Secondary prevention in heart failure: a special focus on aspirin, statins and exercise

"Well-established interventions in patients with coronary artery disease"

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April 2013

Abstract

Heart failure (HF) is a leading killer in the Western world and is a serious financial burden on health care budgets. Moreover, the life quality of many HF patients decreases through multiple morbidities. In order to improve the prognosis of HF patients, evidence-based treatments are developing.

This thesis investigated areas of secondary prevention in HF without evidence. Subjects included those accessing cardiac rehabilitation (CR) referral, exercise-based CR and aspirin and statin prescription. Outcomes consisted of all-cause mortality, hospital admission and exercise capacities. HF was evaluated mainly as the reduced ejection fraction (HF-REF) subtype, while applied statistical models were parametric and non-parametric. Missing values were assessed through multiple imputations.

First, the CR referral effect on mortality after an acute myocardial infarction event was evaluated. The Evaluation of Methods and Management of Acute Coronary Events (EMMACE)-I and II observational studies demonstrated CR referral as an independent predictor of survival in 2003, but not in 1995. Similar results were shown in HF subgroups. Although decreasing between the studies, CR referral was associated with treatment inequalities, thus suggesting a risk-treatment paradox.

Second, the effect of enrolment in exercise-based CR in HF patients was assessed through a meta-analysis incorporating randomised controlled trials (RCTs). Over a minimum of six months, follow-up exercise capacities and hospital admissions significantly improved in the exercise intervention group as compared with the control group. In contrast, mortality was not significantly improved through exercise, although a trend suggested exercise to be superior to a sedentary lifestyle.

Confounders were patient selection in RCT recruitment and the unequal quality of care.

Third, the average treatment effects of aspirin and statins in HF patients (EMMACE studies) improved survival rates during 90 months follow-up.

In HF populations, CR attendance influenced key outcomes significantly, whereas aspirin and statins were beneficial to survival in observational studies.

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Acknowledgements

This thesis is dedicated to the memory of my mother and father, Hanne and Richard Lewinter, and my grandparents, Edel and Ove Justesen.

I wish to express my gratitude to my leading supervisor, Martin Bland, for introducing me to medical statistics and supervising me patiently all the way through this thesis. Furthermore, he shepherded me when necessary and provided me with the chance to experience the art of academic work. I would also like to thank my second supervisor Patrick Doherty for his eternal support and guidance during the last part of the PhD.

At the same time I wish to express my appreciation to the other members of my TAP group: Simon Crouch and Christopher Gale. Together, they have provided the rigidity and a scientific environment in which to mould the thesis, and they have been supportive individually, whenever it was needed.

Bob Lewin and Gill Furze receive my full gratitude for introducing me to health sciences. In addition, I wish to thank Mona Kanaan for her inspiring teaching of statistics and her ongoing support. I would also like to thank Lisa Stirk and Kath Wright for their helpfulness in constructing syntaxes for the data searches. Furthermore, I wish to thank all my PhD co-fellows at Health Sciences for sharing the up- and downsides in the research learning process.

Clinically, I must thank Lars Køber and John GF Cleland for the introduction to and teaching of heart failure, as without them my interest in heart failure may not have been evoked. Moreover, I appreciate all the hard work by my NHS colleagues at the hospitals in Bridlington, Hull, and Scarborough where I worked during my stay in the UK.

Of family and friends I must thank Birte and Mogens Bak for their readiness and unselfishness in helping my family. Equally, I appreciate the helpfulness and hospitality of Ulla, Per, Anne Sofie and Elisabeth Knudsen on all occasions. I wish to thank Michael and Louise Storgaard for their help and support at all times, and I am indebted to Susan O'Neill for supporting me with my English, which has not always been easy. I will not forget the helpfulness and effectiveness of Stefan Bovien Nielsen, who was always ready to solve any computer problems, including my back-up system. Casper and Anne Hyldekvist, Claus

Meldgaard Rasmussen and Tina Mathiesen have left an indelible mark with their hospitality and friendliness, in Copenhagen and London. I also wish to thank Torsten Holm Nielsen for his long-distance support at any time of the day, and I wish to express my gratitude to Gitte Hansen for helping my mother while I was away. Finally, I must thank the foundation of Aase og Ejnar Danielsens Fond for giving me a research grant in 2008, which gave me the courage and opportunity to travel to the UK.

