clin Pharmacol.* 1986, **21**(4), pp.349-357.
152. Musso, C.G. and Oreopoulos, D.G. Aging and physiological changes of the kidneys including changes in glomerular filtration rate. *Nephron Physiol.* 2011, **119 Suppl 1**, pp.p1-5.
153. Klabunde, R. *Normal and Abnormal Blood Pressure.* [Online]. Indianapolis, Indiana, 2013.
154. Guyenet, P.G. The sympathetic control of blood pressure. *Nat Rev Neurosci.* 2006, **7**(5), pp.335-346.
155. Mancia, G. and Grassi, G. The autonomic nervous system and hypertension. *Circ Res.* 2014, **114**(11), pp.1804-1814.
156. DiBona, G.F. Sympathetic nervous system and hypertension. *Hypertension.* 2013, **61**(3), pp.556-560.
157. Augustyniak, R.A., Tuncel, M., Zhang, W., Toto, R.D. and Victor, R.G. Sympathetic overactivity as a cause of hypertension in chronic renal failure. *J Hypertens.* 2002, **20**(1), pp.3-9.
158. Fujita, T. Mechanism of salt-sensitive hypertension: focus on adrenal and sympathetic nervous systems. *J Am Soc Nephrol.* 2014, **25**(6), pp.1148-1155.
159. Harrison, D.G.B., K. E.;. Inflammation and Hypertension. In: Bakris, G.L.S.M. ed. *Hypertension: A Companion to Braunwald's Heart Disease*. 3rd ed. Philadelphia: Elsevier, 2018, pp.60-69.
160. Harrison, D.G., Guzik, T.J., Lob, H.E., Madhur, M.S., Marvar, P.J., Thabet, S.R., Vinh, A. and Weyand, C.M. Inflammation, immunity, and hypertension. *Hypertension.* 2011, **57**(2), pp.132-140.
161. Lipsitz, L.A. A 91-year-old woman with difficult-to-control hypertension: a clinical review. *JAMA.* 2013, **310**(12), pp.1274-1280.

162. Gribbin, B., Pickering, T.G., Sleight, P. and Peto, R. Effect of age and high blood pressure on baroreflex sensitivity in man. *Circ Res.* 1971, **29**(4), pp.424-431.
163. Shimada, K., Kitazumi, T., Ogura, H., Sadakane, N. and Ozawa, T. Differences in age-independent effects of blood pressure on baroreflex sensitivity between normal and hypertensive subjects. *Clin Sci (Lond).* 1986, **70**(5), pp.489-494.
164. McGarry, K., Laher, M., Fitzgerald, D., Horgan, J., O'Brien, E. and O'Malley, K. Baroreflex function in elderly hypertensives. *Hypertension.* 1983, **5**(5), pp.763-766.
165. Sung, J., Choi, S.H., Choi, Y.H., Kim, D.K. and Park, W.H. The relationship between arterial stiffness and increase in blood pressure during exercise in normotensive persons. *J Hypertens.* 2012, **30**(3), pp.587-591.
166. Uetani, E., Tabara, Y., Igase, M., Guo, H., Kido, T., Ochi, N., Takita, R., Kohara, K. and Miki, T. Postprandial hypertension, an overlooked risk marker for arteriosclerosis. *Atherosclerosis.* 2012, **224**(2), pp.500-505.
167. Liu, Y.P., Gu, Y.M., Thijs, L., Asayama, K., Jin, Y., Jacobs, L., Kuznetsova, T., Verhamme, P., Van Bortel, L., Struijker-Boudier, H.A. and Staessen, J.A. Do level and variability of systolic blood pressure predict arterial properties or vice versa? *J Hum Hypertens.* 2014, **28**(5), pp.316-322.
168. Bertinieri, G., Grassi, G., Rossi, P., Meloni, A., Ciampa, M., Annoni, G., Vergani, C. and Mancia, G. 24-hour blood pressure profile in centenarians. *J Hypertens.* 2002, **20**(9), pp.1765-1769.
169. Muller, M., Smulders, Y.M., de Leeuw, P.W. and Stehouwer, C.D. Treatment of hypertension in the oldest old: a critical role for frailty? *Hypertension.* 2014, **63**(3), pp.433-441.
170. Holwerda, S.W., Luehrs, R.E., DuBose, L., Collins, M.T., Wooldridge, N.A., Stroud, A.K., Fadel, P.J., Abboud, F.M. and Pierce, G.L. Elevated Muscle Sympathetic Nerve Activity Contributes to Central Artery Stiffness in Young and Middle-Age/Older Adults. *Hypertension.* 2019, **73**(5), pp.1025-1035.
171. Rowe, J.W. and Troen, B.R. Sympathetic nervous system and aging in man. *Endocr Rev.* 1980, **1**(2), pp.167-179.
172. Veith, R.C., Featherstone, J.A., Linares, O.A. and Halter, J.B. Age differences in plasma norepinephrine kinetics in humans. *J Gerontol.* 1986, **41**(3), pp.319-324.
173. Abrass, I.B., Davis, J.L. and Scarpace, P.J. Isoproterenol responsiveness and myocardial beta-adrenergic receptors in young and old rats. *J Gerontol.* 1982, **37**(2), pp.156-160.
174. Abrass, I.B. and Scarpace, P.J. Human lymphocyte beta-adrenergic receptors are unaltered with age. *J Gerontol.* 1981, **36**(3), pp.298-301.
175. van Brummelen, P., Buhler, F.R., Kiowski, W. and Amann, F.W. Age-related decrease in cardiac and peripheral vascular responsiveness to isoprenaline: studies in normal subjects. *Clin Sci (Lond).* 1981, **60**(5), pp.571-577.

176. Pan, H.Y., Hoffman, B.B., Pershe, R.A. and Blaschke, T.F. Decline in beta adrenergic receptor-mediated vascular relaxation with aging in man. *J Pharmacol Exp Ther.* 1986, **239**(3), pp.802-807.
177. Feldman, R.D., Limbird, L.E., Nadeau, J., Robertson, D. and Wood, A.J. Alterations in leukocyte beta-receptor affinity with aging. A potential explanation for altered beta-adrenergic sensitivity in the elderly. *N Engl J Med.* 1984, **310**(13), pp.815-819.
178. Ruskin, A. *Classics in Arterial Hypertension.* Springfield, Ilinois, USA: Charles C Thomas, 1956.
179. Freis, E. A History of Hypertension. In: Oparil, S.W., MA ed. *Hypertension: Companion to Brenner and Rector's The Kidney*. 2nd ed. Philadelphia, Pennsylvania, USA: Elsevier Saunders, 2005.
180. Bright, R. Cases and observations, illusrrative of renal disease accopanied with the secretion of albuminous urine. *Guy's Hosp Rep.* 1836, **I**, pp.338-379.
181. Gull, W.S., HG;. On the pathology of the morbid state commonly called chronic Bright's disease with contracted kidney ("arteropcapillary fibrosis"). *Med Chir Trans Lond.* 1872, **65**, pp.273-326.
182. Mahomed, F. Remarks on arterio-capillary fibrosis and its clinical recognition. *The Lancet.* 1877, **110**(2816), pp.232-234.
183. Hales, S. *Statistical Essays: Containing Haemostatics; or an Account of Some Hydraulick and Hydrostatistical Experiments Made on the Blood and Blood-vessels of Animals.* London, UK: Innys and Manby, 1933.
184. Poiseuille, J. Recherches expérimental sur le movement des liquides dan les tubes de tres petite diametres. *Arch Gen Med.* 1828, pp.550-554.
185. Ludwig, C. Beitraege zur Kenntniss des einfluesses der respirations-bewegungeb aug den Blutlauf im Aortensysteme. *Arch Anat Physiol Wissen Med (Muller's Arch).* 1847, pp.242-302.
186. Riva-Rocci, S. Un nuovosfigmomanometro. *Gaza Med Torino.* 1896, **47**, pp.981-1001.
187. Korotkov, N. K voprosu metodakh uzsledovaniyah krovyanovo davleniya. [A contribution to the problem of methods for the determination of blood pressure]. *Izvestiya Imperatorskoi Voenno-Meditsinskoy Akademii (Rep ImperMil-Med Acca St Petersburg).* 1905, **11**, pp.365-367.
188. Oldham, P.D., Pickering, G., Roberts, J.A. and Sowry, G.S. The nature of essential hypertension. *Lancet.* 1960, **1**(7134), pp.1085-1093.
189. Parati, G.O., JE;. White-Coat and Masked Hypertension. In: Bakris, G.S., M; ed. *Hypertension*. 3rd ed. Philadelphia: Elsevier, 2018.
190. Potter, J.M.P. Hypertension. In: J, F.H.R.K.Y. ed. *Brocklehurst's Textbook of Geriatric Medicine and Gerontology*. Philadelphia, USA: Elsevier, 2017.
191. Stevens, S.L., McManus, R.J. and Stevens, R.J. The utility of long-term blood pressure variability for cardiovascular risk prediction in primary care. *J Hypertens.* 2019, **37**(3), pp.522-529.
192. Hippisley-Cox, J., Coupland, C. and Brindle, P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk

of cardiovascular disease: prospective cohort study. *BMJ.* 2017, **357**, p.j2099.

193. Aronow, W.S., Fleg, J.L., Pepine, C.J., Artinian, N.T., Bakris, G., Brown, A.S., Ferdinand, K.C., Ann Forciea, M., Frishman, W.H., Jaigobin, C., Kostis, J.B., Mancia, G., Oparil, S., Ortiz, E., Reisin, E., Rich, M.W., Schocken, D.D., Weber, M.A. and Wesley, D.J. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus documents developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. *J Am Coll Cardiol.* 2011, **57**(20), pp.2037-2114.
194. Kohli, P., Whelton, S.P., Hsu, S., Yancy, C.W., Stone, N.J., Chrispin, J., Gilotra, N.A., Houston, B., Ashen, M.D., Martin, S.S., Joshi, P.H., McEvoy, J.W., Gluckman, T.J., Michos, E.D., Blaha, M.J. and Blumenthal, R.S. Clinician's guide to the updated ABCs of cardiovascular disease prevention. *J Am Heart Assoc.* 2014, **3**(5), p.e001098.
195. Cutler, J.A., Sorlie, P.D., Wolz, M., Thom, T., Fields, L.E. and Roccella, E.J. Trends in hypertension prevalence, awareness, treatment, and control rates in United States adults between 1988-1994 and 1999-2004. *Hypertension.* 2008, **52**(5), pp.818-827.
196. Rocchini, A.P., Key, J., Bondie, D., Chico, R., Moorehead, C., Katch, V. and Martin, M. The effect of weight loss on the sensitivity of blood pressure to sodium in obese adolescents. *N Engl J Med.* 1989, **321**(9), pp.580-585.
197. Sarzani, R., Salvi, F., Dessi-Fulgheri, P. and Rappelli, A. Renin-angiotensin system, natriuretic peptides, obesity, metabolic syndrome, and hypertension: an integrated view in humans. *J Hypertens.* 2008, **26**(5), pp.831-843.
198. Morse, S.A., Zhang, R., Thakur, V. and Reisin, E. Hypertension and the metabolic syndrome. *Am J Med Sci.* 2005, **330**(6), pp.303-310.
199. Mulrow, C.D., Chiquette, E., Angel, L., Cornell, J., Summerbell, C., Anagnostelis, B., Grimm, R., Jr. and Brand, M.B. Dieting to reduce body weight for controlling hypertension in adults. *Cochrane Database Syst Rev.* 2000, (2), p.CD000484.
200. Uretsky, S., Messerli, F.H., Bangalore, S., Champion, A., Cooper-Dehoff, R.M., Zhou, Q. and Pepine, C.J. Obesity paradox in patients with hypertension and coronary artery disease. *Am J Med.* 2007, **120**(10), pp.863-870.
201. Egan, B.M., Li, J., Qanungo, S. and Wolfman, T.E. Blood pressure and cholesterol control in hypertensive hypercholesterolemic patients: national health and nutrition examination surveys 1988-2010. *Circulation.* 2013, **128**(1), pp.29-41.
202. Johnson, M.L., Pietz, K., Battleman, D.S. and Beyth, R.J. Prevalence of comorbid hypertension and dyslipidemia and associated cardiovascular disease. *Am J Manag Care.* 2004, **10**(12), pp.926-932.
203. Frost, P.H., Davis, B.R., Burlando, A.J., Curb, J.D., Guthrie, G.P., Jr., Isaacsohn, J.L., Wassertheil-Smoller, S., Wilson, A.C. and Stamler, J.

Serum lipids and incidence of coronary heart disease. Findings from the Systolic Hypertension in the Elderly Program (SHEP). *Circulation.* 1996, **94**(10), pp.2381-2388.

204. Prospective Studies, C., Lewington, S., Whitlock, G., Clarke, R., Sherliker, P., Emberson, J., Halsey, J., Qizilbash, N., Peto, R. and Collins, R. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet.* 2007, **370**(9602), pp.1829-1839.
205. Strandberg, T.E., Kolehmainen, L. and Vuorio, A. Evaluation and treatment of older patients with hypercholesterolemia: a clinical review. *JAMA.* 2014, **312**(11), pp.1136-1144.
206. Role of cardiovascular risk factors in prevention and treatment of macrovascular disease in diabetes. American Diabetes Association. *Diabetes Care.* 1989, **12**(8), pp.573-579.
207. Task Force on diabetes, p.-d., cardiovascular diseases of the European Society of, C., European Association for the Study of, D., Ryden, L., Grant, P.J., Anker, S.D., Berne, C., Cosentino, F., Danchin, N., Deaton, C., Escaned, J., Hammes, H.P., Huikuri, H., Marre, M., Marx, N., Mellbin, L., Ostergren, J., Patrono, C., Seferovic, P., Uva, M.S., Taskinen, M.R., Tendera, M., Tuomilehto, J., Valensi, P. and Zamorano, J.L. ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD - summary. *Diab Vasc Dis Res.* 2014, **11**(3), pp.133-173.
208. Webster, A.C., Nagler, E.V., Morton, R.L. and Masson, P. Chronic Kidney Disease. *Lancet.* 2017, **389**(10075), pp.1238-1252.
209. Muntner, P., He, J., Astor, B.C., Folsom, A.R. and Coresh, J. Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: results from the atherosclerosis risk in communities study. *J Am Soc Nephrol.* 2005, **16**(2), pp.529-538.
210. Kdoqi. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. *Am J Kidney Dis.* 2007, **49**(2 Suppl 2), pp.S12-154.
211. Sleight, P. Smoking and hypertension. *Clin Exp Hypertens.* 1993, **15**(6), pp.1181-1192.
212. Halimi, J.M., Giraudeau, B., Vol, S., Caces, E., Nivet, H. and Tichet, J. The risk of hypertension in men: direct and indirect effects of chronic smoking. *J Hypertens.* 2002, **20**(2), pp.187-193.
213. Oncken, C.A., White, W.B., Cooney, J.L., Van Kirk, J.R., Ahluwalia, J.S. and Giacco, S. Impact of smoking cessation on ambulatory blood pressure and heart rate in postmenopausal women. *Am J Hypertens.* 2001, **14**(9 Pt 1), pp.942-949.
214. Houston, T.K., Allison, J.J., Person, S., Kovac, S., Williams, O.D. and Kiefe, C.I. Post-myocardial infarction smoking cessation counseling: associations with immediate and late mortality in older Medicare patients. *Am J Med.* 2005, **118**(3), pp.269-275.
215. Donze, J., Ruffieux, C. and Cornuz, J. Determinants of smoking and cessation in older women. *Age Ageing.* 2007, **36**(1), pp.53-57.

216. Appel, L. Diet and Blood Pressure. In: Bakris, G.S., M; ed. *Hypertension: A Companion to Braunwald's Heart Disease*. 3rd ed. Philadelphia, PA: Elsevier, 2018.
217. Pimenta, E., Gaddam, K.K., Oparil, S., Aban, I., Husain, S., Dell'Italia, L.J. and Calhoun, D.A. Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension: results from a randomized trial. *Hypertension.* 2009, **54**(3), pp.475-481.
218. Naismith, D.J. and Braschi, A. The effect of low-dose potassium supplementation on blood pressure in apparently healthy volunteers. *Br J Nutr.* 2003, **90**(1), pp.53-60.
219. Xin, X., He, J., Frontini, M.G., Ogden, L.G., Motsamai, O.I. and Whelton, P.K. Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension.* 2001, **38**(5), pp.1112-1117.
220. Yokoyama, Y., Nishimura, K., Barnard, N.D., Takegami, M., Watanabe, M., Sekikawa, A., Okamura, T. and Miyamoto, Y. Vegetarian diets and blood pressure: a meta-analysis. *JAMA Intern Med.* 2014, **174**(4), pp.577-587.
221. Nordmann, A.J., Suter-Zimmermann, K., Bucher, H.C., Shai, I., Tuttle, K.R., Estruch, R. and Briel, M. Meta-analysis comparing Mediterranean to low-fat diets for modification of cardiovascular risk factors. *Am J Med.* 2011, **124**(9), pp.841-851 e842.
222. Sacks, F.M. and Campos, H. Dietary therapy in hypertension. *N Engl J Med.* 2010, **362**(22), pp.2102-2112.
223. Byrd, J.B., RD;. Alternative Approaches for Lowering Blood Pressure. In: Bakris, G.S., M; ed. *Hypertension: A Companion to Braunwald's Heart Disease*. 3rd ed. Philadelphia, PA: Elsevier, 2018.
224. Cornelissen, V.A. and Smart, N.A. Exercise training for blood pressure: a systematic review and meta-analysis. *J Am Heart Assoc.* 2013, **2**(1), p.e004473.
225. Molmen-Hansen, H.E., Stolen, T., Tjonna, A.E., Aamot, I.L., Ekeberg, I.S., Tyldum, G.A., Wisloff, U., Ingul, C.B. and Stoylen, A. Aerobic interval training reduces blood pressure and improves myocardial function in hypertensive patients. *Eur J Prev Cardiol.* 2012, **19**(2), pp.151-160.
226. Collier, S.R., Frechette, V., Sandberg, K., Schafer, P., Ji, H., Smulyan, H. and Fernhall, B. Sex differences in resting hemodynamics and arterial stiffness following 4 weeks of resistance versus aerobic exercise training in individuals with pre-hypertension to stage 1 hypertension. *Biol Sex Differ.* 2011, **2**(1), p.9.
227. Pescatello, L.S., MacDonald, H.V., Lamberti, L. and Johnson, B.T. Exercise for Hypertension: A Prescription Update Integrating Existing Recommendations with Emerging Research. *Curr Hypertens Rep.* 2015, **17**(11), p.87.
228. Officers, A., Coordinators for the, A.C.R.G.T.A. and Lipid-Lowering Treatment to Prevent Heart Attack, T. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA.* 2002, **288**(23), pp.2998-3007.

229. Group, N.S., McMurray, J.J., Holman, R.R., Haffner, S.M., Bethel, M.A., Holzhauer, B., Hua, T.A., Belenkov, Y., Boolell, M., Buse, J.B., Buckley, B.M., Chacra, A.R., Chiang, F.T., Charbonnel, B., Chow, C.C., Davies, M.J., Deedwania, P., Diem, P., Einhorn, D., Fonseca, V., Fulcher, G.R., Gaciong, Z., Gaztambide, S., Giles, T., Horton, E., Ilkova, H., Jenssen, T., Kahn, S.E., Krum, H., Laakso, M., Leiter, L.A., Levitt, N.S., Mareev, V., Martinez, F., Masson, C., Mazzone, T., Meaney, E., Nesto, R., Pan, C., Prager, R., Raptis, S.A., Rutten, G.E., Sandstroem, H., Schaper, F., Scheen, A., Schmitz, O., Sinay, I., Soska, V., Stender, S., Tamas, G., Tognoni, G., Tuomilehto, J., Villamil, A.S., Vozar, J. and Califf, R.M. Effect of valsartan on the incidence of diabetes and cardiovascular events. *N Engl J Med.* 2010, **362**(16), pp.1477-1490.
230. Telmisartan Randomised AssessmeNt Study in, A.C.E.i.s.w.c.D.I., Yusuf, S., Teo, K., Anderson, C., Pogue, J., Dyal, L., Copland, I., Schumacher, H., Dagenais, G. and Sleight, P. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet.* 2008, **372**(9644), pp.1174-1183.
231. Law, M.R., Morris, J.K. and Wald, N.J. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ.* 2009, **338**, p.b1665.
232. Morgan, T.O., Anderson, A.I. and MacInnis, R.J. ACE inhibitors, beta-blockers, calcium blockers, and diuretics for the control of systolic hypertension. *Am J Hypertens.* 2001, **14**(3), pp.241-247.
233. Ettehad, D., Emdin, C.A., Kiran, A., Anderson, S.G., Callender, T., Emberson, J., Chalmers, J., Rodgers, A. and Rahimi, K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet.* 2016, **387**(10022), pp.957-967.
234. Cheng, S., Claggett, B., Correia, A.W., Shah, A.M., Gupta, D.K., Skali, H., Ni, H., Rosamond, W.D., Heiss, G., Folsom, A.R., Coresh, J. and Solomon, S.D. Temporal trends in the population attributable risk for cardiovascular disease: the Atherosclerosis Risk in Communities Study. *Circulation.* 2014, **130**(10), pp.820-828.
235. MacMahon, S., Peto, R., Cutler, J., Collins, R., Sorlie, P., Neaton, J., Abbott, R., Godwin, J., Dyer, A. and Stamler, J. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet.* 1990, **335**(8692), pp.765-774.
236. Kannel, W.B. Epidemiology and prevention of cardiac failure: Framingham Study insights. *Eur Heart J.* 1987, **8 Suppl F**, pp.23-26.
237. Orofino, L., Quereda, C., Lamas, S., Orte, L., Gonzalo, A., Mampaso, F. and Ortuno, J. Hypertension in primary chronic glomerulonephritis: analysis of 288 biopsied patients. *Nephron.* 1987, **45**(1), pp.22-26.
238. Kalaria, R.N., Maestre, G.E., Arizaga, R., Friedland, R.P., Galasko, D., Hall, K., Luchsinger, J.A., Ogunniyi, A., Perry, E.K., Potocnik, F., Prince, M., Stewart, R., Wimo, A., Zhang, Z.X., Antuono, P. and World Federation of Neurology Dementia Research, G. Alzheimer's

disease and vascular dementia in developing countries: prevalence, management, and risk factors. *Lancet Neurol.* 2008, **7**(9), pp.812-826.

239. Lane, C.A., Barnes, J., Nicholas, J.M., Sudre, C.H., Cash, D.M., Parker, T.D., Malone, I.B., Lu, K., James, S.N., Keshavan, A., Murray-Smith, H., Wong, A., Buchanan, S.M., Keuss, S.E., Gordon, E., Coath, W., Barnes, A., Dickson, J., Modat, M., Thomas, D., Crutch, S.J., Hardy, R., Richards, M., Fox, N.C. and Schott, J.M. Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (Insight 46): an epidemiological study. *Lancet Neurol.* 2019, **18**(10), pp.942-952.
240. Gottesman, R.F., Schneider, A.L., Zhou, Y., Coresh, J., Green, E., Gupta, N., Knopman, D.S., Mintz, A., Rahmim, A., Sharrett, A.R., Wagenknecht, L.E., Wong, D.F. and Mosley, T.H. Association Between Midlife Vascular Risk Factors and Estimated Brain Amyloid Deposition. *JAMA.* 2017, **317**(14), pp.1443-1450.
241. Jack, C.R., Jr., Wiste, H.J., Weigand, S.D., Therneau, T.M., Knopman, D.S., Lowe, V., Vemuri, P., Mielke, M.M., Roberts, R.O., Machulda, M.M., Senjem, M.L., Gunter, J.L., Rocca, W.A. and Petersen, R.C. Age-specific and sex-specific prevalence of cerebral beta-amyloidosis, tauopathy, and neurodegeneration in cognitively unimpaired individuals aged 50-95 years: a cross-sectional study. *Lancet Neurol.* 2017, **16**(6), pp.435-444.
242. Elias, M.F., Wolf, P.A., D'Agostino, R.B., Cobb, J. and White, L.R. Untreated blood pressure level is inversely related to cognitive functioning: the Framingham Study. *Am J Epidemiol.* 1993, **138**(6), pp.353-364.
243. Singh-Manoux, A., Britton, A.R. and Marmot, M. Vascular disease and cognitive function: evidence from the Whitehall II Study. *J Am Geriatr Soc.* 2003, **51**(10), pp.1445-1450.
244. Cerhan, J.R., Folsom, A.R., Mortimer, J.A., Shahar, E., Knopman, D.S., McGovern, P.G., Hays, M.A., Crum, L.D. and Heiss, G. Correlates of cognitive function in middle-aged adults. Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Gerontology.* 1998, **44**(2), pp.95-105.
245. Glynn, R.J., Beckett, L.A., Hebert, L.E., Morris, M.C., Scherr, P.A. and Evans, D.A. Current and remote blood pressure and cognitive decline. *JAMA.* 1999, **281**(5), pp.438-445.
246. Scherr, P.A., Hebert, L.E., Smith, L.A. and Evans, D.A. Relation of blood pressure to cognitive function in the elderly. *Am J Epidemiol.* 1991, **134**(11), pp.1303-1315.
247. Farmer, M.E., White, L.R., Abbott, R.D., Kittner, S.J., Kaplan, E., Wolz, M.M., Brody, J.A. and Wolf, P.A. Blood pressure and cognitive performance. The Framingham Study. *Am J Epidemiol.* 1987, **126**(6), pp.1103-1114.
248. Peters, R., Beckett, N., Forette, F., Tuomilehto, J., Clarke, R., Ritchie, C., Waldman, A., Walton, I., Poulter, R., Ma, S., Comsa, M., Burch, L., Fletcher, A., Bulpitt, C. and investigators, H. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. *Lancet Neurol.* 2008, **7**(8), pp.683-689.

249. Peters, R., Ee, N., Peters, J., Beckett, N., Booth, A., Rockwood, K. and Anstey, K.J. Common risk factors for major noncommunicable disease, a systematic overview of reviews and commentary: the implied potential for targeted risk reduction. *Ther Adv Chronic Dis.* 2019, **10**, p.2040622319880392.
250. Peters, R., Warwick, J., Anstey, K.J. and Anderson, C.S. Blood pressure and dementia: What the SPRINT-MIND trial adds and what we still need to know. *Neurology.* 2019, **92**(21), pp.1017-1018.
251. Hajjar, I., Quach, L., Yang, F., Chaves, P.H., Newman, A.B., Mukamal, K., Longstreth, W., Jr., Inzitari, M. and Lipsitz, L.A. Hypertension, white matter hyperintensities, and concurrent impairments in mobility, cognition, and mood: the Cardiovascular Health Study. *Circulation.* 2011, **123**(8), pp.858-865.
252. Tzourio, C., Dufouil, C., Ducimetiere, P. and Alperovitch, A. Cognitive decline in individuals with high blood pressure: a longitudinal study in the elderly. EVA Study Group. Epidemiology of Vascular Aging. *Neurology.* 1999, **53**(9), pp.1948-1952.
253. Goldring, W.C., H;. Antihypertensive drug therapy: An appraisal. In: Ingelfinger, F.R., AS; Finland, M; ed. *Controversies in Internal Medicine*. Philadelphia: WB Saunders, 1966, pp.83--91.
254. Thomopoulos, C., Parati, G. and Zanchetti, A. Effects of blood pressure-lowering treatment on cardiovascular outcomes and mortality: 14 - effects of different classes of antihypertensive drugs in older and younger patients: overview and meta-analysis. *J Hypertens.* 2018, **36**(8), pp.1637-1647.
255. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. *JAMA.* 1967, **202**(11), pp.1028-1034.
256. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *JAMA.* 1970, **213**(7), pp.1143-1152.
257. The Australian therapeutic trial in mild hypertension. Report by the Management Committee. *Lancet.* 1980, **1**(8181), pp.1261-1267.
258. Amery, A., Birkenhager, W., Brixko, P., Bulpitt, C., Clement, D., Deruyttere, M., De Schaepdryver, A., Dollery, C., Fagard, R., Forette, F. and et al. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. *Lancet.* 1985, **1**(8442), pp.1349-1354.
259. MRC trial of treatment of mild hypertension: principal results. Medical Research Council Working Party. *Br Med J (Clin Res Ed).* 1985, **291**(6488), pp.97-104.
260. Coope, J. and Warrender, T.S. Randomised trial of treatment of hypertension in elderly patients in primary care. *Br Med J (Clin Res Ed).* 1986, **293**(6555), pp.1145-1151.
261. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA.* 1991, **265**(24), pp.3255-3264.
262. Kostis, J.B., Davis, B.R., Cutler, J., Grimm, R.H., Jr., Berge, K.G., Cohen, J.D., Lacy, C.R., Perry, H.M., Jr., Blaufox, M.D., Wassertheil-Smoller, S., Black, H.R., Schron, E., Berkson, D.M., Curb, J.D., Smith,

W.M., McDonald, R. and Applegate, W.B. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. SHEP Cooperative Research Group. *JAMA.* 1997, **278**(3), pp.212-216.