Author's declaration

I, Christian Lewinter, declare that all the contents of this thesis are the result of my own work. The EMMACE studies used in Chapters 2 and 4 were collected by the EMMACE investigators in Leeds in 1995 and 2003, respectively. My role involved combining the data sets and quality checking data. I also led the interrogation of data in terms of meeting the aims of the PhD thesis. I was responsible for; identifying available common variables from both decades, selecting the appropriate models, analysing the data and interpreting the outcomes. Each chapter includes appendices with examples of how the calculations were processed in Stata. Because all the results chapters have been or are currently peer-reviewed in cardiovascular journals, co-authors and journal reviewers have commented on essential parts of the work. There is no funding underlying this thesis. Finally, Mark Jones from Pro Proofreading and Copy-editing has edited the grammar, punctuation and readability of the thesis.

Chapter 1–General introduction

1.1 Introduction

Improved care in acute cardiac events increases the need for chronic care. Substantial improvements in invasive treatments of acute myocardial infarction (MI) have led to a large population of chronic heart patients. People within this group face the risk of future ill-health, disability and early death. Among patients diagnosed with heart failure (HF) the prognosis is even direr.

Therefore, although less effective than primary prevention, secondary prevention has been allocated a central place in treating HF patients. An effective introduction to a healthy lifestyle through cardiac rehabilitation (CR) has been successful mainly in heart patients without HF. Moreover, aspirin and statins have shown considerable benefits in patients with coronary artery disease (CAD), but paradoxically not in HF patients. The following chapter will explain the background of HF and its treatment interventions, including secondary preventions offered through aspirin, statins and CR. The literature of the following background chapter has all been gathered in the PubMed database. A substantial part of the randomised controlled trials (RCTs) were included in the latest guidelines of HF published by the European society of Cardiology (ESC). Most of these RCTs are recognised automatically in PubMed, which means that it is sufficient to write the abbreviation of the trial one wants to find. The PubMed database will then suggest a number of publications frequently differentiated by the subgroups, which may interest the reader.

1.1.1 Incitements

The inspiration for this thesis was built on discrepancies between the evidence on treatment in patients with CAD complicated by HF as compared with patients with CAD but without HF. Particular treatments chosen here in this thesis were exercise-based CR, statins and aspirin.

As a student, while working 20 hours a week as an observer of patients with CAD monitored through telemetry, I became interested in ischemic heart disease. This experience during

medical school gave me an excellent opportunity to learn about arrhythmia and how fragile patients are after a heart attack. While working in the heart unit in this central Copenhagen hospital I met Professor Lars Kober, a specialist in HF, and I was lucky enough to be introduced to data from the TRACE trial (1). From that very moment I realised that thrombosis in coronary arteries causes many patients to suffer from failing heart functions. In other words, patients with CAD risk developing HF, although the TRACE study demonstrated that the angiotensin-converting enzyme-inhibitor (ACE) trandolapril improves the prognosis of patients with a decreased left ventricular ejection fraction (LVEF).

After my residency, I started to work at a HF clinic in Hull, Humberside and East Yorkshire Riding, as a way of gaining experience abroad. In addition to investigating the respiratory function of HF patients, I became aware of the sinister prognosis with which these patients are associated. Although HF patients do indeed are benefit from beta-blockers, ACEIs and aldosterone antagonists, they have been linked in some studies to severe prognoses similar to those of cancer patients(2). Approximately two-thirds of patients with HF have CAD(3). and it became evident to me after accessing the relevant literature that despite their common disease traits, patients with HF and CAD have far from the same benefits provided by widely used secondary preventive medications as compared to patients with CAD but without HF. RCTs underscoring these disagreements highlighted primarily aspirin and statins to be neutral in HF patients as compared to CAD patients alone(4, 5).