263. Dahlof, B., Lindholm, L.H., Hansson, L., Schersten, B., Ekbom, T. and Wester, P.O. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet.* 1991, **338**(8778), pp.1281-1285.
264. Medical Research Council trial of treatment of hypertension in older adults: principal results. MRC Working Party. *BMJ.* 1992, **304**(6824), pp.405-412.
265. Staessen, J.A., Fagard, R., Thijs, L., Celis, H., Arabidze, G.G., Birkenhager, W.H., Bulpitt, C.J., de Leeuw, P.W., Dollery, C.T., Fletcher, A.E., Forette, F., Leonetti, G., Nachev, C., O'Brien, E.T., Rosenfeld, J., Rodicio, J.L., Tuomilehto, J. and Zanchetti, A. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet.* 1997, **350**(9080), pp.757-764.
266. Hansson, L., Zanchetti, A., Carruthers, S.G., Dahlof, B., Elmfeldt, D., Julius, S., Menard, J., Rahn, K.H., Wedel, H. and Westerling, S. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet.* 1998, **351**(9118), pp.1755-1762.
267. Beckett, N.S., Peters, R., Fletcher, A.E., Staessen, J.A., Liu, L., Dumitrascu, D., Stoyanovsky, V., Antikainen, R.L., Nikitin, Y., Anderson, C., Belhani, A., Forette, F., Rajkumar, C., Thijs, L., Banya, W., Bulpitt, C.J. and Group, H.S. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med.* 2008, **358**(18), pp.1887-1898.
268. Liu, L., Wang, J.G., Gong, L., Liu, G. and Staessen, J.A. Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. Systolic Hypertension in China (Syst-China) Collaborative Group. *J Hypertens.* 1998, **16**(12 Pt 1), pp.1823-1829.
269. Wright, J.T., Jr., Bakris, G., Greene, T., Agodoa, L.Y., Appel, L.J., Charleston, J., Cheek, D., Douglas-Baltimore, J.G., Gassman, J., Glassock, R., Hebert, L., Jamerson, K., Lewis, J., Phillips, R.A., Toto, R.D., Middleton, J.P., Rostand, S.G., African American Study of Kidney, D. and Hypertension Study, G. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA.* 2002, **288**(19), pp.2421-2431.
270. Group, J.S. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). *Hypertens Res.* 2008, **31**(12), pp.2115-2127.
271. Verdecchia, P., Staessen, J.A., Angeli, F., de Simone, G., Achilli, A., Ganau, A., Mureddu, G., Pede, S., Maggioni, A.P., Lucci, D., Reboldi, G. and Cardio-Sis, i. Usual versus tight control of systolic blood

pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial. *Lancet.* 2009, **374**(9689), pp.525-533.

272. Group, A.S., Cushman, W.C., Evans, G.W., Byington, R.P., Goff, D.C., Jr., Grimm, R.H., Jr., Cutler, J.A., Simons-Morton, D.G., Basile, J.N., Corson, M.A., Probstfield, J.L., Katz, L., Peterson, K.A., Friedewald, W.T., Buse, J.B., Bigger, J.T., Gerstein, H.C. and Ismail-Beigi, F. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med.* 2010, **362**(17), pp.1575-1585.
273. Group, S.P.S.S., Benavente, O.R., Coffey, C.S., Conwit, R., Hart, R.G., McClure, L.A., Pearce, L.A., Pergola, P.E. and Szychowski, J.M. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet.* 2013, **382**(9891), pp.507-515.
274. Ogihara, T., Saruta, T., Rakugi, H., Matsuoka, H., Shimamoto, K., Shimada, K., Imai, Y., Kikuchi, K., Ito, S., Eto, T., Kimura, G., Imaizumi, T., Takishita, S., Ueshima, H. and Valsartan in Elderly Isolated Systolic Hypertension Study, G. Target blood pressure for treatment of isolated systolic hypertension in the elderly: valsartan in elderly isolated systolic hypertension study. *Hypertension.* 2010, **56**(2), pp.196-202.
275. Sprint Research Group, Wright, J.T., Jr., Williamson, J.D., Whelton, P.K., Snyder, J.K., Sink, K.M., Rocco, M.V., Reboussin, D.M., Rahman, M., Oparil, S., Lewis, C.E., Kimmel, P.L., Johnson, K.C., Goff, D.C., Jr., Fine, L.J., Cutler, J.A., Cushman, W.C., Cheung, A.K. and Ambrosius, W.T. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med.* 2015, **373**(22), pp.2103-2116.
276. Lonn, E.M., Bosch, J., Lopez-Jaramillo, P., Zhu, J., Liu, L., Pais, P., Diaz, R., Xavier, D., Sliwa, K., Dans, A., Avezum, A., Piegas, L.S., Keltai, K., Keltai, M., Chazova, I., Peters, R.J., Held, C., Yusoff, K., Lewis, B.S., Jansky, P., Parkhomenko, A., Khunti, K., Toff, W.D., Reid, C.M., Varigos, J., Leiter, L.A., Molina, D.I., McKelvie, R., Pogue, J., Wilkinson, J., Jung, H., Dagenais, G., Yusuf, S. and Investigators, H.-. Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease. *N Engl J Med.* 2016, **374**(21), pp.2009-2020.
277. Sheppard J, L.M., Burt J, Temple E, Lowe R, Ashby H, Todd O, Allen J, Ford G, Fraser R, Heneghan C, Hobbs R, Jowett S, Little P, Mant J, Mollison J, Payne R, Williams M, Yu L, McManus R. Generalisability of blood pressure lowering trials to older patients in primary care: a comparison of patient characteristics (in print). *J Am Geriatr Soc.* 2020.
278. Todd, O. and Clegg, A. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med.* 2016, **374**(23), p.2292.
279. Sheppard, J.P., Burt, J., Lown, M., Temple, E., Lowe, R., Fraser, R., Allen, J., Ford, G.A., Heneghan, C., Hobbs, F.D.R., Jowett, S., Kodabuckus, S., Little, P., Mant, J., Mollison, J., Payne, R.A., Williams, M., Yu, L.M., McManus, R.J. and Investigators, O. Effect of Antihypertensive Medication Reduction vs Usual Care on Short-term Blood Pressure Control in Patients With Hypertension Aged 80 Years and Older: The OPTIMISE Randomized Clinical Trial. *JAMA.* 2020, **323**(20), pp.2039-2051.

280. Lockett, J., Sauma, S., Radziszewska, B. and Bernard, M.A. Adequacy of Inclusion of Older Adults in NIH-Funded Phase III Clinical Trials. *J Am Geriatr Soc.* 2019, **67**(2), pp.218-222.
281. Pinho-Gomes, A.C. and Rahimi, K. Blood pressure management in the elderly: the need for more randomised evidence. *Heart.* 2019, **105**(14), pp.1055-1056.
282. Musini, V.M., Tejani, A.M., Bassett, K., Puil, L. and Wright, J.M. Pharmacotherapy for hypertension in adults 60 years or older. *Cochrane Database Syst Rev.* 2019, **6**, p.CD000028.
283. Budnitz, D.S., Lovegrove, M.C., Shehab, N. and Richards, C.L. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med.* 2011, **365**(21), pp.2002-2012.
284. Franse, L.V., Pahor, M., Di Bari, M., Somes, G.W., Cushman, W.C. and Applegate, W.B. Hypokalemia associated with diuretic use and cardiovascular events in the Systolic Hypertension in the Elderly Program. *Hypertension.* 2000, **35**(5), pp.1025-1030.
285. Palmer, B.F. Renal dysfunction complicating the treatment of hypertension. *N Engl J Med.* 2002, **347**(16), pp.1256-1261.
286. Zanchetti, A. Blood pressure targets of antihypertensive treatment: up and down the J-shaped curve. *Eur Heart J.* 2010, **31**(23), pp.2837-2840.
287. Franklin, S.S., Gokhale, S.S., Chow, V.H., Larson, M.G., Levy, D., Vasan, R.S., Mitchell, G.F. and Wong, N.D. Does low diastolic blood pressure contribute to the risk of recurrent hypertensive cardiovascular disease events? The Framingham Heart Study. *Hypertension.* 2015, **65**(2), pp.299-305.
288. Cruickshank, J. The J-curve in hypertension. *Curr Cardiol Rep.* 2003, **5**(6), pp.441-452.
289. Messerli, F.H., Bangalore, S., Messerli, A.W. and Raber, L. The muddy waters of the J-curve and coronary revascularization. *Eur Heart J.* 2020, **41**(17), pp.1684-1686.
290. Rabkin, S.W., Waheed, A., Poulter, R.S. and Wood, D. Myocardial perfusion pressure in patients with hypertension and coronary artery disease: implications for DBP targets in hypertension management. *J Hypertens.* 2013, **31**(5), pp.975-982.
291. Thygesen, K., Alpert, J.S., Jaffe, A.S., Simoons, M.L., Chaitman, B.R., White, H.D., Joint, E.S.C.A.A.H.A.W.H.F.T.F.f.U.D.o.M.I., Authors/Task Force Members, C., Thygesen, K., Alpert, J.S., White, H.D., Biomarker, S., Jaffe, A.S., Katus, H.A., Apple, F.S., Lindahl, B., Morrow, D.A., Subcommittee, E.C.G., Chaitman, B.R., Clemmensen, P.M., Johanson, P., Hod, H., Imaging, S., Underwood, R., Bax, J.J., Bonow, J.J., Pinto, F., Gibbons, R.J., Classification, S., Fox, K.A., Atar, D., Newby, L.K., Galvani, M., Hamm, C.W., Intervention, S., Uretsky, B.F., Steg, P.G., Wijns, W., Bassand, J.P., Menasche, P., Ravkilde, J., Trials, Registries, S., Ohman, E.M., Antman, E.M., Wallentin, L.C., Armstrong, P.W., Simoons, M.L., Trials, Registries, S., Januzzi, J.L., Nieminen, M.S., Gheorghiade, M., Filippatos, G., Trials, Registries, S., Luepker, R.V., Fortmann, S.P., Rosamond, W.D., Levy, D., Wood, D., Trials, Registries, S., Smith, S.C., Hu, D., Lopez-Sendon, J.L., Robertson, R.M., Weaver, D., Tendera, M., Bove, A.A., Parkhomenko, A.N., Vasilieva, E.J., Mendis, S.,

Guidelines, E.S.C.C.f.P., Bax, J.J., Baumgartner, H., Ceconi, C., Dean, V., Deaton, C., Fagard, R., Funck-Brentano, C., Hasdai, D., Hoes, A., Kirchhof, P., Knuuti, J., Kolh, P., McDonagh, T., Moulin, C., Popescu, B.A., Reiner, Z., Sechtem, U., Sirnes, P.A., Tendera, M., Torbicki, A., Vahanian, A., Windecker, S., Document, R., Morais, J., Aguiar, C., Almahmeed, W., Arnar, D.O., Barili, F., Bloch, K.D., Bolger, A.F., Botker, H.E., Bozkurt, B., Bugiardini, R., Cannon, C., de Lemos, J., Eberli, F.R., Escobar, E., Hlatky, M., James, S., Kern, K.B., Moliterno, D.J., Mueller, C., Neskovic, A.N., Pieske, B.M., Schulman, S.P., Storey, R.F., Taubert, K.A., Vranckx, P. and Wagner, D.R. Third universal definition of myocardial infarction. *J Am Coll Cardiol.* 2012, **60**(16), pp.1581-1598.

292. (NHS);, N.H.S. *Falls.* [Online]. 2018. [Accessed 25.10.2020]. Available from: https://www.nhs.uk/conditions/falls/
293. (NHS), N.H.S. *Indicator Facts.* [Online]. 2017. [Accessed 25.10.2020]. Available from: https://www.nhs.uk/Scorecard/Pages/IndicatorFacts.aspx?MetricId=8135
294. Studenski, S.V.S., J;. Falls. In: J;, F.H.R.K.Y. ed. *Brocklehurst's Textbook of Geriatric Medicine and Gerontology*. 8th ed. Philadelphia, PA: Elsevier, 2017.
295. WHO, W.H.O. *The ICD-10 classification of mental and behavioral disorders.* Geneva, Switzerland: World Health Organization, 1992.
296. Gaieski, D.M., ME;. Evaluation of and initial approach to the adult patients with undifferentiated hypotension and shock. In: G, P.P.H.R.F. ed. *UpToDate*. Version 25.0, last updated June 2020 ed. Wolters Kluwer, 2020.
297. Beijer, H.J. and de Blaey, C.J. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. *Pharm World Sci.* 2002, **24**(2), pp.46-54.
298. Flaherty, J.H., Perry, H.M., 3rd, Lynchard, G.S. and Morley, J.E. Polypharmacy and hospitalization among older home care patients. *J Gerontol A Biol Sci Med Sci.* 2000, **55**(10), pp.M554-559.
299. Moonen, J.E., Foster-Dingley, J.C., de Ruijter, W., van der Grond, J., de Craen, A.J. and van der Mast, R.C. Effect of discontinuation of antihypertensive medication on orthostatic hypotension in older persons with mild cognitive impairment: the DANTE Study Leiden. *Age Ageing.* 2016, **45**(2), pp.249-255.
300. Gulla, C., Flo, E., Kjome, R.L. and Husebo, B.S. Deprescribing antihypertensive treatment in nursing home patients and the effect on blood pressure. *J Geriatr Cardiol.* 2018, **15**(4), pp.275-283.
301. Stewart, I.M. Relation of reduction in pressure to first myocardial infarction in patients receiving treatment for severe hypertension. *Lancet.* 1979, **1**(8121), pp.861-865.
302. Cruickshank, J.M., Thorp, J.M. and Zacharias, F.J. Benefits and potential harm of lowering high blood pressure. *Lancet.* 1987, **1**(8533), pp.581-584.
303. Samuelsson, O., Wilhelmsen, L., Andersson, O.K., Pennert, K. and Berglund, G. Cardiovascular morbidity in relation to change in blood pressure and serum cholesterol levels in treated hypertension.

Results from the primary prevention trial in Goteborg, Sweden. *JAMA.* 1987, **258**(13), pp.1768-1776.

304. Farnett, L., Mulrow, C.D., Linn, W.D., Lucey, C.R. and Tuley, M.R. The J-curve phenomenon and the treatment of hypertension. Is there a point beyond which pressure reduction is dangerous? *JAMA.* 1991, **265**(4), pp.489-495.
305. Bohm, M., Ferreira, J.P., Mahfoud, F., Duarte, K., Pitt, B., Zannad, F. and Rossignol, P. Myocardial reperfusion reverses the J-curve association of cardiovascular risk and diastolic blood pressure in patients with left ventricular dysfunction and heart failure after myocardial infarction: insights from the EPHESUS trial. *Eur Heart J.* 2020, **41**(17), pp.1673-1683.
306. Messerli, F.H., Mancia, G., Conti, C.R., Hewkin, A.C., Kupfer, S., Champion, A., Kolloch, R., Benetos, A. and Pepine, C.J. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med.* 2006, **144**(12), pp.884-893.
307. Bangalore, S., Messerli, F.H., Wun, C.C., Zuckerman, A.L., DeMicco, D., Kostis, J.B., LaRosa, J.C., Treating to New Targets Steering, C. and Investigators. J-curve revisited: An analysis of blood pressure and cardiovascular events in the Treating to New Targets (TNT) Trial. *Eur Heart J.* 2010, **31**(23), pp.2897-2908.
308. Mattila, K., Haavisto, M., Rajala, S. and Heikinheimo, R. Blood pressure and five year survival in the very old. *Br Med J (Clin Res Ed).* 1988, **296**(6626), pp.887-889.
309. Heikinheimo, R.J., Haavisto, M.V., Kaarela, R.H., Kanto, A.J., Koivunen, M.J. and Rajala, S.A. Blood pressure in the very old. *J Hypertens.* 1990, **8**(4), pp.361-367.
310. Langer, R.D., Ganiats, T.G. and Barrett-Connor, E. Factors associated with paradoxical survival at higher blood pressures in the very old. *Am J Epidemiol.* 1991, **134**(1), pp.29-38.
311. Rastas, S., Pirttila, T., Viramo, P., Verkkoniemi, A., Halonen, P., Juva, K., Niinisto, L., Mattila, K., Lansimies, E. and Sulkava, R. Association between blood pressure and survival over 9 years in a general population aged 85 and older. *J Am Geriatr Soc.* 2006, **54**(6), pp.912-918.
312. Kagiyama, S., Takata, Y., Ansai, T., Matsumura, K., Soh, I., Awano, S., Sonoki, K., Yoshida, A., Torisu, T., Hamasaki, T., Nakamichi, I., Takehara, T. and Iida, M. Does decreased diastolic blood pressure associate with increased mortality in 80-year-old Japanese? *Clin Exp Hypertens.* 2009, **31**(8), pp.639-647.
313. van Bemmel, T., Gussekloo, J., Westendorp, R.G. and Blauw, G.J. In a population-based prospective study, no association between high blood pressure and mortality after age 85 years. *J Hypertens.* 2006, **24**(2), pp.287-292.
314. Molander, L., Lovheim, H., Norman, T., Nordstrom, P. and Gustafson, Y. Lower systolic blood pressure is associated with greater mortality in people aged 85 and older. *J Am Geriatr Soc.* 2008, **56**(10), pp.1853-1859.
315. Poortvliet, R.K., Blom, J.W., de Craen, A.J., Mooijaart, S.P., Westendorp, R.G., Assendelft, W.J., Gussekloo, J. and de Ruijter, W.

Low blood pressure predicts increased mortality in very old age even without heart failure: the Leiden 85-plus Study. *Eur J Heart Fail.* 2013, **15**(5), pp.528-533.

316. Badia Farré T, F.P.F., Almeda Ortega J, Ferrer Feliu A, Rojas-Farreras S, Grupo Octabaix,. Relationship between blood pressure and mortality at 4years of follow up in a cohort of individuals aged over 80 years. *Med Clin (Barc).* 2011, **137**, pp.97-103.
317. Douros, A., Tolle, M., Ebert, N., Gaedeke, J., Huscher, D., Kreutz, R., Kuhlmann, M.K., Martus, P., Mielke, N., Schneider, A., Schuchardt, M., van der Giet, M. and Schaeffner, E. Control of blood pressure and risk of mortality in a cohort of older adults: the Berlin Initiative Study. *Eur Heart J.* 2019, **40**(25), pp.2021-2028.
318. Lv, Y.B., Gao, X., Yin, Z.X., Chen, H.S., Luo, J.S., Brasher, M.S., Kraus, V.B., Li, T.T., Zeng, Y. and Shi, X.M. Revisiting the association of blood pressure with mortality in oldest old people in China: community based, longitudinal prospective study. *BMJ.* 2018, **361**, p.k2158.
319. Damen, J.A., Hooft, L., Schuit, E., Debray, T.P., Collins, G.S., Tzoulaki, I., Lassale, C.M., Siontis, G.C., Chiocchia, V., Roberts, C., Schlussel, M.M., Gerry, S., Black, J.A., Heus, P., van der Schouw, Y.T., Peelen, L.M. and Moons, K.G. Prediction models for cardiovascular disease risk in the general population: systematic review. *BMJ.* 2016, **353**, p.i2416.
320. National Institute for Health and Care Excellence, N. *Clinical Guideline [CG136] Hypertension in adults: diagnosis and management*. 2019. [Accessed 27.03.2021]. Available from: https://www.nice.org.uk/guidance/ng143
321. Nerenberg, K.A., Zarnke, K.B., Leung, A.A., Dasgupta, K., Butalia, S., McBrien, K., Harris, K.C., Nakhla, M., Cloutier, L., Gelfer, M., Lamarre-Cliche, M., Milot, A., Bolli, P., Tremblay, G., McLean, D., Padwal, R.S., Tran, K.C., Grover, S., Rabkin, S.W., Moe, G.W., Howlett, J.G., Lindsay, P., Hill, M.D., Sharma, M., Field, T., Wein, T.H., Shoamanesh, A., Dresser, G.K., Hamet, P., Herman, R.J., Burgess, E., Gryn, S.E., Gregoire, J.C., Lewanczuk, R., Poirier, L., Campbell, T.S., Feldman, R.D., Lavoie, K.L., Tsuyuki, R.T., Honos, G., Prebtani, A.P.H., Kline, G., Schiffrin, E.L., Don-Wauchope, A., Tobe, S.W., Gilbert, R.E., Leiter, L.A., Jones, C., Woo, V., Hegele, R.A., Selby, P., Pipe, A., McFarlane, P.A., Oh, P., Gupta, M., Bacon, S.L., Kaczorowski, J., Trudeau, L., Campbell, N.R.C., Hiremath, S., Roerecke, M., Arcand, J., Ruzicka, M., Prasad, G.V.R., Vallee, M., Edwards, C., Sivapalan, P., Penner, S.B., Fournier, A., Benoit, G., Feber, J., Dionne, J., Magee, L.A., Logan, A.G., Cote, A.M., Rey, E., Firoz, T., Kuyper, L.M., Gabor, J.Y., Townsend, R.R., Rabi, D.M., Daskalopoulou, S.S. and Hypertension, C. Hypertension Canada's 2018 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults and Children. *Can J Cardiol.* 2018, **34**(5), pp.506-525.
322. Williams, B., Mancia, G., Spiering, W., Agabiti Rosei, E., Azizi, M., Burnier, M., Clement, D.L., Coca, A., de Simone, G., Dominiczak, A., Kahan, T., Mahfoud, F., Redon, J., Ruilope, L., Zanchetti, A., Kerins, M., Kjeldsen, S.E., Kreutz, R., Laurent, S., Lip, G.Y.H., McManus, R.,

Narkiewicz, K., Ruschitzka, F., Schmieder, R.E., Shlyakhto, E., Tsioufis, C., Aboyans, V., Desormais, I. and Group, E.S.C.S.D. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J.* 2018, **39**(33), pp.3021-3104.

323. Whelton, P.K., Carey, R.M., Aronow, W.S., Casey, D.E., Jr., Collins, K.J., Dennison Himmelfarb, C., DePalma, S.M., Gidding, S., Jamerson, K.A., Jones, D.W., MacLaughlin, E.J., Muntner, P., Ovbiagele, B., Smith, S.C., Jr., Spencer, C.C., Stafford, R.S., Taler, S.J., Thomas, R.J., Williams, K.A., Sr., Williamson, J.D. and Wright, J.T., Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2018, **71**(19), pp.e127-e248.
324. Gabb, G.M., Mangoni, A.A., Anderson, C.S., Cowley, D., Dowden, J.S., Golledge, J., Hankey, G.J., Howes, F.S., Leckie, L., Perkovic, V., Schlaich, M., Zwar, N.A., Medley, T.L. and Arnolda, L. Guideline for the diagnosis and management of hypertension in adults - 2016. *Med J Aust.* 2016, **205**(2), pp.85-89.
325. Clegg, A., Young, J., Iliffe, S., Rikkert, M.O. and Rockwood, K. Frailty in elderly people. *Lancet.* 2013, **381**(9868), pp.752-762.
326. Zhou, J., Lo, O.Y., Halko, M.A., Harrison, R., Lipsitz, L.A. and Manor, B. The functional implications and modifiability of resting-state brain network complexity in older adults. *Neurosci Lett.* 2020, **720**, p.134775.
327. Hoogendijk, E.O., Afilalo, J., Ensrud, K.E., Kowal, P., Onder, G. and Fried, L.P. Frailty: implications for clinical practice and public health. *Lancet.* 2019, **394**(10206), pp.1365-1375.
328. Corretge, M.D., F; Mead, G;. Atypical presentation of disease in older age: A review. *CME Journla Geriatric Medicine.* 2010, **12**(3), pp.128-140.
329. Isaacs, B. *The Challenge of Geriatric Medicine.* Oxford University Press, 1992.
330. Seeman, T.E., McEwen, B.S., Rowe, J.W. and Singer, B.H. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *Proc Natl Acad Sci U S A.* 2001, **98**(8), pp.4770-4775.
331. Lakatta, E.G. So! What's aging? Is cardiovascular aging a disease? *J Mol Cell Cardiol.* 2015, **83**, pp.1-13.
332. Mitnitski, A.B., Mogilner, A.J. and Rockwood, K. Accumulation of deficits as a proxy measure of aging. *ScientificWorldJournal.* 2001, **1**, pp.323-336.
333. Fried, L.P., Tangen, C.M., Walston, J., Newman, A.B., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W.J., Burke, G., McBurnie, M.A. and Cardiovascular Health Study Collaborative Research, G. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* 2001, **56**(3), pp.M146-156.
334. Searle, S.D., Mitnitski, A., Gahbauer, E.A., Gill, T.M. and Rockwood, K. A standard procedure for creating a frailty index. *BMC Geriatr.* 2008, **8**, p.24.

335. United Nations (UN). *World Population Ageing 2019.* New York, USA: Department of Economic and Social Affairs, 2020.
336. (ONS), O.f.N.S. *Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2019.* [Online]. 2020. [Accessed 16.07.2020]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2019estimates
337. Office for National Statistics (ONS). *Health state life expectancies by national deprivation deciles, England: 2016 to 2018.* Newport, UK: Office for National Statistics (ONS), 2020.
338. Tabor, D. *Health state life expectancies, UK: 2016 to 2018.* Newport, UK: Office for National Statistics (ONS), 2018.
339. England;, P.H. *Chapter 1: population change and trends in life expectancy.* London, UK: Public Health England, 2018.
340. Barnett, K., Mercer, S.W., Norbury, M., Watt, G., Wyke, S. and Guthrie, B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet.* 2012, **380**(9836), pp.37-43.
341. Clegg, A., Bates, C., Young, J., Ryan, R., Nichols, L., Ann Teale, E., Mohammed, M.A., Parry, J. and Marshall, T. Development and validation of an electronic frailty index using routine primary care electronic health record data. *Age Ageing.* 2016, **45**(3), pp.353-360.
342. Franklin, S.S., Gustin, W.t., Wong, N.D., Larson, M.G., Weber, M.A., Kannel, W.B. and Levy, D. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation.* 1997, **96**(1), pp.308-315.
343. Todd OM, W.C., Hale M, Wong NL, Hall M, Sheppard JP, McManus RJ, Rockwood K, Young J, Gale CP, Clegg A. Is the association between blood pressure and mortality in older adults different with frailty? A systematic review and meta-analysis. *Age Ageing.* 2019.
344. Stroup, D.F., Berlin, J.A., Morton, S.C., Olkin, I., Williamson, G.D., Rennie, D., Moher, D., Becker, B.J., Sipe, T.A. and Thacker, S.B. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA.* 2000, **283**(15), pp.2008-2012.
345. Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gotzsche, P.C., Ioannidis, J.P., Clarke, M., Devereaux, P.J., Kleijnen, J. and Moher, D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med.* 2009, **6**(7), p.e1000100.
346. Clegg, A., Rogers, L. and Young, J. Diagnostic test accuracy of simple instruments for identifying frailty in community-dwelling older people: a systematic review. *Age Ageing.* 2015, **44**(1), pp.148-152.
347. *Covidence systematic review software.* [Online database]. Melbourne, Australia.
348. Kim, S.Y., Park, J.E., Lee, Y.J., Seo, H.J., Sheen, S.S., Hahn, S., Jang, B.H. and Son, H.J. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. *J Clin Epidemiol.* 2013, **66**(4), pp.408-414.

349. Egger, M., Schneider, M. and Davey Smith, G. Spurious precision? Meta-analysis of observational studies. *BMJ.* 1998, **316**(7125), pp.140-144.
350. Gutierrez-Misis, A., Sanchez-Santos, M.T., Banegas, J.R., Castell, M.V., Gonzalez-Montalvo, J.I. and Otero, A. Walking speed and high blood pressure mortality risk in a Spanish elderly population. *J Hum Hypertens.* 2015, **29**(9), pp.566-572.
351. Post Hospers, G., Smulders, Y.M., Maier, A.B., Deeg, D.J. and Muller, M. Relation between blood pressure and mortality risk in an older population: role of chronological and biological age. *J Intern Med.* 2015, **277**(4), pp.488-497.
352. Odden, M.C., Peralta, C.A., Haan, M.N. and Covinsky, K.E. Rethinking the association of high blood pressure with mortality in elderly adults: the impact of frailty. *Arch Intern Med.* 2012, **172**(15), pp.1162-1168.
353. Peralta, C.A., Katz, R., Newman, A.B., Psaty, B.M. and Odden, M.C. Systolic and diastolic blood pressure, incident cardiovascular events, and death in elderly persons: the role of functional limitation in the Cardiovascular Health Study. *Hypertension.* 2014, **64**(3), pp.472-480.
354. Streit, S., Poortvliet, R.K.E. and Gussekloo, J. Lower blood pressure during antihypertensive treatment is associated with higher all-cause mortality and accelerated cognitive decline in the oldest-old-data from the Leiden 85-plus Study. *Age Ageing.* 2018.
355. Vaes, B., Depoortere, D., Van Pottelbergh, G., Mathei, C., Neto, J. and Degryse, J. Association between traditional cardiovascular risk factors and mortality in the oldest old: untangling the role of frailty. *BMC Geriatr.* 2017, **17**(1), p.234.
356. Weidung, B., Bostrom, G., Toots, A., Nordstrom, P., Carlberg, B., Gustafson, Y. and Littbrand, H. Blood pressure, gait speed, and mortality in very old individuals: a population-based cohort study. *J Am Med Dir Assoc.* 2015, **16**(3), pp.208-214.
357. Wu, C., Smit, E., Peralta, C.A., Sarathy, H. and Odden, M.C. Functional Status Modifies the Association of Blood Pressure with Death in Elders: Health and Retirement Study. *J Am Geriatr Soc.* 2017, **65**(7), pp.1482-1489.
358. Collaboration, T.C. *Cochrane Handbook for Systematic Reviews of Interventions.* London, UK: Wiley-Blackwell, 2008.
359. Williamson, J.D., Supiano, M.A., Applegate, W.B., Berlowitz, D.R., Campbell, R.C., Chertow, G.M., Fine, L.J., Haley, W.E., Hawfield, A.T., Ix, J.H., Kitzman, D.W., Kostis, J.B., Krousel-Wood, M.A., Launer, L.J., Oparil, S., Rodriguez, C.J., Roumie, C.L., Shorr, R.I., Sink, K.M., Wadley, V.G., Whelton, P.K., Whittle, J., Woolard, N.F., Wright, J.T., Jr., Pajewski, N.M. and Group, S.R. Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged >/=75 Years: A Randomized Clinical Trial. *JAMA.* 2016, **315**(24), pp.2673-2682.
360. Benetos, A., Buatois, S., Salvi, P., Marino, F., Toulza, O., Dubail, D., Manckoundia, P., Valbusa, F., Rolland, Y., Hanon, O., Gautier, S., Miljkovic, D., Guillemin, F., Zamboni, M., Labat, C. and Perret-Guillaume, C. Blood pressure and pulse wave velocity values in the

institutionalized elderly aged 80 and over: baseline of the PARTAGE study. *J Hypertens.* 2010, **28**(1), pp.41-50.

361. Supiano, M.A., Pajewski, N.M. and Williamson, J.D. Systolic Blood Pressure and Mortality: Role of Reverse Causation. *J Am Geriatr Soc.* 2018, **66**(1), pp.205-206.
362. Warwick, J., Falaschetti, E., Rockwood, K., Mitnitski, A., Thijs, L., Beckett, N., Bulpitt, C. and Peters, R. No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people: an investigation of the impact of frailty upon treatment effect in the HYpertension in the Very Elderly Trial (HYVET) study, a double-blind, placebo-controlled study of antihypertensives in people with hypertension aged 80 and over. *BMC Med.* 2015, **13**, p.78.
363. Pajewski, N.M., Williamson, J.D., Applegate, W.B., Berlowitz, D.R., Bolin, L.P., Chertow, G.M., Krousel-Wood, M.A., Lopez-Barrera, N., Powell, J.R., Roumie, C.L., Still, C., Sink, K.M., Tang, R., Wright, C.B., Supiano, M.A. and Group, S.S.R. Characterizing Frailty Status in the Systolic Blood Pressure Intervention Trial. *J Gerontol A Biol Sci Med Sci.* 2016, **71**(5), pp.649-655.
364. Sheppard JP, B.J., Lown M, Temple E, Lowe R, Ashby H, Todd O, Diment B, Oliver S, Allen J, Ford G, Heneghan C, Hobbs R, Jowett S, Little P, Mant J, Mollison J, Payne R, Williams M, Yu L, McManus R. Do these data apply to me? Examining the applicability of trials assessing strategies for optimal management of blood pressure to older patients in UK primary care. *Eur Heart J.* 2019, **40**.
365. Ravindrarajah, R., Hazra, N.C., Hamada, S., Charlton, J., Jackson, S.H.D., Dregan, A. and Gulliford, M.C. Systolic Blood Pressure Trajectory, Frailty, and All-Cause Mortality >80 Years of Age: Cohort Study Using Electronic Health Records. *Circulation.* 2017, **135**(24), pp.2357-2368.
366. Masoli, J.A.H., Delgado, J., Pilling, L., Strain, D. and Melzer, D. Blood pressure in frail older adults: associations with cardiovascular outcomes and all-cause mortality. *Age Ageing.* 2020, **49**(5), pp.807-813.
367. Lewington, S., Clarke, R., Qizilbash, N., Peto, R., Collins, R. and Prospective Studies, C. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* 2002, **360**(9349), pp.1903-1913.
368. Clarke, R., Shipley, M., Lewington, S., Youngman, L., Collins, R., Marmot, M. and Peto, R. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol.* 1999, **150**(4), pp.341-353.
369. Riley, R.D., van der Windt DA, Croft P, Moons KGM. *Prognosis research in Healthcare: Concepts, Methods and Impact.* Oxford: Oxford University Press, 2019.
370. Peat, G., Riley, R.D., Croft, P., Morley, K.I., Kyzas, P.A., Moons, K.G., Perel, P., Steyerberg, E.W., Schroter, S., Altman, D.G., Hemingway, H. and Group, P. Improving the transparency of prognosis research: the role of reporting, data sharing, registration, and protocols. *PLoS Med.* 2014, **11**(7), p.e1001671.

371. Hemingway, H., Croft, P., Perel, P., Hayden, J.A., Abrams, K., Timmis, A., Briggs, A., Udumyan, R., Moons, K.G., Steyerberg, E.W., Roberts, I., Schroter, S., Altman, D.G., Riley, R.D. and Group, P. Prognosis research strategy (PROGRESS) 1: a framework for researching clinical outcomes. *BMJ.* 2013, **346**, p.e5595.
372. Hingorani, A.D., Windt, D.A., Riley, R.D., Abrams, K., Moons, K.G., Steyerberg, E.W., Schroter, S., Sauerbrei, W., Altman, D.G., Hemingway, H. and Group, P. Prognosis research strategy (PROGRESS) 4: stratified medicine research. *BMJ.* 2013, **346**, p.e5793.
373. Riley, R.D., Hayden, J.A., Steyerberg, E.W., Moons, K.G., Abrams, K., Kyzas, P.A., Malats, N., Briggs, A., Schroter, S., Altman, D.G., Hemingway, H. and Group, P. Prognosis Research Strategy (PROGRESS) 2: prognostic factor research. *PLoS Med.* 2013, **10**(2), p.e1001380.
374. Steyerberg, E.W., Moons, K.G., van der Windt, D.A., Hayden, J.A., Perel, P., Schroter, S., Riley, R.D., Hemingway, H., Altman, D.G. and Group, P. Prognosis Research Strategy (PROGRESS) 3: prognostic model research. *PLoS Med.* 2013, **10**(2), p.e1001381.
375. Porta, M., Vineis, P. and Bolumar, F. The current deconstruction of paradoxes: one sign of the ongoing methodological "revolution". *Eur J Epidemiol.* 2015, **30**(10), pp.1079-1087.
376. Kirkwood, B.S., JAC. *Essential Medical Statistics.* 2nd ed. Oxford, UK: Blackwell Science, 2005.
377. Musini, V.M., Tejani, A.M., Bassett, K. and Wright, J.M. Pharmacotherapy for hypertension in the elderly. *Cochrane Database Syst Rev.* 2009, (4), p.CD000028.
378. Williams, B., Poulter, N.R., Brown, M.J., Davis, M., McInnes, G.T., Potter, J.F., Sever, P.S., Thom, S.M. and Bhs guidelines working party, f.t.B.H.S. British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. *BMJ.* 2004, **328**(7440), pp.634-640.
379. McCormack, T., Krause, T. and O'Flynn, N. Management of hypertension in adults in primary care: NICE guideline. *Br J Gen Pract.* 2012, **62**(596), pp.163-164.
380. England., N. *General Medical Services (GMS) contract Quality and Outcomes Framework (QOF): guidence for GMS contract 2013/2014.* Leeds, England: NHS Employers, 2013.
381. Fenton, K.K., MP; Newton, J; Patrick, Z; Richards, M. *NHS Health Check: our approach to the evidence.* [Online]. 2013. [Accessed 22.10.2020]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/224537/NHS_Health_Check_our_approach_to_the_evidence_v2.pdf
382. Franks, P., Clancy, C.M. and Nutting, P.A. Gatekeeping revisited--protecting patients from overtreatment. *N Engl J Med.* 1992, **327**(6), pp.424-429.
383. Digital, N. *Patients Registered at a GP Practice in England.* [Online]. 2019. [Accessed]. Available from: https://app.powerbi.com/view?r=eyJrIjoiNjQxMTI5NTEtYzlkNi00MzljL

WE0OGItNGVjM2QwNjAzZGQ0IiwidCI6IjUwZjYwNzFmLWJiZmUtNDAxYS04ODAzLTY3Mzc0OGU2MjllMiIsImMiOjh9

384. Benson, T. Why general practitioners use computers and hospital doctors do not--Part 1: incentives. *BMJ.* 2002, **325**(7372), pp.1086-1089.
385. Kontopantelis, E., Stevens, R.J., Helms, P.J., Edwards, D., Doran, T. and Ashcroft, D.M. Spatial distribution of clinical computer systems in primary care in England in 2016 and implications for primary care electronic medical record databases: a cross-sectional population study. *BMJ Open.* 2018, **8**(2), p.e020738.
386. Lawrence, M., Coulter, A. and Jones, L. A total audit of preventive procedures in 45 practices caring for 430,000 patients. *BMJ.* 1990, **300**(6738), pp.1501-1503.
387. NHS Digital. *National Data Opt-Out.* [Online]. 2018. [Accessed]. Available from: https://digital.nhs.uk/services/national-data-opt-out-programme
388. European Union (EU). *General Data Protection Regulation (GDPR).* [Online]. 2017. [Accessed 29.05.2019]. Available from: https://eugdpr.org/
389. Jick, H., Jick, S.S. and Derby, L.E. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. *BMJ.* 1991, **302**(6779), pp.766-768.
390. Hippisley-Cox, J., Stables, D. and Pringle, M. QRESEARCH: a new general practice database for research. *Inform Prim Care.* 2004, **12**(1), pp.49-50.
391. *ResearchOne Health and Care Database.* [Online]. [Accessed 19.07.2019]. Available from: http://www.researchone.org/
392. Blak, B.T., Thompson, M., Dattani, H. and Bourke, A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Inform Prim Care.* 2011, **19**(4), pp.251-255.
393. Lyons, R.A., Jones, K.H., John, G., Brooks, C.J., Verplancke, J.P., Ford, D.V., Brown, G. and Leake, K. The SAIL databank: linking multiple health and social care datasets. *BMC Med Inform Decis Mak.* 2009, **9**, p.3.
394. Information Services Division, N.S.S. *Scottish Primary Care Information Resource.* [Online]. [Accessed]. Available from: https://www.isdscotland.org/Health-Topics/General-Practice/SPIRE/index.asp
395. Herrett, E., Gallagher, A.M., Bhaskaran, K., Forbes, H., Mathur, R., van Staa, T. and Smeeth, L. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol.* 2015, **44**(3), pp.827-836.
396. Wolf, A., Dedman, D., Campbell, J., Booth, H., Lunn, D., Chapman, J. and Myles, P. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. *Int J Epidemiol.* 2019, **48**(6), pp.1740-1740g.
397. Kontopantelis, E. *Primary Care data signposting: CPRD, THIN and other databases.* Oxford, UK: Farr Institute, 2015.
398. Hippisley-Cox, J. and Coupland, C. Development and validation of risk prediction equations to estimate survival in patients with colorectal cancer: cohort study. *BMJ.* 2017, **357**, p.j2497.

399. Crossfield S, B.C., Parry J. ResearchOne Database Protocol. *Copyright TPP ResearchOne.* 2012.
400. Adderley, N., Nirantharakumar, K. and Marshall, T. Temporal variation in the diagnosis of resolved atrial fibrillation and the influence of performance targets on clinical coding: cohort study. *BMJ Open.* 2019, **9**(11), p.e030454.
401. Fanning, L., Lau, W.C.Y., Mongkhon, P., Man, K.K.C., Bell, J.S., Ilomaki, J., Darzins, P., Lau, K.K., Wei, L. and Wong, I.C.K. Safety and Effectiveness of Direct Oral Anticoagulants vs Warfarin in People With Atrial Fibrillation and Dementia. *J Am Med Dir Assoc.* 2020, **21**(8), pp.1058-1064 e1056.
402. Ford, D.V., Jones, K.H., Verplancke, J.P., Lyons, R.A., John, G., Brown, G., Brooks, C.J., Thompson, S., Bodger, O., Couch, T. and Leake, K. The SAIL Databank: building a national architecture for e-health research and evaluation. *BMC Health Serv Res.* 2009, **9**, p.157.
403. Gaertner, B., Seitz, I., Fuchs, J., Busch, M.A., Holzhausen, M., Martus, P. and Scheidt-Nave, C. Baseline participation in a health examination survey of the population 65 years and older: who is missed and why? *BMC Geriatr.* 2016, **16**, p.21.
404. McMurdo, M.E., Roberts, H., Parker, S., Wyatt, N., May, H., Goodman, C., Jackson, S., Gladman, J., O'Mahony, S., Ali, K., Dickinson, E., Edison, P., Dyer, C., Age and Ageing Specialty Group, N.C.C.R.N. Improving recruitment of older people to research through good practice. *Age Ageing.* 2011, **40**(6), pp.659-665.
405. Nohr, E.A. and Liew, Z. How to investigate and adjust for selection bias in cohort studies. *Acta Obstet Gynecol Scand.* 2018, **97**(4), pp.407-416.
406. Goldstein, B.A., Bhavsar, N.A., Phelan, M. and Pencina, M.J. Controlling for Informed Presence Bias Due to the Number of Health Encounters in an Electronic Health Record. *Am J Epidemiol.* 2016, **184**(11), pp.847-855.
407. Hollinghurst, J., Fry, R., Akbari, A., Clegg, A., Lyons, R.A., Watkins, A. and Rodgers, S.E. External validation of the electronic Frailty Index using the population of Wales within the Secure Anonymised Information Linkage Databank. *Age Ageing.* 2019, **48**(6), pp.922-926.
408. Hollinghurst, J.A., A; Fry, R; Rodgers, S;. Detecting Care Homes: Using Residential Anonymous Linking Fields to Identify Care Homes in Administrative Data. *International Journal of Population Data Science* 2018, **3**.
409. Jones KH, F.D., Thompson S, Lyons R. A Profile of the SAIL Databank on the UK Secure Research Platform. *International Journal of Population Data Science.* 2019, **4**(3), pp.1-12.
410. Jones, K.H., Ford, D.V., Jones, C., Dsilva, R., Thompson, S., Brooks, C.J., Heaven, M.L., Thayer, D.S., McNerney, C.L. and Lyons, R.A. A case study of the Secure Anonymous Information Linkage (SAIL) Gateway: a privacy-protecting remote access system for health-related research and evaluation. *J Biomed Inform.* 2014, **50**, pp.196-204.
411. *NHS Wales Informatics Service (NWIS).* [Online]. [Accessed 14.10.2020]. Available from: http://www.wales.nhs.uk/sitesplus/956/

412. Schneir C, W.T., Akbari A, Orton C, Gallacher J, Lyons RA. Cohort profile: The Secure Anonymised Information Linkage databank Dementia e-cohort (SAIL-DeC). *International Journal of Population Data Science.* 2020, **5**(7).
413. Hollinghurst, J., Akbari, A., Fry, R., Watkins, A., Berridge, D., Clegg, A., Hillcoat-Nalletamby, S., Williams, N., Lyons, R., Mizen, A., Walters, A., Johnson, R. and Rodgers, S. Study protocol for investigating the impact of community home modification services on hospital utilisation for fall injuries: a controlled longitudinal study using data linkage. *BMJ Open.* 2018, **8**(10), p.e026290.
414. Rodgers, S.E., Lyons, R.A., Dsilva, R., Jones, K.H., Brooks, C.J., Ford, D.V., John, G. and Verplancke, J.P. Residential Anonymous Linking Fields (RALFs): a novel information infrastructure to study the interaction between the environment and individuals' health. *J Public Health (Oxf).* 2009, **31**(4), pp.582-588.
415. (SAIL);, S.A.I.L.d. *SAIL Datasets.* [Online]. 2020. [Accessed]. Available from: https://data.ukserp.ac.uk/Organisation/Category?nodeId=1&orgId=0
416. Dennis, M., Shine, L., John, A., Marchant, A., McGregor, J., Lyons, R.A. and Brophy, S. Risk of Adverse Outcomes for Older People with Dementia Prescribed Antipsychotic Medication: A Population Based e-Cohort Study. *Neurol Ther.* 2017, **6**(1), pp.57-77.
417. Digital, N. *National Clinical Coding Standards ICD-10 5th Edition (2020).* Leeds, UK: NHS Digital, 2020.
418. Chisholm, J. The Read clinical classification. *BMJ.* 1990, **300**(6732), p.1092.
419. Jones R, B.N., Culpepper L, Gass D, Grol R, Mant D, Silagy C. *Oxford Textbook of Primary Care.* Oxford: Oxford University Press, 2005.
420. Mahmood, T.C., S; Dhillon, C; La Corte, B; Cromwell, D; van der Meulen, J;. *Hospital Episode Statistics as a source of information on safety and quality in gynaecology to support revalidation.* London, UK: Royal College of Obstetricians and Gynaecologists, 2012.
421. Commission, A. *Improving Data Quality in the NHS: Annual report on the Payment by Results (PbR) assurance programme: Health 2010.* London, UK: UK Government, 2010.
422. Herbert, A., Wijlaars, L., Zylbersztejn, A., Cromwell, D. and Hardelid, P. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). *Int J Epidemiol.* 2017, **46**(4), pp.1093-1093i.
423. Harp, C. *Understanding ICD-10-CM - Part II - What's In A Code?* [Online]. 2015. [Accessed 20.10.2020]. Available from: https://blog.clinicalarchitecture.com/understanding-icd-10-cm-part-ii-whats-in-a-code
424. John, S. *User guide to mortality statistics.* [Online]. 2019. [Accessed 23.10.2020]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/methodologies/userguidetomortalitystatisticsjuly2017#certification-of-cause-of-death
425. (WHO);, W.H.O. *Medical Certification of Cause of Death: Instructions for Physicians on Use of International Form of Medical Certificate of*

Cause of Death. Geneva, Switzerland: World Health Organisation (WHO);, 1979.
426. (CDC);, C.f.D.C.a.P. *About the Mortality Medical Data System.* [Online]. 2015. [Accessed 23.10.2020]. Available from: https://www.cdc.gov/nchs/nvss/mmds/about_mmds.htm
427. (ONS), O.f.N.S. *Impact of the Implementation of IRIS Software for ICD-10 Cause of Death Coding on Mortality Statistics, England and Wales.* Newport, UK: Office for National Statistics, 2014.
428. *Yubikey.* [Online]. [Accessed 14.10.2020]. Available from: https://www.yubico.com/setup/
429. Little JA, R.D. *Statistical Analysis with Missing Data.* New York: John Wiley and Sons, 2002.
430. Rubin, D.B. Inference and missing data. *Biometrika.* 1976, **63**, pp.581-592.
431. *Getting Started with Mulitple Imputation in R.* [Online]. 2019. [Accessed 17.08.2020]. Available from: https://uvastatlab.github.io/2019/05/01/getting-started-with-multiple-imputation-in-r/
432. Rubin, D.B.S., H. S,; Vehovar, V;. Handling "Don't Know" Survey Responses: The Case of the Slovenian Plebiscite. *Journal of the American Statistical Association.* 1995, **90**, pp.822-828.
433. Kropko, J.G., B; Gelman A; Hill, J. Multiple imputation for continuous and categorical data: Comparing joint multivariate normal and conditional approaches. *Political Analysis* 2014, **22**(4), pp.497-519.
434. van Laar, M. *Variation in Cancer Outcomes Amongst Children and Young Adults in Yorkshire*. PhD thesis, University of Leeds, 2015.
435. Williams, B., Lindholm, L.H. and Sever, P. Systolic pressure is all that matters. *Lancet.* 2008, **371**(9631), pp.2219-2221.
436. Mourad, J.J. The evolution of systolic blood pressure as a strong predictor of cardiovascular risk and the effectiveness of fixed-dose ARB/CCB combinations in lowering levels of this preferential target. *Vasc Health Risk Manag.* 2008, **4**(6), pp.1315-1325.
437. Galton, F. *Natural Inheritance.* London, UK: Macmillan, 1889.
438. Stigler, S.M. *The Seven Pillars of Statistical Wisdom.* Cambridge, Massachusetts, USA: Harvard University Press, 2016.
439. Stigler, S.M. Studies in the history of probability and statistics, L: Karl Pearson and the rule of three. *Biometrika.* 2012, **99**, pp.1-14.
440. Crowther MJ, A.K.L.P. Joint modeling of longitudinal and survival data. *Stata Journal.* 2013, **13**(1), pp.165-184.
441. Crowther, M.J., Lambert, P.C. and Abrams, K.R. Adjusting for measurement error in baseline prognostic biomarkers included in a time-to-event analysis: a joint modelling approach. *BMC Med Res Methodol.* 2013, **13**, p.146.
442. Luepker, R.V., Apple, F.S., Christenson, R.H., Crow, R.S., Fortmann, S.P., Goff, D., Goldberg, R.J., Hand, M.M., Jaffe, A.S., Julian, D.G., Levy, D., Manolio, T., Mendis, S., Mensah, G., Pajak, A., Prineas, R.J., Reddy, K.S., Roger, V.L., Rosamond, W.D., Shahar, E., Sharrett, A.R., Sorlie, P., Tunstall-Pedoe, H., Epidemiology, A.H.A.C.o., Prevention, Committee, A.H.A.S., World Heart Federation Council on, E., Prevention, European Society of Cardiology Working Group on, E., Prevention, Centers for Disease, C., Prevention,

National Heart, L. and Blood, I. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. *Circulation.* 2003, **108**(20), pp.2543-2549.