At the University of York, where during my first year of the PhD program I learned about general statistical tools from my main supervisor, Martin Bland, I was also introduced to the CR research group at the university. Through observation of their national CR database, named “National Audit of Cardiac Rehabilitation” (NACR), I realised not only that this instrument of secondary prevention was frequently ignored by clinicians, but also the fact that HF patients only were referred for CR on very rare occasions(6). Similar to aspirin and statins, treatment differences in CR, measured in key clinical outcomes, were reported in systematic Cochrane reviews of HF and CAD patients through pooled effect sizes when comparing their results(7, 8).

The main research questions for my PhD thesis were established because of the imbalance between HF and CAD patients and their outcomes. They are as follows:

1) What are the prognoses for HF patients attending exercise-based CR?

2) Do aspirin and statins improve the lives of patients, based on the contemporary analyses of observational and experimental data?"

In order to answer these questions, local EMMACE-I and II data from West Yorkshire were employed(9). They included information on CR referral and aspirin and statin prescription following discharge from hospital after an MI event. Additionally, exercise-based CR attendance was evaluated in a new meta-analysis incorporating RCTs adjusted for contemporary treatments.

The thesis is constructed as follows. Chapter 1 is a general introduction to HF, the medications used in HF and the contents of CR. Furthermore, it establishes this study's aims, objectives and research questions.

Chapter 2 investigates the all-cause mortality of CR-referred MI patients with and without HF in the EMMACE-I and II studies. Furthermore, this chapter evaluates independent predictors for CR referral in 1995 and 2003 (years of the EMMACE studies). Finally, missing data are assessed and adjusted through multiple imputations.

Chapter 3 evaluates effect sizes of exercise-based CR on all-cause mortality and hospital admissions for HF patients when RCTs published between 1999 and to August 2010 were applied. The inclusion criterion involved a minimum follow-up of six months for the included trials. In addition to this modification to the previous Cochrane analysis by Davies et al., it was also decided to investigate the long-term effects (≥6 months) of exercise-based CR on exercise capacities measured through exercise time, the 6-MWT, exercise power (Watts) and peak PVO_2. Rees et al. (2004) measured these elements, but they did not distinguish between short- and long-term effects(10).

Chapter 4 evaluates the impact of aspirin and statins on the HF population, based on the findings of the EMMACE studies. In contrast to statins, where rosuvastatin has been shown as neutral in the CORONA and GISSI-HF RCTs, aspirin has not recently been compared to a placebo in a robust experimental design(11, 12). The WARCEF study compared aspirin with warfarin in patients by examining sinus rhythm. However, the study did not investigate whether or not aspirin was superior to a placebo. The EMMACE studies included patients with MI, and the majority would be candidates for aspirin and statins according to leading guidelines(13). My main question in Chapter 4 is therefore as follows: Would the subgroup of patients with HF in the EMMACE studies have received an improved prognosis following the prescription of aspirin and statins?

In Chapter 5, a general discussion of the thesis is undertaken and Chapter 6 includes a conclusion.

1.2 Heart failure

1.2.1 Definition

According to leading cardiovascular disease (CVD) societies, the definition of HF combines the clinical picture of symptoms with objective findings in abnormal heart function(14, 15). Patients with HF suffer from symptoms such as tiredness, breathlessness, impaired physical function and depression. From a health professional's viewpoint, symptoms can be deciphered from leg oedema, respiratory crackles, systolic murmurs, decreased muscle volume, weight loss and lower mood. With respect to objective findings of abnormal heart function, the European Society of Cardiology (ESC) defined the following biometrics as evidence: left ventricular systolic dysfunction (LVSD) indicated by a left ventricular ejection fraction (LVEF) of less than 45%, or a blood sample measuring NT- proBNP $\geq$ 400 mg/ml.

1.2.2 Epidemiology

Overall, as many as 10 million people in Europe are estimated to have HF(15). Of these, 900,000 live in the United Kingdom(15), while the HF population in the United States of America is around 5 million(16). Concerning the emerging world, HF has not been a serious health problem in the past, but is now starting to increase the strain on these countries' health systems(17). Such a surge in HF incidence can be explained by changes to sedentary lifestyles which are associated with the boom in the economies of emerging markets(18, 19).