443. Rosamond, W.D., Chang, P.P., Baggett, C., Johnson, A., Bertoni, A.G., Shahar, E., Deswal, A., Heiss, G. and Chambless, L.E. Classification of heart failure in the atherosclerosis risk in communities (ARIC) study: a comparison of diagnostic criteria. *Circ Heart Fail.* 2012, **5**(2), pp.152-159.
444. (WHO), W.H.O. *Cerebrovascular Disorders.* Geneva: Offset Publications, 1978.
445. Lamb, S.E., Jorstad-Stein, E.C., Hauer, K., Becker, C., Prevention of Falls Network, E. and Outcomes Consensus, G. Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe consensus. *J Am Geriatr Soc.* 2005, **53**(9), pp.1618-1622.
446. Hippisley-Cox, J., Coupland, C., Vinogradova, Y., Robson, J., May, M. and Brindle, P. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. *BMJ.* 2007, **335**(7611), p.136.
447. Li Y, S.M.a.v.S.T. R package “QRISK3”: an unofficial research purposed implementation of ClinRisk’s QRISK3 algorithm into R. *F1000Research 2020.* 2020, **8**.
448. Ogunsua, A.A., Shaikh, A.Y., Ahmed, M. and McManus, D.D. Atrial Fibrillation and Hypertension: Mechanistic, Epidemiologic, and Treatment Parallels. *Methodist Debakey Cardiovasc J.* 2015, **11**(4), pp.228-234.
449. National Institute for Health and Care Excellence (NICE). *Cardiovascular disease: risk assessment and reduction, including lipid modification. CG181.* London: NICE, 2014.
450. Vlachopoulos, C.V., Terentes-Printzios, D.G., Ioakeimidis, N.K., Aznaouridis, K.A. and Stefanadis, C.I. Prediction of cardiovascular events and all-cause mortality with erectile dysfunction: a systematic review and meta-analysis of cohort studies. *Circ Cardiovasc Qual Outcomes.* 2013, **6**(1), pp.99-109.
451. Thompson, I.M., Tangen, C.M., Goodman, P.J., Probstfield, J.L., Moinpour, C.M. and Coltman, C.A. Erectile dysfunction and subsequent cardiovascular disease. *JAMA.* 2005, **294**(23), pp.2996-3002.
452. Shamloul, R. and Ghanem, H. Erectile dysfunction. *Lancet.* 2013, **381**(9861), pp.153-165.
453. Kurth, T., Winter, A.C., Eliassen, A.H., Dushkes, R., Mukamal, K.J., Rimm, E.B., Willett, W.C., Manson, J.E. and Rexrode, K.M. Migraine and risk of cardiovascular disease in women: prospective cohort study. *BMJ.* 2016, **353**, p.i2610.
454. Crowson, C.S., Liao, K.P., Davis, J.M., 3rd, Solomon, D.H., Matteson, E.L., Knutson, K.L., Hlatky, M.A. and Gabriel, S.E. Rheumatoid

arthritis and cardiovascular disease. *Am Heart J.* 2013, **166**(4), pp.622-628 e621.
455. Adler, A.I., Stratton, I.M., Neil, H.A., Yudkin, J.S., Matthews, D.R., Cull, C.A., Wright, A.D., Turner, R.C. and Holman, R.R. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ.* 2000, **321**(7258), pp.412-419.
456. Arsenault, B.J., Boekholdt, S.M. and Kastelein, J.J. Lipid parameters for measuring risk of cardiovascular disease. *Nat Rev Cardiol.* 2011, **8**(4), pp.197-206.
457. Townsend, P.D.N. *The Black Report.* London: Penguin, 1982.
458. George, J., Mathur, R., Shah, A.D., Pujades-Rodriguez, M., Denaxas, S., Smeeth, L., Timmis, A. and Hemingway, H. Ethnicity and the first diagnosis of a wide range of cardiovascular diseases: Associations in a linked electronic health record cohort of 1 million patients. *PLoS One.* 2017, **12**(6), p.e0178945.
459. England;, N.H.S.N. *2019/20 General Medical Services (GMS) contract Quality and Outcomes Framework (QOF).* Leeds, England: NHS England, 2019.
460. Denaxas, S., González-Izquierdo, A., Direk, K., Fitzpatrick, N., Banerjee, A., Dobson, R., Fatemifar, G., Kuan, V., Lumbers, T., Pasea, L., Patel, R., Hingorani, A., Sudlow, C. and Hemingway, H. *UK phenomics platform for developing and validating EHR phenotypes: CALIBER.* 2019.
461. Springate, D.A., Kontopantelis, E., Ashcroft, D.M., Olier, I., Parisi, R., Chamapiwa, E. and Reeves, D. ClinicalCodes: an online clinical codes repository to improve the validity and reproducibility of research using electronic medical records. *PLoS One.* 2014, **9**(6), p.e99825.
462. CPRD@Cambridge. *Clinical Code Repository.* [Online]. 2017. [Accessed 30.07.2020]. Available from: https://www.phpc.cam.ac.uk/pcu/research/research-groups/crmh/cprd_cam/codelists/v10/
463. Joseph, R.M., Movahedi, M., Dixon, W.G. and Symmons, D.P. Risks of smoking and benefits of smoking cessation on hospitalisations for cardiovascular events and respiratory infection in patients with rheumatoid arthritis: a retrospective cohort study using the Clinical Practice Research Datalink. *RMD Open.* 2017, **3**(2), p.e000506.
464. Grant, R.L., Drennan, V.M., Rait, G., Petersen, I. and Iliffe, S. First diagnosis and management of incontinence in older people with and without dementia in primary care: a cohort study using The Health Improvement Network primary care database. *PLoS Med.* 2013, **10**(8), p.e1001505.
465. Abel, K.M., Hope, H., Swift, E., Parisi, R., Ashcroft, D.M., Kosidou, K., Osam, C.S., Dalman, C. and Pierce, M. Prevalence of maternal mental illness among children and adolescents in the UK between 2005 and 2017: a national retrospective cohort analysis. *Lancet Public Health.* 2019, **4**(6), pp.e291-e300.
466. O'Connell, N.E., Smith, K.J., Peterson, M.D., Ryan, N., Liverani, S., Anokye, N., Victor, C. and Ryan, J.M. Incidence of osteoarthritis, osteoporosis and inflammatory musculoskeletal diseases in adults

with cerebral palsy: A population-based cohort study. *Bone.* 2019, **125**, pp.30-35.
467. Gilbert, T., Neuburger, J., Kraindler, J., Keeble, E., Smith, P., Ariti, C., Arora, S., Street, A., Parker, S., Roberts, H.C., Bardsley, M. and Conroy, S. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. *Lancet.* 2018, **391**(10132), pp.1775-1782.
468. Digital., N. *Technology Reference data Update Distribution.* [Online]. 2019. [Accessed 05.08.2019]. Available from: https://isd.digital.nhs.uk/trud3/user/guest/group/0/home
469. Committee;, J.F. *British National Formulary (BNF).* London, UK: BMJ Group and Pharmaceutical Press, 2020.
470. White, I.R., Royston, P. and Wood, A.M. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med.* 2011, **30**(4), pp.377-399.
471. Sterne, J.A., White, I.R., Carlin, J.B., Spratt, M., Royston, P., Kenward, M.G., Wood, A.M. and Carpenter, J.R. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ.* 2009, **338**, p.b2393.
472. Tilling, K., Williamson, E.J., Spratt, M., Sterne, J.A. and Carpenter, J.R. Appropriate inclusion of interactions was needed to avoid bias in multiple imputation. *J Clin Epidemiol.* 2016, **80**, pp.107-115.
473. Rubin, D.B. *Mulitple Imputation for Nonresponse in Surveys.* John Wiley and Sons, 1987.
474. Altman, D.G. and Bland, J.M. Parametric v non-parametric methods for data analysis. *BMJ.* 2009, **338**, p.a3167.
475. Haynes, R.S., DL; Guyatt, GH; Tugwell, P. *Clinical Epidemiology: How to Do Clinical Practice Research.* 3rd ed. Philadelphia, USA: Lippincott Williams and Wilkins, 2006.
476. Riley, R. *Statisitical Methods for Risk Prediction and Prognosis Models.* Keele University: Centre for Prognosis Research, Research Institute of Primary, Community and Social care, 2019.
477. Burnham, K.A., DR;. *Model Selection and Multimodel Inference: A Practical Information-Theoretic Approach.* 2nd ed. New York, USA: Springer, 2004.
478. Harrell, F. *Regresssion Modeling Strategies with Applications to Linear Models, Logistic Regression and Survival Analysis.* New York: Springer, 2001
479. Harrell, F.E., Jr., Lee, K.L. and Mark, D.B. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med.* 1996, **15**(4), pp.361-387.
480. Royston, P. and Sauerbrei, W. A new measure of prognostic separation in survival data. *Stat Med.* 2004, **23**(5), pp.723-748.
481. Royston, P. Explained variation for survival models. *Stata Journal.* 2006, **6**, pp.1-14.
482. Collins, G.S. and Altman, D.G. An independent and external validation of QRISK2 cardiovascular disease risk score: a prospective open cohort study. *BMJ.* 2010, **340**, p.c2442.

483. Riley, R.D., Snell, K.I., Ensor, J., Burke, D.L., Harrell, F.E., Jr., Moons, K.G. and Collins, G.S. Minimum sample size for developing a multivariable prediction model: PART II - binary and time-to-event outcomes. *Stat Med.* 2019, **38**(7), pp.1276-1296.
484. Chobanian, A.V., Bakris, G.L., Black, H.R., Cushman, W.C., Green, L.A., Izzo, J.L., Jr., Jones, D.W., Materson, B.J., Oparil, S., Wright, J.T., Jr., Roccella, E.J., National Heart, L., Blood Institute Joint National Committee on Prevention, D.E., Treatment of High Blood, P. and National High Blood Pressure Education Program Coordinating, C. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA.* 2003, **289**(19), pp.2560-2572.
485. Tong, A., Sainsbury, P. and Craig, J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care.* 2007, **19**(6), pp.349-357.
486. Coyne, I.T. Sampling in qualitative research. Purposeful and theoretical sampling; merging or clear boundaries? *J Adv Nurs.* 1997, **26**(3), pp.623-630.
487. Patton, M. *Qualitative research and evaluation methods.* 3rd ed. Thousand Oaks, CA: Sage Publications, 2002.
488. Palinkas, L.H., SM; Green, CA; Wisdom, JP; Duan, N; Hoagwood, K. Purposeful sampling for qualitative data collection and analysis in mixed method implementation research. *Adm Policy Ment Health.* 2016, **42**, pp.533-544.
489. Charmaz, K. *Constructing Grounded Theory.* London, UK: SAGE Publications, 2006.
490. Heaven, A., Brown, L., Young, J., Teale, E., Hawkins, R., Spilsbury, K., Mountain, G., Young, T., Goodwin, V., Hanratty, B., Chew-Graham, C., Brundle, C., Mahmood, F., Jacob, I., Daffu-O'Reilly, A. and Clegg, A. Community ageing research 75+ study (CARE75+): an experimental ageing and frailty research cohort. *BMJ Open.* 2019, **9**(3), p.e026744.
491. *Mental Capacity Act 2005*. Legislation.gov.uk: UK Government;.
492. *Edge Clinical Research.* [Online database]. Faculty of Medicine; University of Southampton, 2020.
493. Green, J.T., N. *Qualitative Methods for Health Research.* London: Sage, 2004.
494. Glaser, B.S., A;. *The Discovery of Grounded Theory; Strategies for Qualitative Research.* Chicago: Aldine, 1967.
495. Starks, H. and Trinidad, S.B. Choose your method: a comparison of phenomenology, discourse analysis, and grounded theory. *Qual Health Res.* 2007, **17**(10), pp.1372-1380.
496. Labov, W. *Language in the Inner City.* Philadelphia: University of Philadelphia Press, 1972.
497. Bell, S. Becoming a political woman: The reconstruction and interpretation of experience through stories. In: Todd AD, F.S. ed. *Gender and discourse: The power of talk*. Norwood, New Jersey: Ablex, 1988, pp.97-123.

498. Agar, M.H., JR;. Interpreting Discourse: Coherence and the Analysis of Ethnographic Interviews. *Discourse Processes.* 1982, **5**(1), pp.1-32.
499. Paget, M. Your son is cured now; you may take him home. *Cult Med Psychiatry.* 1982, **6**(3), pp.237 - 259.
500. Paget, M. Experience and knowledge. *Human Studies.* 1983, **6**, pp.67 - 90.
501. Steedman, P.H. On the Relations between Seeing, Interpreting and Knowing. In: Steier, F. ed. *Research and Reflexivity*. London: Sage, 1991.
502. Corbin, J.S., A. *Basics of Qualitative Research.* Thousand Oaks, Ca: SAGE, 2008.
503. Sidhu, K., Jones, R. and Stevenson, F. Publishing qualitative research in medical journals. *Br J Gen Pract.* 2017, **67**(658), pp.229-230.
504. Warmoth K, L.I., Phoenix C, Abraham C, Andrew MK, Hubbard RE, Tarrant M. 'Thinking you're old and frail': a qualitative study of frialty in older adults. *Ageing and Society.* 2016, **36**(7), pp.1483-1500
505. Nicholson, C., Meyer, J., Flatley, M., Holman, C. and Lowton, K. Living on the margin: understanding the experience of living and dying with frailty in old age. *Soc Sci Med.* 2012, **75**(8), pp.1426-1432.
506. Puts, M.T., Shekary, N., Widdershoven, G., Heldens, J., & Deeg, D. J. The meaning of frailty according to Dutch older frail and non-frail persons. *Journal of Aging Studies.* 2009, **23**(4), pp.258-266.
507. Doyle, P.J. and Rubinstein, R.L. Person-centered dementia care and the cultural matrix of othering. *Gerontologist.* 2014, **54**(6), pp.952-963.
508. Baltes PB, B.M. *Successful Aging: perspectives from the Behavioural Sciences.* Cambridge University Press, 1993.
509. Corbin, J.S., A;. Managing Chronic Illness at Home: Three Lines of Work. *Qualitative Sociology.* 1985, **8**(3).
510. Andrew, M.K. Social capital, health, and care home residence among older adults: a secondary analysis of the Health Survey for England 2000. *Eur J Ageing.* 2005, **2**(2), pp.137-148.
511. Kelley-Moore, J.A., Schumacher, J.G., Kahana, E. and Kahana, B. When do older adults become "disabled"? Social and health antecedents of perceived disability in a panel study of the oldest old. *J Health Soc Behav.* 2006, **47**(2), pp.126-141.
512. O'Brien, E.L., Hess, T.M., Kornadt, A.E., Rothermund, K., Fung, H. and Voss, P. Context Influences on the Subjective Experience of Aging: The Impact of Culture and Domains of Functioning. *Gerontologist.* 2017, **57**(suppl_2), pp.S127-S137.
513. Grenier, A.H., J;. Older Women and 'Frailty': Aged, Gendered and Embodied Resistance. *Current Sociology.* 2007.
514. World Health Organisation (WHO). *Global Health Estimates, 2016: Disease by Cause, Age, Sex, by Country and by Region 2000 -2016.* [Online]. 2016. [Accessed 14.01.2020].
515. Barker, C.J., EA;. *Cultural Studies,* 5th ed. [Exhibition catalogue]. London, UK: SAGE, 2016.
516. Lay-Flurrie, S.L., Sheppard, J.P., Stevens, R.J., Mallen, C., Heneghan, C., Hobbs, F.D.R., Williams, B., Mant, J. and McManus, R.J. Impact of Changes to National Hypertension Guidelines on

Hypertension Management and Outcomes in the United Kingdom. *Hypertension.* 2020, **75**(2), pp.356-364.

517. Tran, J., Norton, R., Conrad, N., Rahimian, F., Canoy, D., Nazarzadeh, M. and Rahimi, K. Patterns and temporal trends of comorbidity among adult patients with incident cardiovascular disease in the UK between 2000 and 2014: A population-based cohort study. *PLoS Med.* 2018, **15**(3), p.e1002513.
518. Rothwell, P.M. External validity of randomised controlled trials: "to whom do the results of this trial apply?". *Lancet.* 2005, **365**(9453), pp.82-93.
519. Rapsomaniki, E., Timmis, A., George, J., Pujades-Rodriguez, M., Shah, A.D., Denaxas, S., White, I.R., Caulfield, M.J., Deanfield, J.E., Smeeth, L., Williams, B., Hingorani, A. and Hemingway, H. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *Lancet.* 2014, **383**(9932), pp.1899-1911.
520. Lacey, B., Lewington, S., Clarke, R., Kong, X.L., Chen, Y., Guo, Y., Yang, L., Bennett, D., Bragg, F., Bian, Z., Wang, S., Zhang, H., Chen, J., Walters, R.G., Collins, R., Peto, R., Li, L., Chen, Z. and China Kadoorie Biobank collaborative, g. Age-specific association between blood pressure and vascular and non-vascular chronic diseases in 0.5 million adults in China: a prospective cohort study. *Lancet Glob Health.* 2018, **6**(6), pp.e641-e649.
521. Lewington, S., Lacey, B., Clarke, R., Guo, Y., Kong, X.L., Yang, L., Chen, Y., Bian, Z., Chen, J., Meng, J., Xiong, Y., He, T., Pang, Z., Zhang, S., Collins, R., Peto, R., Li, L., Chen, Z. and China Kadoorie Biobank, C. The Burden of Hypertension and Associated Risk for Cardiovascular Mortality in China. *JAMA Intern Med.* 2016, **176**(4), pp.524-532.
522. Wallace, L.M., Theou, O., Kirkland, S.A., Rockwood, M.R., Davidson, K.W., Shimbo, D. and Rockwood, K. Accumulation of non-traditional risk factors for coronary heart disease is associated with incident coronary heart disease hospitalization and death. *PLoS One.* 2014, **9**(3), p.e90475.
523. Farooqi, M.A.M., Gerstein, H., Yusuf, S. and Leong, D.P. Accumulation of Deficits as a Key Risk Factor for Cardiovascular Morbidity and Mortality: A Pooled Analysis of 154 000 Individuals. *J Am Heart Assoc.* 2020, **9**(3), p.e014686.
524. Noble, W.S. How does multiple testing correction work? *Nat Biotechnol.* 2009, **27**(12), pp.1135-1137.
525. Benetos, A., Labat, C., Rossignol, P., Fay, R., Rolland, Y., Valbusa, F., Salvi, P., Zamboni, M., Manckoundia, P., Hanon, O. and Gautier, S. Treatment With Multiple Blood Pressure Medications, Achieved Blood Pressure, and Mortality in Older Nursing Home Residents: The PARTAGE Study. *JAMA Intern Med.* 2015, **175**(6), pp.989-995.
526. Tinetti, M.E., Han, L., Lee, D.S., McAvay, G.J., Peduzzi, P., Gross, C.P., Zhou, B. and Lin, H. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. *JAMA Intern Med.* 2014, **174**(4), pp.588-595.
527. Mansfield, K.E., Nitsch, D., Smeeth, L., Bhaskaran, K. and Tomlinson, L.A. Prescription of renin-angiotensin system blockers and risk of

acute kidney injury: a population-based cohort study. *BMJ Open.* 2016, **6**(12), p.e012690.

528. Muscedere, J., Afilalo, J., Araujo de Carvalho, I., Cesari, M., Clegg, A., Eriksen, H.E., Evans, K.R., Heckman, G., Hirdes, J.P., Kim, P.M., Laffon, B., Lynn, J., Martin, F., Prorok, J.C., Rockwood, K., Rodrigues Manas, L., Rolfson, D., Shaw, G., Shea, B., Sinha, S., Theou, O., Tugwell, P., Valdiglesias, V., Vellas, B., Veronese, N., Wallace, L.M.K. and Williamson, P.R. Moving Towards Common Data Elements and Core Outcome Measures in Frailty Research. *J Frailty Aging.* 2020, **9**(1), pp.14-22.
529. van Oppen, J.D., Valderas, J.M., Mackintosh, N.J. and Conroy, S.P. Patient-reported outcome and experience measures in geriatric emergency medicine. *Z Gerontol Geriatr.* 2020.
530. Schick-Makaroff, K., Karimi-Dehkordi, M., Cuthbertson, L., Dixon, D., Cohen, S.R., Hilliard, N. and Sawatzky, R. Using Patient- and Family-Reported Outcome and Experience Measures Across Transitions of Care for Frail Older Adults Living at Home: A Meta-Narrative Synthesis. *Gerontologist.* 2020.
531. Johnson, R.A., Huntley, A., Hughes, R.A., Cramer, H., Turner, K.M., Perkins, B. and Feder, G. Interventions to support shared decision making for hypertension: A systematic review of controlled studies. *Health Expect.* 2018, **21**(6), pp.1191-1207.
532. Veenhuizen, M., Todd, O., Anand, A. and Whiteley, W. How to design a hypertension treatment trial that informs care of older people with frailty: a survey of clinicians in Ireland and the UK. *Age Ageing.* 2020.
533. Buisson, L. *Care homes for older people – Market Report.* Laing Buisson, 2019.
534. (ONS);, O.f.N.S. *UK population by ethnicity: Population statistics and 2011 Census data.* [Online]. 2020. [Accessed 15.10.2020]. Available from: https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/demographics/age-groups/latest
535. Official Labour Market Statistics, N. *Census 2011.* [Online]. 2011. [Accessed 14.01.2020]. Available from: https://www.nomisweb.co.uk/census/2011/dc2101ew
536. Mathur, R., Bhaskaran, K., Chaturvedi, N., Leon, D.A., vanStaa, T., Grundy, E. and Smeeth, L. Completeness and usability of ethnicity data in UK-based primary care and hospital databases. *J Public Health (Oxf).* 2014, **36**(4), pp.684-692.
537. Hutt, P.G., S;. *Tackling inequalities in general practice*. An Inquiry into the Quality of General Practice in England. London: The King's Fund. 2010. Available from: https://www.kingsfund.org.uk/sites/default/files/field/field_document/health-inequalities-general-practice-gp-inquiry-research-paper-mar11.pdf
538. Baird, B.C., A; Honeyman, M; Maguire, D; Das, P;. *Understanding pressures in general practice.* London, UK: The King's Fund, 2016.
539. Bakris, G.L. The Implications of Blood Pressure Measurement Methods on Treatment Targets for Blood Pressure. *Circulation.* 2016, **134**(13), pp.904-905.
540. McManus, R.J., Mant, J., Hull, M.R. and Hobbs, F.D. Does changing from mercury to electronic blood pressure measurement influence

recorded blood pressure? An observational study. *Br J Gen Pract.* 2003, **53**(497), pp.953-956.

541. Stevens, S.L., McManus, R.J. and Stevens, R.J. Current practice of usual clinic blood pressure measurement in people with and without diabetes: a survey and prospective 'mystery shopper' study in UK primary care. *BMJ Open.* 2018, **8**(4), p.e020589.
542. Royston, P., Altman, D.G. and Sauerbrei, W. Dichotomizing continuous predictors in multiple regression: a bad idea. *Stat Med.* 2006, **25**(1), pp.127-141.
543. England, N. *NHS England Standard General Medical Services Contract 2017/18.* [Online]. 2018. [Accessed 06.06.2019]. Available from: https://www.england.nhs.uk/wp-content/uploads/2018/01/17-18-gms-contract.pdf
544. Faller, J.W., Pereira, D.D.N., de Souza, S., Nampo, F.K., Orlandi, F.S. and Matumoto, S. Instruments for the detection of frailty syndrome in older adults: A systematic review. *PLoS One.* 2019, **14**(4), p.e0216166.
545. Brundle, C., Heaven, A., Brown, L., Teale, E., Young, J., West, R. and Clegg, A. Convergent validity of the electronic frailty index. *Age Ageing.* 2019, **48**(1), pp.152-156.
546. Xue, Q.L., Tian, J., Walston, J.D., Chaves, P.H.M., Newman, A.B. and Bandeen-Roche, K. Discrepancy in Frailty Identification: Move Beyond Predictive Validity. *J Gerontol A Biol Sci Med Sci.* 2020, **75**(2), pp.387-393.
547. Koller, M.T., Leening, M.J., Wolbers, M., Steyerberg, E.W., Hunink, M.G., Schoop, R., Hofman, A., Bucher, H.C., Psaty, B.M., Lloyd-Jones, D.M. and Witteman, J.C. Development and validation of a coronary risk prediction model for older U.S. and European persons in the Cardiovascular Health Study and the Rotterdam Study. *Ann Intern Med.* 2012, **157**(6), pp.389-397.
548. Ahmadi, S.F., Streja, E., Zahmatkesh, G., Streja, D., Kashyap, M., Moradi, H., Molnar, M.Z., Reddy, U., Amin, A.N., Kovesdy, C.P. and Kalantar-Zadeh, K. Reverse Epidemiology of Traditional Cardiovascular Risk Factors in the Geriatric Population. *J Am Med Dir Assoc.* 2015, **16**(11), pp.933-939.
549. Beer, C., Alfonso, H., Flicker, L., Norman, P.E., Hankey, G.J. and Almeida, O.P. Traditional risk factors for incident cardiovascular events have limited importance in later life compared with the health in men study cardiovascular risk score. *Stroke.* 2011, **42**(4), pp.952-959.
550. Eurelings, L.S., van Dalen, J.W., Ter Riet, G., Moll van Charante, E.P., Richard, E., van Gool, W.A., Almeida, O.P., Alexandre, T.S., Baune, B.T., Bickel, H., Cacciatore, F., Cooper, C., de Craen, T.A., Degryse, J.M., Di Bari, M., Duarte, Y.A., Feng, L., Ferrara, N., Flicker, L., Gallucci, M., Guaita, A., Harrison, S.L., Katz, M.J., Lebrao, M.L., Leung, J., Lipton, R.B., Mengoni, M., Ng, T.P., Ostbye, T., Panza, F., Polito, L., Sander, D., Solfrizzi, V., Syddall, H.E., van der Mast, R.C., Vaes, B., Woo, J., Yaffe, K. and Group, I.S. Apathy and depressive symptoms in older people and incident myocardial infarction, stroke, and mortality: a systematic review and meta-analysis of individual participant data. *Clin Epidemiol.* 2018, **10**, pp.363-379.

551. de Ruijter, W., Westendorp, R.G., Assendelft, W.J., den Elzen, W.P., de Craen, A.J., le Cessie, S. and Gussekloo, J. Use of Framingham risk score and new biomarkers to predict cardiovascular mortality in older people: population based observational cohort study. *BMJ.* 2009, **338**, p.a3083.
552. van Bussel, E.F., Richard, E., Busschers, W.B., Steyerberg, E.W., van Gool, W.A., Moll van Charante, E.P. and Hoevenaar-Blom, M.P. A cardiovascular risk prediction model for older people: Development and validation in a primary care population. *J Clin Hypertens (Greenwich).* 2019, **21**(8), pp.1145-1152.
553. Moll van Charante, E.P., Richard, E., Eurelings, L.S., van Dalen, J.W., Ligthart, S.A., van Bussel, E.F., Hoevenaar-Blom, M.P., Vermeulen, M. and van Gool, W.A. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. *Lancet.* 2016, **388**(10046), pp.797-805.
554. Herrett, E., Shah, A.D., Boggon, R., Denaxas, S., Smeeth, L., van Staa, T., Timmis, A. and Hemingway, H. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. *BMJ.* 2013, **346**, p.f2350.
555. Siddiqi, N., House, A.O. and Holmes, J.D. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. *Age Ageing.* 2006, **35**(4), pp.350-364.
556. Matthews, F.E., Stephan, B.C., Robinson, L., Jagger, C., Barnes, L.E., Arthur, A., Brayne, C., Cognitive, F. and Ageing Studies, C. A two decade dementia incidence comparison from the Cognitive Function and Ageing Studies I and II. *Nat Commun.* 2016, **7**, p.11398.
557. British Geriatrics Society (BGS). *Big Data in Geriatric Research.* [Online]. 2019. [Accessed]. Available from: https://www.bgs.org.uk/resources/big-data-in-geriatric-research
558. Freemantle, N., Marston, L., Walters, K., Wood, J., Reynolds, M.R. and Petersen, I. Making inferences on treatment effects from real world data: propensity scores, confounding by indication, and other perils for the unwary in observational research. *BMJ.* 2013, **347**, p.f6409.
559. National Institute for Health and Care Excellence, N. *Hypertension in adults: diagnosis and management - Full Guideline.* [Online]. 2011. [Accessed]. Available from: https://www.nice.org.uk/guidance/ng136/evidence/full-guideline-august-2011-6898565197?tab=evidence
560. England., P.H. *NHS health check: our approach to the evidence.* [Online]. 2013. [Accessed]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/224537/NHS_Health_Check_our_approach_to_the_evidence_v2.pdf
561. Pearl, J.M., D;. *The Book of Why: The New Science of Cause and Effect.* USA: Allen Lane, 2018.
562. *A dictionary of epidemiology.* 6th ed. New York, USA: Oxford University Press, 2014.

563. Hernan, M.A., Clayton, D. and Keiding, N. The Simpson's paradox unraveled. *Int J Epidemiol.* 2011, **40**(3), pp.780-785.
564. Yerushalmy, J. The relationship of parents' cigarette smoking to outcome of pregnancy--implications as to the problem of inferring causation from observed associations. *Am J Epidemiol.* 1971, **93**(6), pp.443-456.
565. Hernandez-Diaz, S., Schisterman, E.F. and Hernan, M.A. The birth weight "paradox" uncovered? *Am J Epidemiol.* 2006, **164**(11), pp.1115-1120.
566. Textor, J., van der Zander, B., Gilthorpe, M.S., Liskiewicz, M. and Ellison, G.T. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. *Int J Epidemiol.* 2016, **45**(6), pp.1887-1894.
567. Greenland, S., Pearl, J. and Robins, J.M. Causal diagrams for epidemiologic research. *Epidemiology.* 1999, **10**(1), pp.37-48.
568. Han, L., Clegg, A., Doran, T. and Fraser, L. The impact of frailty on healthcare resource use: a longitudinal analysis using the Clinical Practice Research Datalink in England. *Age Ageing.* 2019, **48**(5), pp.665-671.
569. Ray, W.A. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol.* 2003, **158**(9), pp.915-920.
570. Hernan, M.A., Alonso, A., Logan, R., Grodstein, F., Michels, K.B., Willett, W.C., Manson, J.E. and Robins, J.M. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. *Epidemiology.* 2008, **19**(6), pp.766-779.
571. Ashenfelter, O.C., D. Using the Longitudinal Structure of Earnings to Estimate the Effect of Training

Programs. *The Review of Economics and Statistics.* 1985, **67**(4), pp.648-660.
572. Streeter, A.J., Lin, N.X., Crathorne, L., Haasova, M., Hyde, C., Melzer, D. and Henley, W.E. Adjusting for unmeasured confounding in nonrandomized longitudinal studies: a methodological review. *J Clin Epidemiol.* 2017, **87**, pp.23-34.
573. VanderWeele, T.J. and Ding, P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med.* 2017, **167**(4), pp.268-274.
574. Carroll, R.J. and Stefanski, L.A. Measurement error, instrumental variables and corrections for attenuation with applications to meta-analyses. *Stat Med.* 1994, **13**(12), pp.1265-1282.
575. Benchimol, E.I., Smeeth, L., Guttmann, A., Harron, K., Moher, D., Petersen, I., Sorensen, H.T., von Elm, E., Langan, S.M. and Committee, R.W. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med.* 2015, **12**(10), p.e1001885.
576. Denaxas, S., Gonzalez-Izquierdo, A., Direk, K., Fitzpatrick, N.K., Fatemifar, G., Banerjee, A., Dobson, R.J.B., Howe, L.J., Kuan, V., Lumbers, R.T., Pasea, L., Patel, R.S., Shah, A.D., Hingorani, A.D., Sudlow, C. and Hemingway, H. UK phenomics platform for developing and validating electronic health record phenotypes: CALIBER. *J Am Med Inform Assoc.* 2019.

577. Goodman, S.F., D; Ionnidis, JPA;. What does research reproducibility mean? *Science Translational Medicine.* 2016, **8**(341).
578. Dewan, P., Jackson, A., Jhund, P.S., Shen, L., Ferreira, J.P., Petrie, M.C., Abraham, W.T., Desai, A.S., Dickstein, K., Kober, L., Packer, M., Rouleau, J.L., Solomon, S.D., Swedberg, K., Zile, M.R. and McMurray, J.J.V. The prevalence and importance of frailty in heart failure with reduced ejection fraction - an analysis of PARADIGM-HF and ATMOSPHERE. *Eur J Heart Fail.* 2020.
579. Fan, H., Onakpoya, I.J. and Heneghan, C.J. 24-h ambulatory blood pressure versus clinic blood pressure as predictors of cardiovascular risk: a systematic review and meta-analysis of prospective studies. *J Hypertens.* 2020, **38**(11), pp.2084-2094.
580. Guthrie, B., Payne, K., Alderson, P., McMurdo, M.E. and Mercer, S.W. Adapting clinical guidelines to take account of multimorbidity. *BMJ.* 2012, **345**, p.e6341.
581. NICE. *Multimorbidity: Clinical Assessment and Management.* [Online]. 2016. [Accessed]. Available from: https://wwwniceorguk/guidance/ng56.
582. (BGS);, B.G.S. *Fit for frailty*. Royal College of General Practitioners (RCP), a.A.U. London, UK: British Geriatrics Society;. 2015. [Accessed 31.10.2020]. Available from: https://www.bgs.org.uk/sites/default/files/content/resources/files/2018-05-23/fff2_full.pdf

Appendix A
Review Search Strategy

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

---

1 late* life.tw. (16019)

2 age factors/ (452959)

3 (frail* or sarcop?eni* or prefrailty).mp. (26267)

4 Sarcopenia/ (2686)

5 function* status.tw. (24184)

6 activities of daily living.tw. (23276)

7 "activities of daily living"/ (63462)

8 (physical adj3 function).tw. (14334)

9 Hypertension/ (238653)

10 ((high or elevat*or rais*) adj2 blood pressure).tw. (16209)

11 (blood pressure adj6 goal?).mp. (2028)

12 Blood Pressure Determination/ (27584)

13 epidemiologic studies/ (8301)

14 exp case control studies/ (998349)

15 exp cohort studies/ (1905682)

16 case control.tw. (116518)

17 (cohort adj (study or studies)).tw. (164282)

18 cohort analy*.tw. (6584)

19 (follow up adj (study or studies)).tw. (48680)

20 (observational adj (study or studies)).tw. (85828)

21 Longitudinal.tw. (219409)

22 retrospective.tw. (451275)

23 cross sectional.tw. (291356)

24 cross-sectional studies/ (283885)

25 survey.tw. (466607)

26 survey/ (429354)

27 or/13-26 [epidemiology filter] (3317120)

28 or/9-12 (264635)

29 or/1-8 (587455)

30 27 and 28 and 29 (

Appendix B
Method of Extraction for Meta-Analyses

Comparison to a standard reference:

Where we have two hazard ratios comparing groups B and C to group A, and we want a hazard ratio comparing group C to group B:

	A	B	C
HR (95% CI)	1	0.89 (0.62, 1.28)	0.94(0.65,1.35)

We will find HRs and SEs, then find SE for log difference, C − B

First we switch A & B:

log(0.89) = −0.11653382

log(0.62) = −0.4780358

log(1.28) = 0.24686008

Switching the signs of these gives the ratio for the log HR for A with B as standard.

Now find the standard error:

(log(1.28) − log(0.62)) /(2*1.96) = 0.18492242

Note that “*” means “multiply”. Later, “^2” means “raised to the power 2” or “squared” and “sqrt” means “square root”.

Convert back to natural scale and find the confidence interval:

exp(−log(0.89) − 1.96*(log(1.28) − log(0.62)) /(2*1.96)) = 0.78198938

exp(−log(0.89) + 1.96*(log(1.28) − log(0.62)) /(2*1.96)) = 1.6144297

Hence the estimate is 1.12 and the 95% confidence interval is 0.78 to 1.61.

Now for C with B as standard, which is more difficult. The problem is that we need to combine both HRs.

log(0.94) = −0.0618754

log(0.65) = −0.43078292

log(1.35) = 0.30010459

SE: (log(1.35) − log(0.65))/(2*1.96) = 0.1864509

Difference, C – B:

log(HR) = log(0.94) − log(0.89) = 0.05465841

HR = exp(log(0.94) − log(0.89)) = 1.0561798

Now, we can calculate the SE for the difference, by taking the square root of the sum of the squares of the two SEs. However, there is an assumption, that the estimates for B/A and C/A are independent, which is clearly false.

SE(difference) = sqrt(((log(1.35) − log(0.65))/(2*1.96))^2 + ((log(1.28) − log(0.62)) /(2*1.96))^2) = 0.26260281

Transform back and get 95% CI:

exp(log(0.94) − log(0.89) − 1.96*sqrt(((log(1.35) − log(0.65))/(2*1.96))^2 + ((log(1.28) − log(0.62)) /(2*1.96))^2)) = 0.63125644

exp(log(0.94) − log(0.89) + 1.96*sqrt(((log(1.35) − log(0.65))/(2*1.96))^2 + ((log(1.28) − log(0.62)) /(2*1.96))^2)) = 1.7671356

The estimated 95% CI for the HR is 0.631 to 1.767.

This is plausible, in that it contains the estimate 1.056 comfortably. It looks wide, compare to the CIs for B/A and C/A. This is because of the false assumption of independence. If we had all the data, we could allow for the dependence and obtain a smaller SE and narrower confidence interval. However, we don’t. So we would use this as an approximation, with the caveat that the standard error may be too big, which may slightly reduce the contribution of this study to the overall estimate.

Appendix C
Source of code lists per study variable

Variable	Reference	Code source	Code type
CTV-2 Read Codes			
BP recording	CALIBER Phenotype	https://caliberresearch.org/portal/phenotypes/bloodpressure	CTV2
BP-lowering medications	BNF	Manual Review of TRUD (see below)	CTV2
Cardiovascular risk factors measured before or at start of study			
BMI		Manual Review of TRUD	CTV2
Cholesterol: HDL Ratio	CALIBER Codelists: lipids	https://www.caliberresearch.org/portal/codelists	CTV2
Coronary heart disease	CALIBER Phenotype	https://caliberresearch.org/portal/phenotypes/coronaryheartdisease	CTV2
Stable angina	CALIBER Codelists	https://caliberresearch.org/portal/codelists	CTV2
Unstable angina	CALIBER Phenotype	https://caliberresearch.org/portal/phenotypes/unstableangina	CTV2
Myocardial infarction	CALIBER Phenotype	https://caliberresearch.org/portal/phenotypes/acutemyocardialinfarction	CTV2
CABG	CALIBER Codelists	https://caliberresearch.org/portal/codelists	CTV2
PCI	CALIBER Codelists	https://caliberresearch.org/portal/codelists	CTV2
Diabetes I & II	CALIBER Phenotype	https://caliberresearch.org/portal/phenotypes/diabetes	CTV2
FH CVD	CALIBER Codelists	https://caliberresearch.org/portal/show/fh_chd_gprd	CTV2
Heart failure	CALIBER Phenotype	https://caliberresearch.org/portal/phenotypes/heartfailure	CTV2
Hypertension	CALIBER Phenotype	https://caliberresearch.org/portal/phenotypes/hypertension	CTV2
Lipid lowering therapy	BNF	NHS TRUD	CTV2
Peripheral arterial disease	CALIBER Phenotype	https://caliberresearch.org/portal/phenotypes/peripheralarterialdisease	CTV2
Smoking	Clinical Codes – Study by Joseph et al (463)	https://clinicalcodes.rss.mhs.man.ac.uk/medcodes/article/52/codelist/res52-smoking-readcodes/	CTV2
Stroke	CALIBER	https://caliberresearch.org/portal/phenoty	CTV2

	Phenoytpe	pes/strokeunspecified) https://caliberresearch.org/portal/phenotypes/strokesubarachnoid https://caliberresearch.org/portal/phenotypes/strokeischaemic	
Frailty			
	eFI with permission of Prof Andy Clegg/ Dr Joe Hollinghurst for code	eFI validation in SAIL(407)	CTV2
Comorbidities measured before or at start of study			
Asthma	QOF Code list	https://clinicalcodes.rss.mhs.man.ac.uk/medcodes/article/1/codelist/asthma/	CTV2
Atrial fibrillation	CALIBER Phenotype	https://www.caliberresearch.org/portal/phenotypes/atrialfibrillation	CTV2
Cancer	DISCO Cancer Team given permission by Dr Willie Hamilton	http://medicine.exeter.ac.uk/research/healthresearch/disco/	CTV2
Chronic kidney disease	CALIBER Codelists	https://caliberresearch.org/portal/show/ckdstage_gprd	CTV2
COPD	CALIBER Codelists	https://www.caliberresearch.org/portal/show/copd_gprd	CTV2
Dementia	Clinical Codes- Study by Grant et al (464)	https://clinicalcodes.rss.mhs.man.ac.uk/medcodes/article/11/codelist/res11-dementia/	CTV2
Ethnicity	2011 UK Census	http://www.datadictionary.wales.nhs.uk/#!WordDocuments/ethnicgroup.htm	CTV2
Epilepsy	QOF	https://clinicalcodes.rss.mhs.man.ac.uk/medcodes/article/1/codelist/epilepsy/	CTV2
Learning Difficulty	NHS England / Southern Health NHS Foundation Trust SystmOne codes	https://bmjopen.bmj.com/content/5/12/e009010	CTV2
Mental health illnesses	Clinical Codes – Study by Abel et al (465)	https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(19)30059-3/fulltext#seccestitle70	CTV2
Osteoporosis	Clinical Codes – Study by O'Connell et al (466)	https://clinicalcodes.rss.mhs.man.ac.uk/medcodes/article/1/codelist/osteoporosis/ https://www.sciencedirect.com/science/article/pii/S875632821930170X	CTV2

Rheumatoid arthritis	CALIBER Phenotype	https://caliberresearch.org/portal/phenotypes/rheumatoidarthritis	CTV2
Outcomes measured during follow up			
Myocardial Infarction	CALIBER Codelists	https://caliberresearch.org/portal/show/mi_hes	ICD10
PCI	CALIBER Codelists	https://www.caliberresearch.org/portal/show/pci_opcs	ICD10
CABG	CALIBER Codelists	https://www.caliberresearch.org/portal/show/cabg_opcs	ICD10
New Heart Failure	CALIBER Phenotypes	https://caliberresearch.org/portal/phenotypes/heartfailure	ICD10
Stroke haemorrhagic	CALIBER Codelists CALIBER Phenoytpe	https://caliberresearch.org/portal/show/cerebral_stroke_hes https://caliberresearch.org/portal/phenotypes/strokeintracerebral	ICD10
Ischaemic	CALIBER Codelists CALIBER Phenoytpe	https://caliberresearch.org/portal/show/ischaem_stroke_hes https://caliberresearch.org/portal/phenotypes/strokeischaemic	ICD10
SAH	CALIBER Codelists CALIBER Phenotype	https://caliberresearch.org/portal/show/haem_stroke_hes https://caliberresearch.org/portal/phenotypes/strokesubarachnoid	ICD10
NOS	CALIBER Phenotype	https://caliberresearch.org/portal/phenotypes/strokeunspecified	ICD10
Sequelae	CALIBER Codelists	https://caliberresearch.org/portal/show/stroke_nos_hes	ICD10
Fall	HFS(467)	https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(18)30668-8.pdf	ICD10
Hypotension	HFS(467)	https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(18)30668-8.pdf	ICD10
AKI	HFS(467)	https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(18)30668-8.pdf	ICD10
Delirium	HFS(467)	https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(18)30668-8.pdf	ICD10
Urinary incontinence	HFS(467)	https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(18)30668-8.pdf	ICD10
Functional dependence	HFS(467)	https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(18)30668-8.pdf	ICD10
Electrolyte disturbance	HFS(467)	https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(18)30668-8.pdf	ICD10
Dementia	CALIBER Codelist	https://caliberresearch.org/portal/show/dementia_hes	ICD10
	HFS(467)	https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(18)30668-8.pdf	ICD10
	Clinical Codes- Study by Grant et al (464)	https://clinicalcodes.rss.mhs.man.ac.uk/medcodes/article/11/codelist/res11-dementia/	CTV2

AKI= acute kidney injury; BMI = body mass index; BNF = British National Formulary; BP= blood pressure; CALIBER = Cardiovascular disease research using linked bespoke studies and electronic health records; CTV-2 = Read

Version 2 codes; DISCO = Discovery of Symptomatic Cancer Optimally team; eFI = electronic Frailty Index; HFS = Hospital Frailty Score; ICD-10 = International Classification of Disease manual, 10th edition. NOS = Not Otherwise Specified; QOF = Quality Outcomes Framework; SAIL = Secure Anonymised Information Linkage; TRUD = Technology Reference data

Appendix D
Code lists for BP-lowering medications

6.9 Alpha blockers

2.5.4 Alpha-adrenoceptor blocking drugs		
Bethanidine	BETHANIDINE SULPHATE	bg1..
	BETANIDINE 10mg tablets	bg11.
	*BETHANIDINE 50mg tablets	bg12.
	*BENDOGEN 10mg tablets	bg13.
	*BENDOGEN 50mg tablets	bg14.
	*ESBATAL 10mg tablets	bg15.
	*ESBATAL 50mg tablets	bg16.
	BETANIDINE SULPHATE 10mg tablets	bg1y.
	BETANIDINE SULPHATE 50mg tablets	bg1z.
Clonidine	CLONIDINE HYDROCHLORIDE [ANTIHYPERTENSIVE]	bf1..
	CATAPRES 100micrograms tablets	bf11.
	CATAPRES 300micrograms tablets	bf12.
	CATAPRES PERLONGETS 250microgram m/r capsules	bf13.
	CATAPRES 150micrograms/mL injection	bf14.
	CLONIDINE 100microgram tablets	bf1w.
	CLONIDINE 300micrograms tablets	bf1x.
	CLONIDINE 250microgram m/r capsules	bf1y.
	CLONIDINE 150microgram/mL injection	bf1z.
Desbrisoquine	DEBRISOQUINE	bg2..
	*DECLINAX 10mg tablets	bg21.
	*DECLINAX 20mg tablets	bg22.
	*DEBRISOQUINE 10mg tablets	bg2y.
	*DEBRISOQUINE 20mg tablets	bg2z.
Doxazosin	DOXAZOSIN	bh6..
	DOXAZOSIN 1mg tablets	bh61.
	DOXAZOSIN 2mg tablets	bh62.
	DOXAZOSIN 4mg tablets	bh63.
	CARDURA 1mg tablets	bh64.
	CARDURA 2mg tablets	bh65.
	*CARDURA 4mg tablets	bh66.
	CARDURA XL 4mg m/r tablets	bh67.
	CARDURA XL 8mg m/r tablets	bh68.
	*CASCOR 2mg tablets	bh69.
	*CASCOR 4mg tablets	bh6A.
	DOXADURA 1mg tablets	bh6B.
	DOXADURA 2mg tablets	bh6C.
	DOXADURA 4mg tablets	bh6D.
	SLOCINX XL 4mg m/r tablets	bh6E.
	DOXADURA XL 4mg m/r tablets	bh6F.

	OXANDOSIN XL 4mg m/r tablets	bh6G.
	RAPORSIN XL 4mg m/r tablets	bh6H.
	DOXAZOSIN 8mg m/r tablets	bh6y.
	DOXAZOSIN 4mg m/r tablets	bh6z.
Indoramin	INDORAMIN	bh1..
	*BARATOL 25mg tablets	bh11.
	*BARATOL 50mg tablets	bh12.
	DORALESE TILTAB 20mg tablets	bh13.
	INDORAMIN 20mg tablets	bh14.
	INDORAMIN 25mg tablets	bh1y.
	INDORAMIN 50mg tablets	bh1z.
Methyldopa	METHYLDOPA	bf2..
	METHYLDOPA 125mg tablets	bf21.
	METHYLDOPA 250mg tablets	bf22.
	METHYLDOPA 500mg tablets	bf23.
	*ALDOMET 125mg tablets	bf24.
	ALDOMET 250mg tablets	bf25.
	ALDOMET 500mg tablets	bf26.
	ALDOMET 250mg/5mL oral mixture	bf27.
	*ALDOMET 250mg/5mL injection	bf28.
	*DOPAMET 125mg tablets	bf29.
	*DOPAMET 250mg tablets	bf2a.
	*DOPAMET 500mg tablets	bf2b.
	MEDOMET 250mg capsules	bf2c.
	MEDOMET 250mg tablets	bf2d.
	MEDOMET 500mg tablets	bf2e.
	*HYDROMET tablets	bf2f.
	*METALPHA 250mg tablets	bf2g.
	*METALPHA 500mg tablets	bf2h.
	METHYLDOPA+HYDROCHLOROTHIAZIDE 250mg/15mg tablets	bf2j.
	METHYLDOPA 250mg/5mL oral mixture	bf2v.
	METHYLDOPATE HYDROCHLORIDE 250mg/5mL injection	bf2w.
	METHYLDOPA 250mg capsules	bf2z.
Metirosine	METIROSINE	bk1..
	*DEMSER 250mg capsules	bk11.
	*METIROSINE 250mg capsules	bk1z.
Phenoxybenzamine	PHENOXYBENZAMINE 10mg capsules	bh2y.
	PHENOXYBENZAMINE 100mg/2mL injection	bh2z.
	PHENOXYBENZAMINE HYDROCHLORIDE [CARDIOVASCULAR USE]	bh2..
	DIBENYLINE [CVS] 10mg capsules	bh21.
	DIBENYLINE 100mg/2mL injection	bh22.
Prazosin	PRAZOSIN HYDROCHLORIDE	bh4..
	HYPOVASE 500micrograms tablets	bh41.
	HYPOVASE 1mg tablets	bh42.
	*HYPOVASE 2mg tablets	bh43.
	*HYPOVASE 5mg tablets	bh44.

	HYPOVASE BD STARTER PACK tablets	bh45.
	ALPHAVASE 500micrograms tablets	bh46.
	*ALPHAVASE 1mg tablets	bh47.
	*ALPHAVASE 2mg tablets	bh48.
	*ALPHAVASE 5mg tablets	bh49.
	KENTOVACE 500micrograms tablets	bh4A.
	KENTOVACE 1mg tablets	bh4B.
	KENTOVACE 2mg tablets	bh4C.
	KENTOVACE 5mg tablets	bh4D.
	PRAZOSIN HYDROCHLORIDE STARTER PACK 500micrograms+1mg tablets	bh4v.
	PRAZOSIN HYROCHLORIDE 500microgram tablets	bh4w.
	PRAZOSIN HYDROCHLORIDE 1mg tablets	bh4x.
	PRAZOSIN HYDROCHLORIDE 2mg tablets	bh4y.
	PRAZOSIN HYDROCHLORIDE 5mg tablets	bh4z.
Terazosin	TERAZOSIN 1mg tablets	bh5x.
	TERAZOSIN 2mg tablets	bh5z.
	TERAZOSIN 5mg tablets	bh55.
	TERAZOSIN 10mg tablets	bh56.
	TERAZOSIN HYDROCHLORIDE	bh5..
	HYTRIN 2mg tablets	bh51.
	HYTRIN 5mg tablets	bh52.
	HYTRIN 10mg tablets	bh53.
	HYTRIN STARTER PACK tablets	bh54.
	TERAZOSIN 5mg tablets	bh55.
	TERAZOSIN 10mg tablets	bh56.
	HYTRIN 1mg tablets	bh57.
	TERAZOSIN 1mg tablets	bh5x.
	TERAZOSIN STARTER PACK 1mg+2mg tablets	bh5y.
	TERAZOSIN 1mg+2mg+5mg tablets starter pack	gc5z.
	TERAZOSIN HYDROCHLORIDE [see chap b for generic preps]	gc5..
	HYTRIN BPH STARTER PACK tablets	gc51.
	HYTRIN BPH 2mg tablets	gc52.
	HYTRIN BPH 5mg tablets	gc53.
	HYTRIN BPH 10mg tablets	gc54.
	HYTRIN BPH 1mg tablets	gc55.

6.10 Angiotensin Converting Enzyme inhibitors (ACEi)

2.5.5 Renin-Angiotensin System Drugs (a) ACEi		
Captopril	CAPTOPRIL	bi1..
	ACEPRIL 12.5mg tablets	bi11.

	ACEPRIL 25mg tablets	bi12.
	ACEPRIL 25mg tablets x56	bi13.
	ACEPRIL 50mg tablets	bi14.
	ACEPRIL 50mg tablets x56	bi15.
	*CAPOTEN 12.5mg tablets	bi16.
	CAPOTEN 25mg tablets	bi17.
	CAPOTEN 25mg tablets x56	bi18.
	CAPOTEN 50mg tablets	bi19.
	*HYPAPRIL 12.5mg tablets	bi1A.
	*HYPAPRIL 25mg tablets	bi1B.
	*HYPAPRIL 50mg tablets	bi1C.
	*CAPTO-CO 25mg/12.5mg tablets	bi1D.
	*CAPTO-CO 50mg/25mg tablets	bi1E.
	CO-ZIDOCAPT 25mg/12.5mg tablet	bi1F.
	*CO-ZIDOCAPT 50mg/25mg tablets	bi1G.
	NOYADA 5mg/5mL oral solution	bi1H.
	CAPTOPRIL 5mg/5mL oral solution	bi1I.
	NOYADA 25mg/5mL oral solution	bi1J.
	CAPTOPRIL 25mg/5mL oral solution	bi1K.
	CAPOTEN 50mg tablets x56	bi1a.
	ACEZIDE 50mg tablets x56	bi1b.
	*CAPOZIDE 50mg tablets x28	bi1c.
	*CAPOZIDE LS 25mg tabletsx28CP	bi1d.
	CAPTOPRIL+HYDROCHLOROTHIAZIDE 25mg/12.5mg tablets	bi1e.
	CAPTOPRIL+HYDROCHLOROTHIAZIDE 50mg/25mg tablets	bi1f.
	ECOPACE 12.5mg tablets	bi1g.
	ECOPACE 25mg tablets	bi1h.
	ECOPACE 50mg tablets	bi1i.
	*KAPLON 12.5mg tablets	bi1j.
	*KAPLON 25mg tablets	bi1k.
	*KAPLON 50mg tablets	bi1l.
	*HYTENEZE 12.5 tablets	bi1m.
	*HYTENEZE 25 tablets	bi1n.
	*HYTENEZE 50 tablets	bi1o.
	*TENSOPRIL 12.5mg tablets	bi1p.
	*TENSOPRIL 25mg tablets	bi1q.
	*TENSOPRIL 50mg tablets	bi1r.
	CAPOZIDE 50mg/25mg tablets	bi1s.
	CAPTOPRIL 12.5mg tablets	bi1v.
	CAPTOPRIL 25mg tablets	bi1w.
	CAPTOPRIL 25mg tablets x56	bi1x.
	CAPTOPRIL 50mg tablets x56	bi1y.
	CAPTOPRIL 50mg tablets	bi1z.
Cilazapril	CILAZAPRIL	bi8..
	CILAZAPRIL 250micrograms tablets	bi81.
	CILAZAPRIL 500micrograms tablets	bi82.
	*CILAZAPRIL 1mg tablets	bi83.
	*CILAZAPRIL 2.5mg tablets	bi84.