Undergoing the transition from being a problem solely associated with the occidental world to becoming a global threat to health care budgets, yearly HF hospital admissions are more than 1 million in the US alone, compared to almost 100,000 in the UK(20, 21). It is generally accepted that HF is more frequent in men, which is true in cases related to ischemic heart disease (IHD). The risk of HF is greater in men, in contrast to the prevalence of HF, which is greater in women.(21) Confining HF to preserved ejection fraction (HF-PEF), these gender differences are explained by a surplus of women (a 2:1 ratio)(22).

In a gradually older population the HF diagnosis becomes more visible, in that the proportion of patients with HF rises sharply at the age of 75 years. Furthermore, this steep increase in HF during the seventies and eighties is underscored by a prevalence rate of 10 to 20% at the age of 80(14).

Understanding the development of HF and how it affects individuals' lives was investigated in the Framingham studies, Massachusetts(23), in which a total of 5,209 subjects were observed for three decades. Of these, 489 men and women developed HF. Independent risk factors for HF in the study were revealed as hypertension, non-specific S-T and T-wave changes, intraventricular conduction disturbances (bundle branch block) and left ventricular hypertrophy, and they were all demonstrated to be striking predictors. In addition, other less powerful risk factors, but still independent, were low vital capacity, rapid heart rate, diabetes, cardiac enlargement, obesity, serum cholesterol, cigarette use, proteinuria and hematocrit.

In the UK, the Echocardiographic Heart of England screening programme and the Hillingdon Heart Failure Studies have provided praiseworthy information on HF prevalence and incidences(24, 25). The Echocardiographic Heart of England screening study investigated 6,289 adults from 16 random general practices (GPs). A total of 139 (3.5%) were identified with LVSD following LVEFs ranging from 40 to 50%. Ascertained HF diagnoses were reported to be prevalent in 124 patients (3.1%).

According to the Hillingdon Heart Failure study, which investigated new incidences of HF in 151,000 patients served by 82 GPs, a crude incidence rate of 1.3 per 1,000 people per year was found for those aged 25 or over. The median age at the time of presentation was 76 years.

1.2.3 Prognosis

The prognosis of HF is similar to other chronic diseases associated with age at the time of diagnosis(26). For instance, in the setting of a HF diagnosis before the seventh decade, a brighter prognosis can be given as compared to patients diagnosed in their eighties, which is due to the likelihood of more frequent comorbidities. An unadjusted estimate of survival in HF has been stated as being 50% after 5 years(27). Pessimistic outlooks for HF patients are comparable with malignant cancers, and in general CVD is in the top six lethal diseases in the industrialised world, together with diabetes, cancer, COPD, stroke and accidents(2). The study by Jemal et al. (2002) highlighted the number of people dying each year in the US in

2002. After age adjustment, death rates per 100,000 inhabitants were 56.1 (stroke), 43.4 (COPD), 240.5 (heart disease), 193.5 (cancer), 25.4 (diabetes) and 36.9 (accidents).

In CVD, LVEF has been a marker of death in HF patients for a substantial period. This is incontestable in the majority of studies measuring the contraction of the heart in HF patients(28). However, the prognoses in patients with HF-PEF and HF-REF, respectively, are very similar, although HF-REF patients have the worst outlook(29).