	*VASCACE 250micrograms tablets	bi85.
	*VASCACE 500micrograms tablets	bi86.
	*VASCACE 1mg tablets	bi87.
	*VASCACE 2.5mg tablets	bi88.
	*VASCACE 5mg tablets	bi89.
	CILAZAPRIL 5mg tablets	bi8a.
Enalapril	ENALAPRIL MALEATE	bi2..
	INNOVACE 2.5mg tablets	bi21.
	INNOVACE 5mg tablets	bi22.
	INNOVACE 5mg tablets x28	bi23.
	INNOVACE 10mg tablets	bi24.
	INNOVACE 10mg tablets x28	bi25.
	INNOVACE 20mg tablets	bi26.
	INNOVACE 20mg tablets x28	bi27.
	INNOZIDE 20/12.5mg tablets	bi28.
	INNOVACE tablets titration pack	bi29.
	*ENALAPRIL MALEATE 2.5mg wafer	bi2A.
	*ENALAPRIL MALEATE 5mg wafer	bi2B.
	*ENALAPRIL MALEATE 10mg wafer	bi2C.
	*ENALAPRIL MALEATE 20mg wafer	bi2D.
	*INNOVACE MELT 2.5mg wafer	bi2E.
	*INNOVACE MELT 5mg wafer	bi2F.
	*INNOVACE MELT 10mg wafer	bi2G.
	*INNOVACE MELT 20mg wafer	bi2H.
	*PRALENAL 2.5mg tablets	bi2J.
	*PRALENAL 5mg tablets	bi2K.
	*PRALENAL 10mg tablets	bi2L.
	*PRALENAL 20mg tablets	bi2M.
	ENALAPRIL MALEATE tablets titration pack	bi2a.
	ENALAPRIL MALEATE+HYDROCHLOROTHIAZIDE 20mg/12.5mg tablets	bi2b.
	ENALAPRIL MALEATE 2.5mg tablets	bi2t.
	ENALAPRIL MALEATE 5mg tablets	bi2u.
	ENALAPRIL MALEATE 5mg tablets x28	bi2v.
	ENALAPRIL MALEATE 10mg tablets	bi2w.
	ENALAPRIL MALEATE 10mg tablets x28	bi2x.
	ENALAPRIL MALEATE 20mg tablets	bi2y.
	ENALAPRIL MALEATE 20mg tablets x28	bi2z.
Sodium Fosinopril	SODIUM FOSINOPRIL	bi7..
	FOSINOPRIL 10mg tablets	bi71.
	FOSINOPRIL 20mg tablets	bi72.
	*STARIL 10mg tablets	bi73.
	*STARIL 20mg tablets	bi74.
Imidapril	IMIDAPRIL HYDROCHLORIDE	biB..
	TANATRIL 5mg tablets	biB1.
	TANATRIL 10mg tablets	biB2.
	TANATRIL 20mg tablets	biB3.
	IMIDAPRIL HYDROCHLORIDE 20mg	biBx.

	tablets	
	IMIDAPRIL HYDROCHLORIDE 5mg tablets	biBy.
	IMIDAPRIL HYDROCHLORIDE 10mg tablets	biBz.
Lisinopril	LISINOPRIL	bi3..
	LISINOPRIL 2.5mg tablets	bi31.
	LISINOPRIL 5mg tablets	bi32.
	LISINOPRIL 10mg tablets	bi33.
	LISINOPRIL 20mg tablets	bi34.
	*CARACE 2.5mg tablets	bi35.
	*CARACE 5mg tablets 28CP	bi36.
	*CARACE 5mg tablets	bi37.
	*CARACE 10mg tablets 28CP	bi38.
	*CARACE 10mg tablets	bi39.
	*CARACE 20mg tablets 28CP	bi3a.
	*CARACE 20mg tablets	bi3b.
	*ZESTRIL 2.5mg tablets 28CP	bi3c.
	*ZESTRIL 2.5mg tablets	bi3d.
	ZESTRIL 5mg tablets 28CP	bi3e.
	ZESTRIL 5mg tablets	bi3f.
	ZESTRIL 10mg tablets 28CP	bi3g.
	ZESTRIL 10mg tablets	bi3h.
	ZESTRIL 20mg tablets 28CP	bi3i.
	ZESTRIL 20mg tablets	bi3j.
	CARACE 20 PLUS tablets	bi3k.
	*CARACE 10 PLUS tablets	bi3l.
	*ZESTORETIC tablets 28CP	bi3m.
	ZESTORETIC 20/12.5mg tablets	bi3n.
	LISINOPRIL+HYDROCHLOROTHIAZIDE 20mg/12.5mg tablets	bi3p.
	*ZESTRIL 2.5mg starter pack	bi3q.
	LISINOPRIL 2.5mg tablets starter pack	bi3r.
	ZESTORETIC 10/12.5mg tablets	bi3s.
	LISINOPRIL+HYDROCHLOROTHIAZIDE 10mg/12.5mg tablets	bi3t.
	*CARALPHA 10/12.5mg tablets	bi3u.
	*CARALPHA 20/12.5mg tablets	bi3v.
	LISICOSTAD HCT 20/12.5mg tablets	bi3w.
	LISICOSTAD HCT 10/12.5mg tablets	bi3x.
Moexipril	MOEXIPRIL	biA..
	MOEXIPRIL HYDROCHLORIDE 7.5mg tablets	biA1.
	MOEXIPRIL HYDROCHLORIDE 15mg tablets	biA2.
	PERDIX 7.5mg tablets	biA3.
	PERDIX 15mg tablets	biA4.
Perindopril Arginine	PERINDOPRIL ARGININE	biC..
	COVERSYL ARGININE 2.5mg tablets	biC1.
	PERINDOPRIL ARGININE 2.5mg tablets	biC2.

	COVERSYL ARGININE 5mg tablets	biC3.
	PERINDOPRIL ARGININE 5mg tablets	biC4.
	COVERSYL ARGININE 10mg tablets	biC5.
	PERINDOPRIL ARGININE 10mg tablets	biC6.
	COVERSYL ARGININE PLUS 5mg/1.25mg tablets	biC7.
	PERINDOPRIL ARGININE+INDAPAMIDE 5mg/1.25mg tablets	biC8.
	PERINDOPRIL ERBUMINE	bi5..
	PERINDOPRIL ERBUMINE 2mg tablets	bi51.
	PERINDOPRIL ERBUMINE 4mg tablets	bi52.
	*COVERSYL 2mg tablets	bi53.
	*COVERSYL 4mg tablets	bi54.
	PERINDOPRIL ERBUMINE+INDAPAMIDE 4mg/1.25mg tablets	bi55.
	COVERSYL PLUS 4mg/1.25mg tablets	bi56.
	PERINDOPRIL ERBUMINE 8mg tablets	bi57.
	*COVERSYL 8mg tablets	bi58.
	PERINDOPRIL TERT-BUTYLAMINE	bi5..
	PERINDOPRIL ERBUMINE 2mg tablets	bi51.
	PERINDOPRIL ERBUMINE 4mg tablets	bi52.
	*COVERSYL 2mg tablets	bi53.
	*COVERSYL 4mg tablets	bi54.
	PERINDOPRIL ERBUMINE+INDAPAMIDE 4mg/1.25mg tablets	bi55.
	COVERSYL PLUS 4mg/1.25mg tablets	bi56.
	PERINDOPRIL ERBUMINE 8mg tablets	bi57.
	*COVERSYL 8mg tablets	bi58.
Quinapril	QUINAPRIL	bi4..
	QUINAPRIL 5mg tablets	bi41.
	QUINAPRIL 10mg tablets	bi42.
	QUINAPRIL 20mg tablets	bi43.
	ACCUPRO 5mg tablets 28CP	bi44.
	ACCUPRO 10mg tablets 28CP	bi45.
	ACCUPRO 20mg tablets 28CP	bi46.
	ACCURETIC tablets	bi47.
	QUINAPRIL+HYDROCHLOROTHIAZIDE 10/12.5mg tablets	bi48.
	ACCUPRO 40mg tablets	bi49.
	QUINAPRIL 40mg tablets	bi4A.
	QUINIL 5mg tablets	bi4B.
	QUINIL 10mg tablets	bi4C.
	QUINIL 20mg tablets	bi4D.
	QUINIL 40mg tablets	bi4E.
Ramipril	RAMIPRIL	bi6..
	RAMIPRIL 1.25mg tablets	bi6B.
	TRITACE 1.25mg tablets	bi6z.
	RAMIPRIL 2.5mg tablets	bi6C.
	TRITACE 2.5mg tablets	bi6y.
	RAMIPRIL 5mg tablets	bi6D.

	TRITACE 5mg tablets	bi6x.
	RAMIPRIL 10mg tablets	bi6E.
	TRITACE 10mg tablets	bi6w.
	RAMIPRIL 1.25mg capsules	bi61.
	*RANACE 1.25mg capsules	bi6s.
	*TRITACE 1.25mg capsules	bi64.
	RAMIPRIL 2.5mg capsules	bi62.
	*LOPACE 2.5mg capsules	bi6t.
	*RANACE 2.5mg capsules	bi6r.
	*TRITACE 2.5mg capsules	bi65.
	RAMIPRIL 5mg capsules	bi63.
	*LOPACE 5mg capsules	bi6u.
	*RANACE 5mg capsules	bi6q.
	RAMIPRIL 10mg capsules	bi67.
	RAMIPRIL 10mg capsules	bi67.
	*LOPACE 10mg capsules	bi6v.
	*RANACE 10mg capsules	bi6p.
	*TRITACE 10mg capsules	bi68.
	RAMIPRIL 2.5mg+5mg+10mg capsules titration pack	bi69.
	TRITACE Titration Pack capsules	bi6A.
	RAMIPRIL 2.5mg/5mL oral solution	bi6G.
	FELODIPINE+RAMIPRIL	bA1..
	FELODIPINE+RAMIPRIL 2.5mg/2.5mg tablets	bA1y.
	TRIAPIN MITE 2.5mg/2.5mg tablets	bA11.
	FELODIPINE+RAMIPRIL 5mg/5mg tablets	bA1z.
	TRIAPIN 5mg/5mg tablets	bA12.
	RAMIPRIL 2.5mg+5mg+10mg tablets titration pack	bi6F.
	TRITACE Titration Pack tablets	bi6o.
Trandolapril	TRANDOLAPRIL	bi9..
	TRANDOLAPRIL 500micrograms capsules	bi91.
	TRANDOLAPRIL 1mg capsules	bi92.
	TRANDOLAPRIL 2mg capsules	bi93.
	*GOPTEN 500micrograms capsules	bi94.
	*GOPTEN 1mg capsules	bi95.
	*GOPTEN 2mg capsules	bi96.
	*ODRIK 500micrograms capsules	bi97.
	*ODRIK 1mg capsules	bi98.
	*ODRIK 2mg capsules	bi99.
	*GOPTEN 4mg capsules	bi9A.
	TRANDOLAPRIL 4mg capsules	bi9z.
	TRANDOLAPRIL+VERAPAMIL HYDROCHLORIDE	bk6..
	TRANDOLAPRIL+VERAPAMIL HYDROCHLORIDE 2mg/180mg m/r capsules	bk61.
	*TARKA 2mg/180mg m/r capsules	bk62.

6.11 Angiotensin Receptor Blockers (ARBs)

(b) Angiotensin Receptor Blockers		
Azilsartan	AZILSARTAN	bkJ..
	EDARBI 20mg tablets	bkJ1.
	AZILSARTAN MEDOXOMIL 20mg tablets	bkJ2.
	EDARBI 40mg tablets	bkJ3.
	AZILSARTAN MEDOXOMIL 40mg tablets	bkJ4.
	EDARBI 80mg tablets	bkJ5.
	AZILSARTAN MEDOXOMIL 80mg tablets	bkJ6.
Candesartan Cilexetil	LOSARTAN	bk3..
	CANDESARTAN CILEXETIL 2mg tablets	bk71.
	CANDESARTAN CILEXETIL 4mg tablets	bk72.
	CANDESARTAN CILEXETIL 8mg tablets	bk73.
	CANDESARTAN CILEXETIL 16mg tablets	bk74.
	AMIAS 2mg tablets	bk75.
	AMIAS 4mg tablets	bk76.
	AMIAS 8mg tablets	bk77.
	AMIAS 16mg tablets	bk78.
	AMIAS 32mg tablets	bk79.
	CANDESARTAN CILEXETIL 32mg tablets	bk7z.
Eprosartan	EPROSARTAN	bk9..
	TEVETEN 300mg tablets	bk91.
	*TEVETEN 400mg tablets	bk92.
	TEVETEN 600mg tablets	bk93.
	EPROSARTAN 300mg tablets	bk9x.
	EPROSARTAN 400mg tablets	bk9y.
	EPROSARTAN 600mg tablets	bk9z.
Irbesartan	IRBESARTAN	bk5..
	IRBESARTAN 75mg tablets	bk51.
	IRBESARTAN 150mg tablets	bk52.
	IRBESARTAN 300mg tablets	bk53.
	APROVEL 75mg tablets	bk54.
	APROVEL 150mg tablets	bk55.
	APROVEL 300mg tablets	bk56.
	COAPROVEL 150mg/12.5mg tablets	bk57.
	COAPROVEL 300mg/12.5mg tablets	bk58.
	COAPROVEL 300mg/25mg tablets	bk59.
	IRBESARTAN+HYDROCHLOROTHIAZIDE 300mg/25mg tablets	bk5x.
	IRBESARTAN+HYDROCHLOROTHIAZIDE 300mg/12.5mg tablets	bk5y.
	IRBESARTAN+HYDROCHLOROTHIAZIDE 150mg/12.5mg tablets	bk5z.
Losartan	LOSARTAN	bk3..
	LOSARTAN POTASSIUM 25mg tablets	bk31.
	LOSARTAN POTASSIUM 50mg tablets	bk32.
	COZAAR HALF-STRENGTH 25mg tablets	bk33.

	COZAAR 50mg tablets	bk34.
	LOSARTAN POTASSIUM+HYDROCHLOROTHIAZIDE 50mg/12.5mg tablets	bk35.
	COZAAR-COMP 50mg/12.5mg tablets	bk36.
	LOSARTAN POTASSIUM 100mg tablets	bk37.
	COZAAR 100mg tablets	bk38.
	COZAAR-COMP 100mg/25mg tablets	bk39.
	COZAAR-COMP 100mg/12.5mg tablets	bk3A.
	COZAAR 12.5mg tablets	bk3B.
	LOSARTAN POTASSIUM 12.5mg tablets	bk3C.
	COZAAR 2.5mg/mL oral suspension	bk3D.
	LOSARTAN POTASSIUM 2.5mg/mL oral suspension	bk3E.
	ZOVENCAL 25mg tablets	bk3F.
	ZOVENCAL 50mg tablets	bk3G.
	ZOVENCAL 100mg tablets	bk3H.
	LOSARTAN POTASSIUM+HYDROCHLOROTHIAZIDE 100mg/12.5mg tablets	bk3y.
	LOSARTAN POTASSIUM+HYDROCHLOROTHIAZIDE 100mg/25mg tablets	bk3z.
Olmesartan	OLMESARTAN	bkB..
	OLMESARTAN MEDOXOMIL 10mg tablets	bkB1.
	OLMESARTAN MEDOXOMIL 20mg tablets	bkB2.
	OLMESARTAN MEDOXOMIL 40mg tablets	bkB3.
	OLMETEC 10mg tablets	bkB4.
	OLMETEC 20mg tablets	bkB5.
	OLMETEC 40mg tablets	bkB6.
	OLMESARTAN+AMLODIPINE	bkH..
	SEVIKAR 20mg/5mg tablets	bkH1.
	SEVIKAR 40mg/5mg tablets	bkH2.
	SEVIKAR 40mg/10mg tablets	bkH3.
	OLMESARTAN MEDOXOMIL+AMLODIPINE 40mg/10mg tablets	bkHx.
	OLMESARTAN MEDOXOMIL+AMLODIPINE 40mg/5mg tablets	bkHy.
	OLMESARTAN MEDOXOMIL+AMLODIPINE 20mg/5mg tablets	bkHz.
	HYDROCHLOROTHIAZIDE + OLMESARTAN	bkC..
	OLMETEC PLUS 20mg/12.5mg tablets	bkC1.
	OLMETEC PLUS 20mg/25mg tablets	bkC2.
	OLMETEC PLUS 40mg/12.5mg tablets	bkC3.
	OLMESARTAN+HYDROCHLOROTHIAZIDE 40mg/12.5mg tablets	bkCx.

	OLMESARTAN + HYDROCHLOROTHIAZIDE 20mg/25mg tablets	bkCy.
	OLMESARTAN + HYDROCHLOROTHIAZIDE 20mg/12.5mg tablets	bkCz.
	OLMESARTAN MEDOXOMIL 10mg tablets	bkB1.
	OLMESARTAN MEDOXOMIL 20mg tablets	bkB2.
	OLMESARTAN MEDOXOMIL 40mg tablets	bkB3.
	OLMESARTAN+AMLODIPINE+HYDROCHLOROTHIAZIDE	bkI..
	SEVIKAR HCT 20mg/5mg/12.5mg tablets	bkI1.
	SEVIKAR HCT 40mg/5mg/12.5mg tablets	bkI2.
	SEVIKAR HCT 40mg/10mg/12.5mg tablets	bkI3.
	SEVIKAR HCT 40mg/5mg/25mg tablets	bkI4.
	SEVIKAR HCT 40mg/10mg/25mg tablets	bkI5.
Telmisartan	TELMISARTAN	bk8..
	TELMISARTAN 40mg tablets	bk81.
	TELMISARTAN 80mg tablets	bk82.
	MICARDIS 40mg tablets	bk83.
	MICARDIS 80mg tablets	bk84.
	MICARDIS 20mg tablets	bk85.
	MICARDISPLUS 40mg/12.5mg tablets	bk86.
	MICARDISPLUS 80mg/12.5mg tablets	bk87.
	MICARDISPLUS 80mg/25mg tablets	bk88.
	TELMISARTAN+HYDROCHLOROTHIAZIDE 80mg/25mg tablets	bk8w.
	TELMISARTAN+HYDROCHLOROTHIAZIDE 40mg/12.5mg tablets	bk8x.
	TELMISARTAN+HYDROCHLOROTHIAZIDE 80mg/12.5mg tablets	bk8y.
	TELMISARTAN 20mg tablets	bk8z.
	VALSARTAN	bk4..
Valsartan	VALSARTAN 40mg capsules	bk41.
	VALSARTAN 80mg capsules	bk42.
	VALSARTAN 160mg capsules	bk43.
	DIOVAN 40mg capsules	bk44.
	DIOVAN 80mg capsules	bk45.
	DIOVAN 160mg capsules	bk46.
	CO-DIOVAN 160mg/12.5mg tablets	bk47.
	CO-DIOVAN 160mg/25mg tablets	bk48.
	CO-DIOVAN 80mg/12.5mg tablets	bk49.
	DIOVAN 40mg tablets	bk4A.
	DIOVAN 40mg tablets	bk4A.
	DIOVAN 3mg/mL oral solution	bk4C.
	VALSARTAN 80mg tablets	bk4s.
	VALSARTAN 160mg tablets	bk4t.
	VALSARTAN 3mg/mL oral solution	bk4u.
	VALSARTAN 320mg tablets	bk4v.
	VALSARTAN 40mg tablets	bk4w.

	VALSARTAN+HYDROCHLOROTHIAZIDE 80mg/12.5mg tablets	bk4x.
	VALSARTAN+HYDROCHLOROTHIAZIDE 160mg/25mg tablets	bk4y.
	VALSARTAN+HYDROCHLOROTHIAZIDE 160mg/12.5mg tablets	bk4z.
	AMLODIPINE + VALSARTAN	bkD..
	AMLODIPINE+VALSARTAN 5mg/80mg tablets	bkD1.
	AMLODIPINE+VALSARTAN 5mg/160mg tablets	bkD2.
	AMLODIPINE+VALSARTAN 10mg/160mg tablets	bkD3.
	EXFORGE 10mg/160mg tablets	bkDx.
	EXFORGE 5mg/160mg tablets	bkDy.
	EXFORGE 5mg/80mg tablets	bkDz.

6.12 Beta-adrenoceptor blocking drugs

BNF Chapter 2.4 Beta-Adrenoceptor Blocking Drugs	Source: NHS TRUD dictionary CTV2 codes	
Beta blocker	BETA-ADRENOCEPTOR BLOCKERS	bd...
Acebutolol	ACEBUTOLOL	bd2..
	SECTRAL 100mg capsules	bd21.
	SECTRAL 200mg capsules	bd22.
	SECTRAL 400mg tablets	bd23.
	*SECTRAL 10mg/2mL injection	bd24.
	ACEBUTOLOL 100mg capsules	bd2w.
	ACEBUTOLOL 200mg capsules	bd2x.
	ACEBUTOLOL 400mg tablets	bd2y.
	*ACEBUTOLOL 10mg/2mL injection	bd2z.
Atenolol	Atenolol	bd3..
	TENORMIN 100mg tablets	bd31.
	TENORMIN 25mg/5mL syrup	bd32.
	TENORMIN 5mg/10mL injection	bd33.
	TENORMIN LS 50mg tablets	bd34.
	ATENOLOL 50mg tablets	bd35.
	ATENOLOL 100mg tablets	bd36.
	*TENORMIN CCU PACK	bd37.
	*BETA-ADALAT 50/20mg capsules	bd38.
	*TENIF 50/20mg capsules	bd39.
	*ANTIPRESSAN 50mg tablets	bd3a.
	*ANTIPRESSAN 100mg tablets	bd3b.
	*TENORMIN 25 tablets	bd3c.
	*VASATEN 50mg tablets	bd3d.
	*VASATEN 100mg tablets	bd3e.

	ATENIX 50mg tablets	bd3f.
	ATENIX 100mg tablets	bd3g.
	*TOTAMOL 50mg tablets	bd3h.
	*TOTAMOL 100mg tablets	bd3i.
	ATENOLOL 25mg tablets	bd3j.
	*TOTAMOL 25mg tablets	bd3k.
	*ANTIPRESSAN 25mg tablets	bd3l.
	ATENOLOL 25mg/5mL syrup	bd3x.
	ATENOLOL 5mg/10mL injection	bd3y.
	ATENIX 25mg tablets	bd3z.
	ATENOLOL+CHLORTHALIDONE 100mg/25mg tablets	bden.
	ATENOLOL+NIFEDIPINE 50mg/20mg m/r capsules	bdez.
	ATENOLOL+CHLORTHALIDONE 50mg/12.5mg tablets	bdem.
	ATENOLOL+CO-AMILOZIDE 50mg/2.5mg/25mg capsules	bdey.
	KALTEN capsules	bde7.
	TENIF 50/20mg capsules	bdet.
	ATENIXCO 50/12.5mg tablets	bdeo.
	ATENOLOL+NIFEDIPINE 50mg/20mg m/r capsules	bdez.
	TENORETIC tablets	bdeh.
	TENORET-50 tablets	bdeg.
	TOTARETIC 100mg/25mg tablets	bdeO.
	TOTARETIC 50mg/12.5mg tablets	bdeN.
Betaxolol	BETAXOLOL HCL [B-BLOCKER]	bd4..
	*KERLONE 20mg tablets	bd41.
	BETAXOLOL HYDROCHLORIDE 20mg tablets	bd4z.
Bisoprolol	BISOPROLOL FUMARATE	bdf..
	BISOPROLOL FUMARATE 5mg tablets	bdf1.
	BISOPROLOL FUMARATE 10mg tablets	bdf2.
	*MONOCOR 5mg tablets	bdf3.
	*MONOCOR 10mg tablets	bdf4.
	*EMCOR LS 5mg tablets	bdf5.
	*EMCOR 10mg tablets	bdf6.
	*MONOZIDE-10 tablets	bdf7.
	BISOPROLOL FUMARATE+HYDROCHLOROTHIAZIDE 10mg/6.25mg tablets	bdf8.
	CARDICOR 1.25mg tablets	bdf9.
	CARDICOR 2.5mg tablets	bdfA.
	CARDICOR 3.75mg tablets	bdfB.
	CARDICOR 5mg tablets	bdfC.
	CARDICOR 7.5mg tablets	bdfD.
	CARDICOR 10mg tablets	bdfE.
	*BIPRANIX 5mg tablets	bdfF.
	*BIPRANIX 10mg tablets	bdfG.

	*SOLOC 5mg tablets	bdfH.
	*SOLOC 10mg tablets	bdfI.
	VIVACOR 10mg tablets	bdfJ.
	VIVACOR 5mg tablets	bdfK.
	CONGESCOR 1.25mg tablets	bdfL.
	CONGESCOR 2.5mg tablets	bdfM.
	BISOPROLOL FUMARATE 1.25mg tablets	bdfw.
	BISOPROLOL FUMARATE 2.5mg tablets	bdfx.
	BISOPROLOL FUMARATE 3.75mg tablets	bdfy.
	BISOPROLOL FUMARATE 7.5mg tablets	bdfz.
Carvedilol	CARVEDILOL	bdl..
	*EUCARDIC 12.5 tablets	bdl1.
	*EUCARDIC 25 tablets	bdl2.
	CARVEDILOL 12.5mg tablets	bdl3.
	CARVEDILOL 25mg tablets	bdl4.
	CARVEDILOL 3.125mg tablets	bdl5.
	CARVEDILOL 6.25mg tablets	bdl6.
	*EUCARDIC 3.125 tablets	bdl7.
	*EUCARDIC 6.25 tablets	bdl8.
Celiprolol	CELIPROLOL HYDROCHLORIDE	bdj..
	CELIPROLOL 200mg tablets	bdj1.
	CELECTOL 200mg tablets 28-CP	bdj2.
	CELECTOL 200mg tablets	bdj3.
	CELIPROLOL 400mg tablets	bdj4.
	CELECTOL 400mg tablets	bdj5.
Esmolol	ESMOLOL HYDROCHLORIDE	bdk..
	ESMOLOL HCL 2.5g/10mL injection	bdk1.
	ESMOLOL HCL 100mg/10mL injection	bdk2.
	BREVIBLOC CONCENTRATE 2.5g/10mL injection	bdk3.
	BREVIBLOC 100mg/10mL injection	bdk4.
	ESMOLOL HYDROCHLORIDE 10mg/mL infusion solution	bdk5.
	BREVIBLOC 10mg/mL infusion solution	bdk6.
Labetolol	LABETALOL 50mg tablets	bd5v.
	LABETALOL 100mg tablets	bd51.
	LABETALOL 200mg tablets	bd52.
	LABETALOL 400mg tablets	bd53.
	LABETALOL HYDROCHLORIDE	bd5..
	*LABROCOL 100mg tablets	bd54.
	*LABROCOL 200mg tablets	bd55.
	*LABROCOL 400mg tablets	bd56.
	TRANDATE 50mg tablets	bd57.
	TRANDATE 100mg tablets	bd58.
	TRANDATE 200mg tablets	bd59.
	TRANDATE 400mg tablets	bd5a.
	*TRANDATE 100mg/20mL injection	bd5b.
	LABETALOL HYDROCHLORIDE 50mg/10mL prefilled syringe	bd5c.
	*LABETALOL 100mg tablets	bd5t.

	*LABETALOL 200mg tablets	bd5u.
	*LABETALOL 100mg tablets	bd5w.
	*LABETALOL 200mg tablets	bd5x.
	*LABETALOL 400mg tablets	bd5y.
	LABETALOL 100mg/20mL injection	bd5z.
Metoprolol	METOPROLOL TARTRATE	bd6..
	*BETALOC 50mg tablets	bd61.
	*BETALOC 100mg tablets	bd62.
	BETALOC 5mg/5mL injection	bd63.
	BETALOC-SA DURULES 200mg m/r tablets	bd64.
	LOPRESOR 50mg tablets	bd65.
	LOPRESOR 100mg tablets	bd66.
	*MEPRANIX 50mg tablets	bd67.
	*MEPRANIX 100mg tablets	bd68.
	*LOPRESOR 5mg/5mL injection	bd6a.
	LOPRESOR SR 200mg m/r tablets	bd6b.
	*ARBRALENE 50mg tablets	bd6c.
	*ARBRALENE 100mg tablets	bd6d.
	*TENSOMEX 100mg tablets	bd6e.
	METOPROLOL 100mg tablets	bd6w.
	METOPROLOL 50mg tablets	bd6x.
	METOPROLOL 5mg/5mL injection	bd6y.
	METOPROLOL 200mg m/r tablets	bd6z.
Nadolol	NADOLOL	bd7..
	*CORGARD 40mg tablets	bd71.
	CORGARD 80mg tablets	bd72.
	*NADOLOL 40mg tablets	bd7y.
	NADOLOL 80mg tablets	bd7z.
Nebivolol	NEBIVOLOL	bdm..
	NEBILET 5mg tablets	bdm1.
	HYPOLOC 5mg tablets	bdm2.
	NEBIVOLOL 2.5mg tablets	bdmy.
	NEBIVOLOL 5mg tablets	bdmz.
Oxprenolol	OXPRENOLOL 20mg tablets	bd81.
	OXPRENOLOL 40mg tablets	bd82.
	OXPRENOLOL 80mg tablets	bd83.
	OXPRENOLOL 160mg tablets	bd84.
	OXPRENOLOL HYDROCHLORIDE	bd8..
	*APSOLOX 20mg tablets	bd85.
	*APSOLOX 40mg tablets	bd86.
	*APSOLOX 80mg tablets	bd87.
	*APSOLOX 160mg tablets	bd88.
	*LARACOR 20mg tablets	bd89.
	*LARACOR 40mg tablets	bd8a.
	*LARACOR 80mg tablets	bd8b.
	*LARACOR 160mg tablets	bd8c.
	*SLOW-PREN 160mg m/r tablets	bd8d.
	SLOW-TRASICOR 160mg m/r tablets	bd8e.
	*TRASICOR 20mg tablets	bd8f.
	*TRASICOR 40mg tablets	bd8g.

	*TRASICOR 80mg tablets	bd8h.
	*TRASICOR 160mg tablets	bd8i.
	*TRASICOR 2mg injection	bd8j.
	*PARITANE 20mg tablets	bd8k.
	*PARITANE 40mg tablets	bd8l.
	*PARITANE 80mg tablets	bd8m.
	*PARITANE 160mg tablets	bd8n.
	*OXYPRENIX 160mg m/r tablets	bd8o.
	OXPRENOLOL 160mg m/r tablets	bd8u.
Pindolol	PINDOLOL	bda..
	VISKEN 5mg tablets	bda1.
	VISKEN 15mg tablets	bda2.
	*BETADREN 5mg tablets	bda3.
	*BETADREN 15mg tablets	bda4.
	PINDOLOL 5mg tablets	bday.
	PINDOLOL 15mg tablets	bdaz.
	PINDOLOL+CLOPAMIDE 10mg/5mg tablets	bdeG.
	VISKALDIX tablets	bdek.
Propranolol	PROPRANOLOL 40mg tablets	bd12.
	PROPRANOLOL 80mg tablets	bd13.
	PROPRANOLOL 10mg tablets	bd11.
	PROPRANOLOL 5mg/5mL syrup	bd1I.
	PROPRANOLOL 160mg tablets	bd14.
	PROPRANOLOL HYDROCHLORIDE	bd1..
	*ANGILOL 10mg tablets	bd15.
	*ANGILOL 40mg tablets	bd16.
	*ANGILOL 80mg tablets	bd17.
	*ANGILOL 160mg tablets	bd18.
	*APSOLOL 10mg tablets	bd19.
	*PROPANIX 10mg tablets	bd1A.
	*PROPANIX 40mg tablets	bd1B.
	*PROPANIX 80mg tablets	bd1C.
	*PROPANIX 160mg tablets	bd1D.
	PROPANIX SR 160mg m/r capsules	bd1E.
	*BETADUR CR 160mg m/r tablets	bd1F.
	BETA-PROGRANE 160mg m/r capsules	bd1G.
	PROPRANOLOL 1mg/1mL injection	bd1H.
	PROPRANOLOL 5mg/5mL syrup	bd1I.
	PROPRANOLOL 50mg/5mL syrup	bd1J.
	HALF-BETADUR CR 80mg m/r capsules	bd1K.
	HALF BETA-PROGRANE 80mg m/r capsules	bd1L.
	*SLOPROLOL 80mg m/r capsules	bd1M.
	*PROBETA LA 160mg m/r capsules	bd1N.
	LOPRANOL LA 160mg m/r capsules	bd1O.
	PROPRANOLOL HYDROCHLORIDE 10mg/5mL syrup	bd1P.
	PROPRANOLOL HYDROCHLORIDE 40mg/5mL syrup	bd1Q.

	PROPRANOLOL HYDROCHLORIDE 80mg/5mL syrup	bd1R.
	HALF PROPANIX LA 80mg m/r capsules	bd1S.
	PROPANIX LA 160mg m/r capsules	bd1T.
	HALF PROPATARD LA 80mg m/r capsules	bd1U.
	PROPATARD LA 160mg m/r capsules	bd1V.
	PROPRANOLOL HYDROCHLORIDE 5mg/5mL sugar free oral solution	bd1W.
	PROPRANOLOL HYDROCHLORIDE 10mg/5mL sugar free oral solution	bd1X.
	PROPRANOLOL HYDROCHLORIDE 50mg/5mL sugar free oral solution	bd1Y.
	SYPROL 5mg/5mL oral solution	bd1Z.
	*APSOLOL 40mg tablets	bd1a.
	*APSOLOL 80mg tablets	bd1b.
	*APSOLOL 160mg tablets	bd1c.
	*BEDRANOL 10mg tablets	bd1d.
	*BEDRANOL 40mg tablets	bd1e.
	*BEDRANOL 80mg tablets	bd1f.
	BEDRANOL SR 160mg m/r capsules	bd1g.
	*BERKOLOL 10mg tablets	bd1h.
	*BERKOLOL 40mg tablets	bd1i.
	*BERKOLOL 80mg tablets	bd1j.
	*BERKOLOL 160mg tablets	bd1k.
	HALF-INDERAL LA 80mg m/r capsules	bd1l.
	*INDERAL 10mg tablets	bd1m.
	*INDERAL 40mg tablets	bd1n.
	*INDERAL 80mg tablets	bd1o.
	*INDERAL 160mg tablets	bd1p.
	*INDERAL 1mg/1mL injection	bd1q.
	*INDERAL-LA 160mg m/r capsules	bd1r.
	*SLOPROLOL 160mg m/r capsules	bd1s.
	*CARDINOL 10mg tablets	bd1t.
	*CARDINOL 40mg tablets	bd1u.
	*CARDINOL 80mg tablets	bd1v.
	*CARDINOL 160mg tablets	bd1w.
	PROPRANOLOL 160mg m/r capsules	bd1x.
	PROPRANOLOL 80mg m/r capsules	bd1y.
	SYPROL 10mg/5mL oral solution	bd1z.
	PROPRANOLOL HYDROCHLORIDE [2]	bdn..
	SYPROL 50mg/5mL oral solution	bdn1.
	BEDRANOL SR 80mg m/r capsules	bdn2.
	*RAPRANOL SR 80mg m/r capsules	bdn3.
	RAPRANOL SR 160mg m/r capsules	bdn4.
	SYPROL 40mg/5mL oral solution	bdn5.
	PROPRANOLOL HYDROCHLORIDE 40mg/5mL sugar free oral solution	bdn6.
Sotalol	SOTALOL HYDROCHLORIDE	bdc..
	BETA-CARDONE 40mg tablets	bdc1.
	BETA-CARDONE 80mg tablets	bdc2.

	BETA-CARDONE 200mg tablets	bdc3.
	SOTACOR 80mg tablets	bdc4.
	*SOTACOR 160mg tablets	bdc5.
	*SOTACOR 10mg/5mL injection	bdc6.
	*SOTACOR 100mg/10mL injection	bdc7.
	*SOTACOR 40mg/4mL injection	bdc8.
	*SOTALOL 40mg/4mL injection	bdcs.
	SOTALOL 40mg tablets	bdcu.
	SOTALOL 80mg tablets	bdcv.
	SOTALOL 200mg tablets	bdcw.
	SOTALOL 160mg tablets	bdcx.
	*SOTALOL 10mg/5mL injection	bdcy.
	*SOTALOL 100mg/10mL injection	bdcz.
Timolol Maleate	TIMOLOL MALEATE [B-BLOCKER]	bdd..
	BETIM 10mg tablets	bdd1.
	TIMOLOL 10mg tablets	bddz.
	PRESTIM tablets	bdeb.
COMPOUND BETA-BLOCKERS	COMPOUND BETA-BLOCKERS	bde..
	*CO-BETALOC tablets	bde1.
	*CO-BETALOC SA m/r tablets	bde2.
	*CORGARETIC-40 tablets	bde3.
	*CORGARETIC-80 tablets	bde4.
	*INDERETIC capsules	bde5.
	*INDEREX m/r capsules	bde6.
	KALTEN capsules	bde7.
	*LASIPRESSIN tablets	bde8.
	*LOPRESORETIC tablets	bde9.
	METOPROLOL TART+HYDROCHLOROTHIAZIDE 100mg/12.5mg tablets	bdeA.
	METOPROLOL TART+HYDROCHLOROTHIAZIDE 200mg/25mg m/r tablets	bdeB.
	METOPROLOL TART+CHLORTHALIDONE 100mg/12.5mg tablets	bdeC.
	NADOLOL+BENDROFLUMETHIAZIDE 40mg/5mg tablets	bdeD.
	NADOLOL+BENDROFLUAZIDE 80mg/5mg tablets	bdeE.
	PENBUTOLOL SULPHATE+FRUSEMIDE 40mg/20mg tablets	bdeF.
	PINDOLOL+CLOPAMIDE 10mg/5mg tablets	bdeG.
	SOTALOL HCL+HYDROCHLOROTHIAZIDE 160mg/25mg tablets	bdeH.
	SOTALOL HCL+HYDROCHLOROTHIAZIDE 80mg/12.5mg tablets	bdeJ.
	TIMOLOL MALEATE+CO-AMILOZIDE	bdeK.

	10mg/2.5mg/25mg tablets	
	TIMOLOL MALEATE+BENDROFLUMETHIAZIDE 10mg/2.5mg tablets	bdeL.
	TIMOLOL MALEATE+BENDROFLUAZIDE 20mg/5mg tablets	bdeM.
	TOTARETIC 50mg/12.5mg tablets	bdeN.
	TOTARETIC 100mg/25mg tablets	bdeO.
	ATENOLOL+BENDROFLUAZIDE 25mg/1.25mg capsules	bdeP.
	*TENBEN capsules	bdeQ.
	COMBITENS m/r capsules	bdeR.
	*MODUCREN tablets	bdea.
	PRESTIM tablets	bdeb.
	*PRESTIM FORTE tablets	bdec.
	*SECADREX tablets	bded.
	*SOTAZIDE tablets	bdee.
	*SPIROPROP tablets	bdef.
	TENORET-50 tablets	bdeg.
	TENORETIC tablets	bdeh.
	*TOLERZIDE tablets	bdei.
	*TRASIDREX tablets	bdej.
	VISKALDIX tablets	bdek.
	*CO-PRENOZIDE tablets	bdel.
	CO-TENIDONE 50/12.5mg tablets	bdem.
	CO-TENIDONE 100/25mg tablets	bden.
	ATENIXCO 50/12.5mg tablets	bdeo.
	*ATENIXCO 100/25mg tablets	bdep.
	*TENCHLOR 50/12.5mg tablets	bdeq.
	*TENCHLOR 100/25mg tablets	bder.
	BETA-ADALAT 50/20mg capsules	bdes.
	TENIF 50/20mg capsules	bdet.
	CO-PRENOZIDE 160/0.25mg m/r tablets	bdeu.
	PROPRANOLOL HCL+BENDROFLUAZIDE 80mg/2.5mg capsules	bdev.
	PROPRANOLOL HCL+BENDROFLUAZIDE 160mg/5mg m/r capsules	bdew.
	ACEBUTOLOL+HYDROCHLOROTHIAZIDE 200mg/12.5mg tablets	bdex.
	ATENOLOL+CO-AMILOZIDE 50mg/2.5mg/25mg capsules	bdey.
	ATENOLOL+NIFEDIPINE 50mg/20mg m/r capsules	bdez.

6.13 Calcium channel blockers (CCB)

Calcium channel blockers

Amlodipine	AMLODIPINE	blb..
	AMLODIPINE 5mg tablets	blb1.
	AMLODIPINE 10mg tablets	blb2.
	ISTIN 5mg tablets	blb3.
	ISTIN 10mg tablets	blb4.
	AMLOSTIN 5mg tablets	blb5.
	AMLOSTIN 10mg tablets	blb6.
	OLMESARTAN+AMLODIPINE	bkH..
	SEVIKAR 20mg/5mg tablets	bkH1.
	SEVIKAR 40mg/5mg tablets	bkH2.
	SEVIKAR 40mg/10mg tablets	bkH3.
	OLMESARTAN MEDOXOMIL+AMLODIPINE 40mg/10mg tablets	bkHx.
	OLMESARTAN MEDOXOMIL+AMLODIPINE 40mg/5mg tablets	bkHy.
	OLMESARTAN MEDOXOMIL+AMLODIPINE 20mg/5mg tablets	bkHz.
	AMLODIPINE + VALSARTAN	bkD..
	AMLODIPINE+VALSARTAN 5mg/80mg tablets	bkD1.
	AMLODIPINE+VALSARTAN 5mg/160mg tablets	bkD2.
	AMLODIPINE+VALSARTAN 10mg/160mg tablets	bkD3.
	EXFORGE 10mg/160mg tablets	bkDx.
	EXFORGE 5mg/160mg tablets	bkDy.
	EXFORGE 5mg/80mg tablets	bkDz.
	OLMESARTAN+AMLODIPINE+HYDROCHLOROTHIAZIDE	bkI..
	SEVIKAR HCT 20mg/5mg/12.5mg tablets	bkI1.
	SEVIKAR HCT 40mg/5mg/12.5mg tablets	bkI2.
	SEVIKAR HCT 40mg/10mg/12.5mg tablets	bkI3.
	SEVIKAR HCT 40mg/5mg/25mg tablets	bkI4.
	SEVIKAR HCT 40mg/10mg/25mg tablets	bkI5.
Diltiazem	DILTIAZEM HYDROCHLORIDE	bl5..
	TILDIEM 60mg tablets	bl51.
	*CALCICARD 60mg tablets	bl52.
	*BRITIAZIM 60mg tablets	bl53.
	ADIZEM-SR 120mg m/r tablets	bl54.
	DILTIAZEM HYDROCHLORIDE 120mg m/r tablets	bl55.
	*ANGIOZEM 60mg tablets	bl56.
	*ADIZEM 60mg tablets	bl57.
	TILDIEM RETARD 90mg m/r tablets	bl58.
	TILDIEM RETARD 120mg m/r tablets	bl59.
	TILDIEM LA 300mg m/r capsules	bl5A.
	ADIZEM-SR 90mg m/r capsules	bl5B.

	ADIZEM-SR 120mg m/r capsules	bl5C.
	ADIZEM-SR 180mg m/r capsules	bl5D.
	ADIZEM-XL 300mg m/r capsules	bl5E.
	DILZEM SR 60mg m/r capsules	bl5F.
	DILZEM SR 90mg m/r capsules	bl5G.
	DILZEM SR 120mg m/r capsules	bl5H.
	ADIZEM-XL 240mg m/r capsules	bl5I.
	ADIZEM-XL 180mg m/r capsules	bl5J.
	ADIZEM-XL 120mg m/r capsules	bl5K.
	DILZEM-XL 120mg m/r capsules	bl5L.
	DILZEM-XL 180mg m/r capsules	bl5M.
	DILZEM-XL 240mg m/r capsules	bl5N.
	SLOZEM 120mg m/r capsules	bl5O.
	SLOZEM 180mg m/r capsules	bl5P.
	SLOZEM 240mg m/r capsules	bl5Q.
	ANGITIL SR 90 m/r capsules	bl5R.
	ANGITIL SR 120 m/r capsules	bl5S.
	*METAZEM 60mg tablets	bl5T.
	ANGITIL SR 180 m/r capsules	bl5U.
	CALCICARD CR 90mg m/r tablets	bl5V.
	CALCICARD CR 120mg m/r tablets	bl5W.
	KENTIAZEM 60mg m/r capsules	bl5X.
	*OPTIL 60mg m/r tablets	bl5Y.
	TILDIEM LA 200mg m/r capsules	bl5Z.
	DILTIAZEM HYDROCHLORIDE 90mg m/r tablets	bl5a.
	DILTIAZEM HYDROCHLORIDE 300mg m/r capsules	bl5b.
	DILTIAZEM HYDROCHLORIDE 90mg m/r capsules	bl5c.
	DILTIAZEM HYDROCHLORIDE 120mg m/r capsules	bl5d.
	DILTIAZEM HYDROCHLORIDE 180mg m/r capsules	bl5e.
	DILTIAZEM HYDROCHLORIDE 60mg m/r capsules	bl5f.
	DILTIAZEM HYDROCHLORIDE 240mg m/r capsules	bl5g.
	DILTIAZEM HYDROCHLORIDE 200mg m/r capsules	bl5h.
	DILTIAZEM HYDROCHLORIDE+HYDROCHLOROTHIAZIDE 150mg/12.5mg m/r capsules	bl5i.
	*ADIZEM-XL PLUS m/r capsules	bl5j.
	*ANGIOZEM CR 90mg m/r tablets	bl5k.
	DILCARDIA SR 60mg m/r capsules	bl5l.
	*ANGIOZEM CR 120mg m/r tablets	bl5m.
	ZEMTARD 300 XL m/r capsules	bl5n.
	VIAZEM XL 120mg m/r capsules	bl5o.
	VIAZEM XL 180mg m/r capsules	bl5p.

	VIAZEM XL 240mg m/r capsules	bl5q.
	VIAZEM XL 300mg m/r capsules	bl5r.
	DILTIAZEM HYDROCHLORIDE 360mg m/r capsules	bl5s.
	VIAZEM XL 360mg m/r capsules	bl5t.
	*CALAZEM 60mg m/r tablets	bl5u.
	DILCARDIA SR 90mg m/r capsules	bl5v.
	DILCARDIA SR 120mg m/r capsules	bl5w.
	ANGITIL XL 240 m/r capsules	bl5x.
	ANGITIL XL 300 m/r capsules	bl5y.
	DILTIAZEM HYDROCHLORIDE 60mg m/r tablets	bl5z.
	DILTIAZEM HYDROCHLORIDE 2	blj..
	ZEMTARD 120 XL m/r capsules	blj1.
	ZEMTARD 180 XL m/r capsules	blj2.
	ZEMTARD 240 XL m/r capsules	blj3.
	*OPTIL SR 90 m/r capsules	blj4.
	*OPTIL SR 120 m/r capsules	blj5.
	*OPTIL SR 180 m/r capsules	blj6.
	*OPTIL XL 240 m/r capsules	blj7.
	*OPTIL XL 300 m/r capsules	blj8.
	DILCARDIA XL 120mg m/r capsules	blj9.
	DILCARDIA XL 180mg m/r capsules	bljA.
	DILCARDIA XL 240mg m/r capsules	bljB.
	BI-CARZEM SR 60mg m/r capsules	bljC.
	BI-CARZEM SR 90mg m/r capsules	bljD.
	BI-CARZEM SR 120mg m/r capsules	bljE.
	*ZILDIL SR 60mg m/r capsules	bljF.
	*ZILDIL SR 90mg m/r capsules	bljG.
	*ZILDIL SR 120mg m/r capsules	bljH.
	SLOZEM 300mg m/r capsules	bljJ.
	BI-CARZEM XL 300mg m/r capsules	bljK.
	BI-CARZEM XL 240mg m/r capsules	bljL.
	ZEMRET 180 XL m/r capsules	bljM.
	ZEMRET 240 XL m/r capsules	bljN.
	ZEMRET 300 XL m/r capsules	bljO.
	ADIZEM-XL 200mg m/r capsules	bljP.
	*DISOGRAM SR 60mg m/r capsules	bljQ.
	*DISOGRAM SR 90mg m/r capsules	bljR.
	DISOGRAM SR 120mg m/r capsules	bljS.
	DISOGRAM SR 180mg m/r capsules	bljT.
	DISOGRAM SR 240mg m/r capsules	bljU.
	DISOGRAM SR 300mg m/r capsules	bljV.
	*HORIZEM SR 90mg m/r capsules	bljW.
	*HORIZEM SR 120mg m/r capsules	bljX.
	DILTIAZEM HYDROCHLORIDE XL 180mg m/r capsules	bljY.
	DILTIAZEM HYDROCHLORIDE XL 240mg m/r capsules	bljZ.
	DILTIAZEM HYDROCHLORIDE XL 300mg	blja.

	m/r capsules	
	RETALZEM MR 60mg m/r tablets	bljb.
	UARD 120XL m/r capsules	bljc.
	UARD 180XL m/r capsules	bljd.
	UARD 240XL m/r capsules	blje.
	UARD 300XL m/r capsules	bljf.
Felodipine	FELODIPINE	blc..
	FELODIPINE 5mg m/r tablets	blc1.
	FELODIPINE 10mg m/r tablets	blc2.
	PLENDIL 5mg m/r tablets	blc3.
	PLENDIL 10mg m/r tablets	blc4.
	FELODIPINE 2.5mg m/r tablets	blc5.
	PLENDIL 2.5mg m/r tablets	blc6.
	CABREN 2.5mg m/r tablets	blc7.
	CABREN 5mg m/r tablets	blc8.
	CABREN 10mg m/r tablets	blc9.
	FELOTENS XL 5mg m/r tablets	blca.
	FELOTENS XL 10mg m/r tablets	blcb.
	FELOGEN XL 5mg m/r tablets	blcc.
	FELENDIL XL 5mg m/r tablets	blcd.
	FELENDIL XL 10mg m/r tablets	blce.
	KELOC SR 5mg m/r tablets	blcf.
	KELOC SR 10mg m/r tablets	blcg.
	FELOGEN XL 10mg m/r tablets	blch.
	VASCALPHA 5mg m/r tablets	blci.
	VASCALPHA 10mg m/r tablets	blcj.
	CARDIOPLEN XL 5mg m/r tablets	blck.
	CARDIOPLEN XL 10mg m/r tablets	blcl.
	NEOFEL XL 5mg m/r tablets	blcm.
	NEOFEL XL 10mg m/r tablets	blcn.
	PARMID XL 5mg m/r tablets	blco.
	PARMID XL 10mg m/r tablets	blcp.
	PINEFELD XL 10mg m/r tablets	blcq.
	CARDIOPLEN XL 2.5mg m/r tablets	blcr.
	NEOFEL XL 2.5mg m/r tablets	blcs.
	FELOTENS XL 2.5mg m/r tablets	blct.
	FELODIPINE+RAMIPRIL	bA1..
	TRIAPIN MITE 2.5mg/2.5mg tablets	bA11.
	TRIAPIN 5mg/5mg tablets	bA12.
	FELODIPINE+RAMIPRIL 2.5mg/2.5mg tablets	bA1y.
	FELODIPINE+RAMIPRIL 5mg/5mg tablets	bA1z.
Isradipine	*ISRADIPINE	bla..
	*ISRADIPINE 2.5mg tablets	bla1.
	*PRESCAL 2.5mg tablets	bla2.
Lacidipine	LACIDIPINE	ble..
	LACIDIPINE 2mg tablets	ble1.
	LACIDIPINE 4mg tablets	ble2.
	MOTENS 2mg tablets	ble3.
	MOTENS 4mg tablets	ble4.

Lercandipine	LERCANIDIPINE HYDROCHLORIDE	blh..
	LERCANIDIPINE HYDROCHLORIDE 10mg tablets	blh1.
	ZANIDIP 10mg tablets	blh2.
	LERCANIDIPINE HYDROCHLORIDE 20mg tablets	blh3.
	ZANIDIP 20mg tablets	blh4.
Mibefradil	MIBEFRADIL	bli..
	*MIBEFRADIL 50mg tablets	bli1.
	*MIBEFRADIL 100mg tablets	bli2.
	*POSICOR 50mg tablets	bli3.
	*POSICOR 100mg tablets	bli4.
Nicardipine	NICARDIPINE HYDROCHLORIDE	bl7..
	CARDENE 20mg capsules	bl71.
	CARDENE 30mg capsules	bl72.
	CARDENE SR 30mg m/r capsules	bl73.
	CARDENE SR 45mg m/r capsules	bl74.
	NICARDIPINE 45mg m/r capsules	bl7w.
	NICARDIPINE 30mg m/r capsules	bl7x.
	NICARDIPINE 20mg capsules	bl7y.
	NICARDIPINE 30mg capsules	bl7z.
Nifedipine	NIFEDIPINE	bl8..
	ADALAT 5mg capsules	bl81.
	ADALAT 10mg capsules	bl82.
	ADALAT RETARD 20mg m/r tablets	bl83.
	ADALAT RETARD 10mg m/r tablets	bl84.
	NIFEDIPINE 5mg capsules	bl85.
	NIFEDIPINE 10mg capsules	bl86.
	ADALAT-IC 200micrograms/2mL injection	bl87.
	NIFEDIPINE-IC 200micrograms/2mL injection	bl88.
	*VASAD 5mg capsules	bl89.
	ADIPINE MR 20 m/r tablets	bl8A.
	ADIPINE MR 10 m/r tablets	bl8B.
	*UNIPINE XL 30mg m/r tablets	bl8C.
	*NIMODREL MR 10 m/r tablets	bl8D.
	*NIMODREL MR 20 m/r tablets	bl8E.
	NIFEDIPINE 40mg m/r tablets	bl8F.
	*ANGIOPINE 40 LA m/r tablets	bl8G.
	*CARDILATE MR 10mg m/r tablets	bl8H.
	TENSIPINE MR 10 m/r tablets	bl8J.
	TENSIPINE MR 20 m/r tablets	bl8K.
	FORTIPINE LA40 m/r tablets	bl8L.
	ADALAT LA 20mg m/r tablets	bl8M.
	*SLOFEDIPINE 20mg m/r tablets	bl8O.
	*ANGIOPINE MR 10mg m/r tablets	bl8P.
	GENALAT RETARD 10mg m/r tablets	bl8Q.
	GENALAT RETARD 20mg m/r tablets	bl8R.
	NIFEDIPRESS MR 10 m/r tablets	bl8S.
	NIVATEN RETARD 10mg m/r tablets	bl8T.

	NIFEDIPRESS MR 20 m/r tablets	bl8U.
	NIFEDIPINE 30mg m/r capsules	bl8V.
	NIFEDIPINE 60mg m/r capsules	bl8W.
	CORACTEN XL 30mg m/r capsules	bl8X.
Nifedipine	CORACTEN XL 60mg m/r capsules	bl8Y.
	NIVATEN RETARD 20mg m/r tablets	bl8Z.
	*VASAD 10mg capsules	bl8a.
	*CALCILAT 10mg capsules	bl8b.
	*CALCIPINE 5mg capsules	bl8c.
	*CALCIPINE 10mg capsules	bl8d.
	CORACTEN SR 20mg m/r capsules	bl8e.
	*ANGIOPINE 5mg capsules	bl8f.
	*ANGIOPINE 10mg capsules	bl8g.
	*NIFENSAR XL 20mg m/r tablets	bl8h.
	ADALAT LA 30mg m/r tablets	bl8i.
	ADALAT LA 60mg m/r tablets	bl8j.
	CORACTEN SR 10mg m/r capsules	bl8k.
	*CARDILATE MR 20mg m/r tablets	bl8l.
	*ANGIOPINE MR 20mg tablets	bl8m.
	*NIFELEASE 20mg m/r tablets	bl8n.
	*CALANIF 10mg capsules	bl8o.
	*CALANIF 5mg capsules	bl8p.
	*HYPOLAR RETARD 20 m/r tablets	bl8q.
	*NIFEDOTARD 20MR m/r tablets	bl8r.
	*CORODAY MR 20mg m/r tablets	bl8s.
	NIFOPRESS RETARD 20mg m/r tablets	bl8t.
	NIFEDIPINE 10mg m/r capsules	bl8u.
	NIFEDIPINE 20mg m/r capsules	bl8v.
	NIFEDIPINE 10mg m/r tablets	bl8w.
	NIFEDIPINE 30mg m/r tablets	bl8x.
	NIFEDIPINE 60mg m/r tablets	bl8y.
	NIFEDIPINE 20mg m/r tablets	bl8z.
	BETA-ADALAT 50/20mg capsules	bdes.
	CALCHAN MR 10mg m/r tablets	bll7.
	CALCHAN MR 20mg m/r tablets	bll6.
	VALNI XL 30mg m/r tablets	bllg.
	VALNI XL 60mg m/r tablets	bllh.
	VALNI 20 RETARD 20mg m/r tablets	bllb.
NIMODIPINE	NIMODIPINE	dt1..
	NIMODIPINE 200microgram/mL intravenous infusion 50mL	dt11.
	NIMOTOP 200micrograms/mL intravenous infusion 50mL	dt12.
	NIMODIPINE 30mg tablets	dt13.
	NIMOTOP 30mg tablets	dt14.
	NIMODIPINE 50mg/250mL intravenous infusion	dt15.
	NIMOTOP IV 50mg/250mL infusion	dt16.
Nisoldipine	NISOLDIPINE	blg..
	*NISOLDIPINE 10mg m/r tablets	blg1.

	*NISOLDIPINE 20mg m/r tablets	blg2.
	*NISOLDIPINE 30mg m/r tablets	blg3.
	*SYSCOR MR 10mg m/r tablets	blg4.
	*SYSCOR MR 20mg m/r tablets	blg5.
	*SYSCOR MR 30mg m/r tablets	blg6.
Slofedipine	SLOFEDIPINE XL 30mg m/r tablets	bll1.
	SLOFEDIPINE XL 60mg m/r tablets	bll2.
Verapamil	VERAPAMIL HYDROCHLORIDE	bb3..
	VERAPAMIL 40mg tablets	bb31.
	VERAPAMIL 80mg tablets	bb32.
	VERAPAMIL 120mg tablets	bb33.
	VERAPAMIL 160mg tablets	bb3w.
	*BERKATENS 40mg tablets	bb34.
	*BERKATENS 80mg tablets	bb35.
	*BERKATENS 120mg tablets	bb36.
	*BERKATENS 160mg tablets	bb37.
	*CORDILOX 40mg tablets	bb38.
	*CORDILOX 80mg tablets	bb39.
	VERAPAMIL 240mg m/r tablets	bb3A.
	HALF SECURON SR 120mg m/r tablets	bb3B.
	VERAPAMIL 120mg m/r tablets	bb3C.
	VERAPAMIL 40mg/5mL sugar free solution	bb3D.
	VERAPAMIL HCL 5mg/2mL prefilled syringe	bb3E.
	HALF-SECURON SR 120mg m/r tablets 28CP	bb3F.
	*HYPANEZE 40 tablets	bb3G.
	*HYPANEZE 80 tablets	bb3H.
	*HYPANEZE 120 tablets	bb3J.
	*VERAPRESS MR 240 m/r tablets	bb3K.
	*ETHIMIL MR 240 m/r tablets	bb3L.
Verapamil	CORDILOX MR 240 m/r tablets	bb3M.
	ZOLVERA 40mg/5mL oral solution	bb3N.
	*RANVERA MR 240mg m/r tablets	bb3O.
	VERA-TIL SR 240mg m/r tablets	bb3P.
	CORDILOX 120mg tablets	bb3a.
	*CORDILOX 160mg tablets	bb3b.
	*CORDILOX 5mg/2mL injection	bb3c.
	*SECURON 40mg tablets	bb3d.
	*SECURON 80mg tablets	bb3e.
	*SECURON 120mg tablets	bb3f.
	*SECURON 120mg tablets 56CP	bb3g.
	*SECURON 160mg tablets 56CP	bb3h.
	*SECURON 160mg tablets	bb3i.
	SECURON SR 240mg m/r tablets	bb3j.
	SECURON SR 240mg m/r tablets 28CP	bb3k.
	UNIVER 120mg m/r capsules x28	bb3l.
	UNIVER 180mg m/r capsules x56	bb3m.
	UNIVER 240mg m/r capsules x28	bb3n.
	SECURON IV 5mg/2mL injection	bb3o.
	*GEANGIN 40mg tablets	bb3p.

	*GEANGIN 80mg tablets	bb3q.
	*GEANGIN 120mg tablets	bb3r.
	VERTAB SR 240 m/r tablets	bb3s.
	VERAPAMIL 5mg/2mL injection	bb3t.
	VERAPAMIL 120mg m/r capsules	bb3v.
	VERAPAMIL 160mg tablets	bb3w.
	VERPAMIL HCL 120mg tablets x56	bb3x.
	VERAPAMIL 240mg m/r capsules	bb3y.
	VERAPAMIL 180mg m/r capsules	bb3z.
	TRANDOLAPRIL+VERAPAMIL HYDROCHLORIDE	bk6..
	TRANDOLAPRIL+VERAPAMIL HYDROCHLORIDE 2mg/180mg m/r capsules	bk61.
	*TARKA 2mg/180mg m/r capsules	bk62.
	CALCICARD CR 90mg m/r tablets	bl5V.
	CALCICARD CR 120mg m/r tablets	bl5W.
Combination with ACEi		bA...
	FELODIPINE+RAMIPRIL	bA1..
	TRIAPIN MITE 2.5mg/2.5mg tablets	bA11.
	TRIAPIN 5mg/5mg tablets	bA12.
	FELODIPINE+RAMIPRIL 2.5mg/2.5mg tablets	bA1y.
	FELODIPINE+RAMIPRIL 5mg/5mg tablets	bA1z.

6.14 Diuretics

2.2 Diuretics		
2.2.1 Thiazides and Related Diuretics		
Thiazide	THIAZIDE DIURETICS	b2...
Bendroflumethiazide	BENDROFLUMETHIAZIDE	b21..
	BENDROFLUMETHIAZIDE 2.5mg tablets	b211.
	BENDROFLUMETHIAZIDE 5mg tablets	b212.
	APRINOX 2.5mg tablets	b213.
	APRINOX 5mg tablets	b214.
	*BERKOZIDE 2.5mg tablets	b215.
	*BERKOZIDE 5mg tablets	b216.
	*CENTYL 2.5mg tablets	b217.
	*CENTYL 5mg tablets	b218.
	NEO-NACLEX 5mg tablets	b219.
	*NEO-BENDROMAX 2.5mg tablets	b21A.
	*NEO-BENDROMAX 5mg tablets	b21B.
	*URIZIDE 5mg tablets	b21a.
	NEO-NACLEX 2.5mg tablets	b21b.
	BENDROFLUMETHIAZIDE+POTASSIUM 2.5mg/8.4mmol m/r tablets	b91h.
	TIMOLOL	bdeL.

	MALEATE+BENDROFLUMETHIAZIDE 10mg/2.5mg tablets	
Chlorothiazide	CHLOROTHIAZIDE	b22..
	*SALURIC 500mg tablets	b221.
	DIURIL 250mg/5mL oral suspension	b222.
	CHLOROTHIAZIDE 250mg/5mL oral suspension	b22y.
	*CHLOROTHIAZIDE 500mg tablets	b22z.
CHLORTALIDONE	CHLORTALIDONE	b23..
	KALSPARE tablets	b518.
	HYGROTON 50mg tablets	b231.
	*HYGROTON 100mg tablets	b232.
	CHLORTALIDONE 50mg tablets	b23y.
	*CHLORTHALIDONE 100mg tablets	b23z.
Clopamide	PINDOLOL+CLOPAMIDE 10mg/5mg tablets	bdeG.
	CLOPAMIDE [INGREDIENT see bdek]	b24..
CYCLOPENTHIAZIDE	CYCLOPENTHIAZIDE	b25..
	NAVIDREX 500micrograms tablets	b251.
	CYCLOPENTHIAZIDE 500microgram tablets	b25z.
Hydrochlorothiazide	HYDROCHLOROTHIAZIDE	b26..
	*ESIDREX 25mg tablets	b261.
	*ESIDREX 50mg tablets	b262.
	*HYDROSALURIC 25mg tablets	b263.
	*HYDROSALURIC 50mg tablets	b264.
	HYDROCHLOROTHIAZIDE 50mg tablets	b26y.
	HYDROCHLOROTHIAZIDE 25mg tablets	b26z.
	MODURETIC tablets	b51b.
	MODURET-25 tablets	b51a.
Hydroflumethiazide	HYDROFLUMETHIAZIDE	b27..
	*HYDRENOX 50mg tablets	b271.
	HYDROFLUMETHIAZIDE 50mg tablets	b27z.
Indapamide	INDAPAMIDE	b28..
	NATRILIX 2.5mg tablets	b281.
	*NINDAXA 2.5mg tablets	b282.
	*NATRAMID 2.5mg tablets	b283.
	*OPUMIDE 2.5mg tablets	b284.
	INDAPAMIDE 1.5mg m/r tablets	b285.
	NATRILIX SR 1.5mg m/r tablets	b286.
	ETHIBIDE XL 1.5mg m/r tablets	b287.
	INDIPAM XL 1.5mg m/r tablets	b288.
	MAPEMID XL 1.5mg m/r tablets	b289.
	INDAPAMIDE 2.5mg tablets	b28z.
	PERINDOPRIL ARGININE+INDAPAMIDE 5mg/1.25mg tablets	biC8.
Mefruside	MEFRUSIDE	b29..
	*BAYCARON 25mg tablets	b291.
	*MEFRUSIDE 25mg tablets	b29z.
Methylclothiazide	*METHYCLOTHIAZIDE	b2a..

	*ENDURON 5mg tablets	b2a1.
	*METHYCLOTHIAZIDE 5mg tablets	b2az.
METOLAZONE	METOLAZONE	b2b..
	*METENIX-5 5mg tablets	b2b1.
	*XURET 500micrograms tablets	b2b2.
	METOLAZONE 500micrograms tablets	b2b3.
	*METOLAZONE 5mg tablets	b2bz.
POLYTHIAZIDE	POLYTHIAZIDE	b2c..
	*NEPHRIL 1mg tablets	b2c1.
	*POLYTHIAZIDE 1mg tablets	b2cz.
XIPAMIDE	XIPAMIDE	b2d..
	DIUREXAN 20mg tablets	b2d1.
	XIPAMIDE 20mg tablets	b2dz.
DIURETICS+ POTASSIUM SUPPLEMENT A-Z	DIURETICS+POTASSIUM SUPPLEMENT A-Z	b91..
	*BRINALDIX K tablets	b911.
	*BURINEX K tablets	b912.
	*CENTYL K m/r tablets	b913.
	*DIUMIDE-K CONTINUS tablets	b914.
	*ESIDREX K tablets	b915.
	HYGROTON K tablets combination pack	b916.
	*LASIKAL tablets	b917.
	LASIX+K tablets 30day-CP combination pack	b918.
	*NAVIDREX-K tablets	b919.
	NEO-NACLEX-K tablets	b91a.
	BUMETANIDE+POTASSIUM 500micrograms/7.7mmol m/r tablets	b91b.
	BENDROFLUMETHIAZIDE+POTASSIUM 2.5mg/7.7mmol m/r tablets	b91c.
	FRUSEMIDE+POTASSIUM 40mg/8mmol m/r tablets	b91d.
	CHLORTHALIDONE tablets+POTASSIUM m/r tablets 25mg/6.7mmol pack	b91e.
	FUROSEMIDE+POTASSIUM 20mg/10mmol m/r tablets	b91f.
	FRUSEMIDE tablets+POTASSIUM m/r tablets 40mg/10mmol pack	b91g.
	BENDROFLUMETHIAZIDE+POTASSIUM 2.5mg/8.4mmol m/r tablets	b91h.
Acetazolamide	ACETAZOLAMIDE [GLAUCOMA]	k81..
	DIAMOX SUSTETS 500mg m/r capsules	k811.
	DIAMOX 250mg tablets	k812.
	*DIAMOX powder	k813.
	DIAMOX PARENTERAL 500mg injection	k814.
	DIAMOX SR 250mg m/r capsules	k815.
	EYTAZOX 250mg m/r capsules	k816.
	*ACETAZOLAMIDE powder	k81v.
	ACETAZOLAMIDE 250mg m/r capsules	k81w.

	ACETAZOLAMIDE 500mg m/r capsules	k81x.
	ACETAZOLAMIDE 250mg tablets	k81y.
	ACETAZOLAMIDE 500mg injection	k81z.
	ACETAZOLAMIDE [EPILEPSY]	dn1..
	DIAMOX [EP] 250mg tablets	dn12.
	DIAMOX [EP] 500mg injection	dn13.
	ACETAZOLAMIDE [EP] 500mg m/r capsules	dn1x.
	ACETAZOLAMIDE [EP] 250mg tablets	dn1y.
	ACETAZOLAMIDE [EP] 500mg injection	dn1z.
2.2.1 Loop diuretics		
Loop	LOOP DIURETICS	b3...
Furosemide	FUROSEMIDE	b31..
	FUROSEMIDE 20mg tablets	b311.
	FUROSEMIDE 40mg tablets	b312.
	FUROSEMIDE 500mg tablets	b313.
	*ALUZINE 20mg tablets	b314.
	*ALUZINE 40mg tablets	b315.
	*ALUZINE 500mg tablets	b316.
	*DIURESAL 40mg tablets	b317.
	*DIURESAL 20mg/2mL injection	b318.
	*DIURESAL 50mg/5mL injection	b319.
	MIN-I-JET FRUSEMIDE 250mg/25mL injection	b31A.
	MIN-I-JET FRUSEMIDE 80mg/8mL injection	b31B.
	FUROSEMIDE 80mg/8mL prefilled syringe	b31C.
	FRUSEMIDE 250mg/25mL prefilled syringe	b31D.
	FROOP 40mg tablets	b31E.
	FRUSOL 20mg/5mL sugar free oral solution	b31F.
	FRUSOL 40mg/5mL sugar free oral solution	b31G.
	FRUSOL 50mg/5mL sugar free oral solution	b31H.
	*DRYPTAL 40mg tablets	b31a.
	*DRYPTAL 500mg tablets	b31b.
	*DRYPTAL 20mg/2mL injection	b31c.
	*DRYPTAL 50mg/5mL injection	b31d.
	*DRYPTAL 250mg/25mL injection	b31e.
	*FRUSETIC 40mg tablets	b31f.
	*FRUSID 40mg tablets	b31g.
	*LASIX 20mg tablets	b31h.
	*LASIX 40mg tablets	b31i.
	*LASIX 500mg tablets	b31j.
	LASIX PAEDIATRIC 1mg/1mL liquid	b31k.
	LASIX 20mg/2mL injection	b31l.
	*LASIX 50mg/5mL injection	b31m.

	*LASIX 250mg/25mL injection	b31n.
	*FRUMAX 40mg tablets	b31o.
	*RUSYDE 20mg tablets	b31p.
	*RUSYDE 40mg tablets	b31q.
	FUROSEMIDE 20mg/5mL sugar free solution	b31r.
	FUROSEMIDE 40mg/5mL sugar free solution	b31s.
	FUROSEMIDE 50mg/5mL sugar free solution	b31t.
	FUROSEMIDE 50mg/5mL injection	b31u.
	*FRUSEMIDE 1mg/1mL liquid	b31x.
	FUROSEMIDE 20mg/2mL injection	b31y.
	TRIAMTERENE+FUROSEMIDE 50mg/40mg tablets	b51H.
	SPIRONOLACTONE+FUROSEMIDE 50mg/20mg capsules	b51J.
	FUROSEMIDE 250mg/25mL injection	b31z.
	LASILACTONE capsules	b519.
	FRUMIL 40/5mg tablets	b516.
	FRUMIL LS 20/2.5mg tablets	b51o.
	FROOP 40mg tablets	b31E.
Bumetanide	BUMETANIDE	b32..
	*BURINEX 1mg tablets	b321.
	*BURINEX 5mg tablets	b322.
	*BURINEX 1mg/5mL liquid	b323.
	*BURINEX 1mg/2mL injection	b324.
	*BURINEX 2mg/4mL injection	b325.
	*BURINEX 5mg/10mL injection	b326.
	*BETINEX 1mg tablets	b327.
	*BETINEX 5mg tablets	b328.
	BUMETANIDE 1mg tablets	b32u.
	BUMETANIDE 5mg tablets	b32v.
	BUMETANIDE 1mg/5mL liquid	b32w.
	*BUMETANIDE 1mg/2mL injection	b32x.
	BUMETANIDE 2mg/4mL injection	b32y.
	*BUMETANIDE 5mg/10mL injection	b32z.
ETACRYNIC ACID	ETACRYNIC ACID	b33..
	*EDECRIN 50mg tablets	b331.
	*EDECRIN 50mg injection	b332.
	*ETHACRYNIC ACID 50mg tablets	b33y.
	ETHACRYNIC ACID 50mg injection	b33z.
PIRETANIDE	PIRETANIDE	b34..
	*ARELIX 6mg m/r capsules	b341.
	*PIRETANIDE 6mg m/r capsules	b34z.
TORASEMIDE	TORASEMIDE	b35..
	TOREM 2.5mg tablets	b351.
	TOREM 5mg tablets	b352.
	TOREM 10mg tablets	b353.
	*TOREM 10mg/2mL injection	b354.

	*TOREM 20mg/4mL injection	b355.
	TORASEMIDE 2.5mg tablets	b356.
	TORASEMIDE 5mg tablets	b357.
	TORASEMIDE 10mg tablets	b358.
	*TORASEMIDE 10mg/2mL injection	b359.
	*TORASEMIDE 20mg/4mL injection	b35A.
Compound Potassium sparing diuretic	POTASSIUM SPARING COMPOUND DIURETICS A-Z	b51..
	ALDACTIDE-25 tablets	b511.
	ALDACTIDE-50 tablets	b512.
	*AMILCO tablets	b513.
	DYAZIDE tablets	b514.
	*DYTIDE capsules	b515.
	FRUMIL 40/5mg tablets	b516.
	FRUSENE tablets	b517.
	KALSPARE tablets	b518.
	LASILACTONE capsules	b519.
	CO-TRIAMTERZIDE 50/25mg tablets	b51A.
	*FRU-CO 40/5mg tablets	b51B.
	AMILORIDE HCL+CYCLOPENTHIAZIDE 2.5mg/250micrograms tablets	b51C.
	AMILORIDE HCL+BUMETANIDE 5mg/1mg tablets	b51D.
	TRIAMTERENE+BENZTHIAZIDE 50mg/25mg capsules	b51E.
	TRIAMTERENE+CHLORTHALIDONE 50mg/25mg tablets	b51F.
	TRIAMTERENE+CHLORTALIDONE 50mg/50mg tablets	b51G.
	TRIAMTERENE+FUROSEMIDE 50mg/40mg tablets	b51H.
	SPIRONOLACTONE+FUROSEMIDE 50mg/20mg capsules	b51J.
	*DELVAS tablets	b51K.
	*ARIDIL 2.5mg/20mg tablets	b51L.
	*ARIDIL 5mg/40mg tablets	b51M.
	*ARIDIL 10mg/80mg tablets	b51N.
	*SPIRO-CO 25mg tablets	b51O.
	*SPIRO-CO 50mg tablets	b51P.
	*ZIDA-CO 5mg/50mg tablets	b51Q.
	*FRUSEMEK 5mg/40mg tablets	b51R.
	*FROOP CO 5mg/40mg tablets	b51S.
	*KOMIL 5/40 tablets	b51T.
	MODURET-25 tablets	b51a.
	MODURETIC tablets	b51b.
	*MODURETIC mixture	b51c.
	*NORMETIC tablets	b51d.
	*SYNURETIC tablets	b51e.
	*TRIAMCO tablets	b51f.
	*HYPERTANE-50 tablets	b51g.

	*LASORIDE tablets	b51h.
	*CO-AMILOFRUSE tablets	b51i.
	CO-AMILOZIDE 2.5/25mg tablets	b51j.
	CO-AMILOZIDE 5/50mg tablets	b51k.
	CO-AMILOZIDE 5mg/50mg/5mL mixture	b51l.
	VASETIC CO-AMILOZIDE 5/50mg tablets	b51m.
	*FRUSENE tablets 56CP	b51n.
	FRUMIL LS 20/2.5mg tablets	b51o.
	CO-FLUMACTONE-25 tablets	b51p.
	CO-FLUMACTONE-50 tablets	b51q.
	NAVISPARE 2.5/0.25mg tablets	b51r.
	*AMILMAXCO 5/50 tablets	b51s.
	*BURINEX A tablets	b51t.
	*FRUMIL FORTE 80/10mg tablets	b51u.
	*TRIAMAXCO 50/25mg tablets	b51v.
	*KALSPARE LS tablets	b51w.
	CO-AMILOFRUSE 2.5/20mg tablets	b51x.
	CO-AMILOFRUSE 5/40mg tablets	b51y.
	CO-AMILOFRUSE 10/80mg tablets	b51z.

2.2.3 Potassium sparing diuretics and aldosterone antagonists		
	POTASSIUM SPARING DIURETICS	b4...
Amiloride	AMILORIDE HYDROCHLORIDE	b41..
	*MIDAMOR 5mg tablets	b411.
	*AMILOSPARE 5mg tablets	b412.
	AMILORIDE 5mg/5mL sugar free solution	b413.
	*BERKAMIL 5mg tablets	b414.
	AMILAMONT 5mg/5mL sugar free oral solution	b415.
	AMILORIDE HCL 5mg tablets	b41z.
	AMILORIDE HCL+BUMETANIDE 5mg/1mg tablets	b51D.
	AMILORIDE HCL+CYCLOPENTHIAZIDE 2.5mg/250micrograms tablets	b51C.
	NAVISPARE 2.5/0.25mg tablets	b51r.
	KALTEN capsules	bde7.
	CO-AMILOFRUSE 5/40mg tablets	b51y.
	CO-AMILOFRUSE 10/80mg tablets	b51z.
	CO-AMILOFRUSE 2.5/20mg tablets	b51x.
POTASSIUM CANRENOATE	POTASSIUM CANRENOATE	b42..
	SPIROCTAN-M 200mg/10mL injection	b421.
	POTASSIUM CANRENOATE 200mg/10mL injection	b42z.
Spironolactone	SPIRONOLACTONE	b43..
	ALDACTIDE-25 tablets	b511.
	ALDACTIDE-50 tablets	b512.
	SPIRONOLACTONE 25mg tablets	b431.
	SPIRONOLACTONE 50mg tablets	b432.
	SPIRONOLACTONE 100mg tablets	b433.

	ALDACTONE 25mg tablets	b434.
	ALDACTONE 50mg tablets	b435.
	ALDACTONE 100mg tablets	b436.
	*DIATENSEC 50mg tablets	b437.
	*LARACTONE 25mg tablets	b438.
	*LARACTONE 100mg tablets	b439.
	*SPIROSPARE 25mg tablets	b43A.
	SPIRETIC 25mg tablets	b43a.
	SPIRETIC 100mg tablets	b43b.
	*SPIROCTAN 25mg tablets	b43c.
	*SPIROCTAN 50mg tablets	b43d.
	*SPIROCTAN 100mg capsules	b43e.
	*SPIROLONE 25mg tablets	b43f.
	*SPIROLONE 50mg tablets	b43g.
	*SPIROLONE 100mg tablets	b43h.
	*LARACTONE 50mg tablets	b43i.
	*SPIROSPARE 100mg tablets	b43j.
	SPIRONOLACTONE 5mg/5mL oral suspension	b43k.
	SPIRONOLACTONE 10mg/5mL oral suspension	b43l.
	SPIRONOLACTONE 25mg/5mL oral suspension	b43m.
	SPIRONOLACTONE 50mg/5mL oral suspension	b43n.
	*SPIRONOLACTONE 100mg capsules	b43z.
	SPIRONOLACTONE+FUROSEMIDE 50mg/20mg capsules	b51J.
TRIAMTERENE	TRIAMTERENE	b44..
	DYTAC 50mg capsules	b441.
	TRIAMTERENE 50mg capsules	b44z.
	TRIAMTERENE+FUROSEMIDE 50mg/40mg tablets	b51H.
	TRIAMTERENE+CHLORTALIDONE 50mg/50mg tablets	b51G.
	DYAZIDE tablets	b514.
	CO-TRIAMTERZIDE 50/25mg tablets	b51A.
Eplerenone	EPLERENONE	b45..
	INSPRA 25mg tablets	b451.
	INSPRA 50mg tablets	b452.
	EPLERENONE 50mg tablets	b45y.
	EPLERENONE 25mg tablets	b45z.

Appendix E
Narrative interview topic guide

The interview may cover topics that interviewees may find sensitive. Participants will be reminded of this prior to the interviews. It will be made clear to them that they do not have to answer any questions they do not wish to, and that they can pause or terminate the interview at any time. Due to the nature of topics to be discussed, it may be appropriate to open with general conversational questions to help put the participant at ease with the interview situation.

The interview will be carried out in two parts, in order to accommodate for anticipated fatigue.

INITIAL INTERVIEW - OLDER PEOPLE TOPICS GUIDE

The topic guide describes questions that attempt to elicit from the participant themselves' their own narrative.

This topic guide is to be used in the initial interview. If not all topics are covered in the first session, the interview may return to questions not used in the second visit. The topic guide will be refined based on the themes and theories emerging from on-going data analysis. (*in brackets and italics, notes for the researcher*).

(Throughout, try to ask people about concrete examples, ask them to describe scenarios etc)

First interview

Open first with biographical questions, changes/ crises

Warm them up

Lay out in the first what the difference between the 2, 2 chapters. Think about particular issues

Might help you open up

GENERAL OPENING QUESTIONS

- Have you lived here a long time/ have you always lived here?
- What did you do for a living?
- Since when have you been retired? How has that been?
-

LATER LIFE / GROWING OLDER / BECOMING FRAIL

To explore perceptions and adjustments to growing older, and how people in later life adjust (or not) themselves to became frail

- In terms of where you are now what are the kind of things you enjoy now? Has this always been the case and how has this changed?

- Can you tell me a bit about yourself and the kind of things you enjoy doing?
- Could you describe a typical day? *[+/- probes]*
- How has your daily life changed over time, over the past few years?
- To what extent do you consider yourself an active person?

- What are positive things of later life? *[significance of family/ friends]*

- What are the difficulties about later life?

- Do you have any health difficulties/ since when have you had ill health?
- Could you explain me how a good day/ bad day look like?
- How do they respond to good days/ bad days

BLOOD PRESSURE

- When were you first diagnosed with high blood pressure? How did that come about?
- Were there symptoms of low BP/ medications?
- Did the patient take the initiative to seek the diagnosis?
- Was there a change with treatment
- How did they feel differently as a result of this?

- Have you had any falls?
- Do you ever feel dizzy when you stand up?
- Has someone talked through the likely effects high blood pressure might have on you?
- Do the medicines make any difference, for better, for worse?
- Are you anxious going to the doctors?

MANAGEMENT

- Do the medicines make any difference, for better, for worse?
- Would you consider stopping treatment?
- What were you told re effects of treatment?
- How far would you want to be involved in options open to them
- Do they usually take the Dr's advice?
- Do they want to be responsible for themselves?
- Good days/ bad days:

- Loss of control doesn’t equal growing old and submitting self.

PRIORITIES

- As you look back over your life, do you see any "turning points"; that is, a key event or experience that changed over the course of your life or set you on a different track? (*consider timeline chart*)

- In particular are there turning points in your health you could identify? When were these? (*consider timeline chart*)

- How do you see the significance of your blood pressure in terms of your overall health and the changes you’ve described?
- What positive/ negative experiences have you experienced concerning your health?

- What do you value as a good life now? *[in what ways have you tried to compensate for losses/ optimise your life]*

- How have you come to terms with the changes you have described in your health?

Second Interview

How has your health been over the last intervening week?

Specifically mention frailty-use it upfront.

Would you consider yourself as frail?

Give them the quandary: Re. BP management in frail old age: Drs don't know

Ask them about a current decision with respect to bp. Ask about stopping meds

POTENTIAL FOR SELF MANAGEMENT

Look at the logistics of the home environment

- Where does the sbp monitor live

- Strategies to fit it in

- Struggle to fit it in

- Energy to do that

- Who does it, carer or family

- How much of life is changing

- How much do they get out of life day to day

- Sense of control

Are you monitoring BP?

- How frequently

- What have your readings been

- Do you worry about them?

- Does it reassure you

Self awareness

- Where does hypertension fit in to their personal priorities?

- How does one condition balance on another?

Socio-emotional context

Throughout the interviews notes will be taken by the interviewer of the context in which the interview takes place, aspects of the setting, any distractions during the interview, facial grimacing, body language or non-verbal cues that the Dictaphone may not record. Features of displayed emotion will also be recorded alongside the timing of what is being said.