Furthermore, the diagnoses of comorbidities such as diabetes, chronic kidney disease, anaemia and COPD are often found subsequent to HF, if the patient is relatively young or the diseases are already established in older patients at the time of HF. The combination of comorbidities and HF exacerbates the prognosis significantly. Several studies have demonstrated the prevalence and influence of comorbid conditions in HF patients(30, 31). One such study examined a sample of 9,442 veterans with HF-REF and HF-PEF and found that most comorbidities, such as diabetes, CVA, peripheral artery disease, renal insufficiency, anaemia, liver disease, cancer, HIV/AIDS and dementia, were all detrimental to survival prospects, irrespective of HF type(32). Conversely, COPD had a worse influence on survival in HF-PEF patients as compared to HF-REF patients (HF for COPD in HF-PEF, 1.62; 95% [CI], 1.36 to 1.92; vs. HR for COPD in HF-REF 1.23; 95% CI, 1.11 to 1.37). Overall, the study concluded that large numbers of comorbidities were more likely to be the underlying reason for hospitalisation in the HF-PEF group rather than in HF-REF patients in non-HF cases of hospital admission. Conversely, the study showed that HF-REF patients as compared to the HF-PEF group were more likely to be admitted due to HF.

In addition to LVEF and comorbidities, diagnostic measurements are important for prognosis. The pivotal role of electrocardiography (ECG) in HF prognosis was demonstrated by the author of the present thesis. During a minimum follow-up of 15 years, 6,676 patients with reduced LVEF in the TRACE study population (< 45%) were randomised between the ACE-I “trandolapril” and a placebo(33). Patients with interventricular disturbances were distinguished between right- and left- bundle branch blocks (R- and L-BBB). The long-term survival analyses showed that RBBB was associated with increased mortality in patients with LVEF ≤ 45% (HR, 1.31; 95% CI, 1.11 to 1.55), where LBBB was an independent marker for death in LVEF above 45% (HR, 1.70; 95% CI, 1.12 to 2.57), thus demonstrating an interaction between bundle branch type and LVEF.

1.2.4 Aetiology

Ischemic heart disease (IHD)

Without doubt, IHD – as an isolated factor – is the most frequent cause of HF. About 70% of all HF patients have a history of CAD(14), while the remaining 30% experience HF as the result of hypertension, congenital disease, obesity, diabetes and several other debilitating illnesses. Seen from the opposite perspective, it is reckoned that 35% of patients with confirmed myocardial infarction (MI) finally develop HF(34).

Atherosclerosis is the response of the vessels in patients exposed to risk factors over a longer period of time, or it can simply be due to genetic heritance. Risk factors are, for instance, smoking, obesity, high calorific intake, alcohol and a sedentary lifestyle. Initially, atherosclerosis starts when the endothelial cells are exposed to either hemodynamic, oxidative or biochemical stimuli (from smoking, hypertension or dyslipidaemia). This exposure changes the permeability of the endothelial cells and at the same time promotes the entry and retention of blood-borne monocytes and cholesterol-containing LDL particles(35). It is essential to understand that atherosclerosis is translated into chronic inflammation of the arteries and is an ongoing process that lasts for decades.

Continuous inflammation and biochemical modification elicit the proliferation of the smooth muscles and endothelial cells, and they generate extracellular matrix molecules and a fibrous cap which covers the developing atheromatous plaque(36). Eventually, this plaque build-up leads to clinical symptoms in the form of unstable angina, which narrows the vessel lumen and prompts deprivation of oxygen to the heart. Plaque can also cause temporary and permanent obstruction of the blood flow via thrombi, which are – through thrombosis – triggered by the rupturing of plaque exposed to pro-coagulant material within the core of plaque-stimulating proteins and lead to platelets coagulating.

Low-density lipoprotein (LDL) cholesterol plays a key role in the generation of atherosclerosis. Different aspects of atherosclerosis have been associated with LDL cholesterol. First, genetic impairment involving the failure of the receptor-mediated removal of LDL cholesterol from plasma is associated with fulminant atherosclerosis(37). Second, animals with low LDL cholesterol levels have very rare bouts of atherosclerosis. If such animals have their LDL cholesterol increased experimentally, then the incidents of disease also rise. Third, humans with low LDL cholesterol have only rudimentary atherosclerosis. Researchers investigating coronary artery disease (CAD) achieved a seminal breakthrough

when the LDL cholesterol pathway was delineated(38), and this discovery led to the concept of feedback regulation for receptors and it is the mechanism that statins utilise in order to lower plasma LDL cholesterol.

In contrast to LDL cholesterol, high high-density lipoprotein (HDL) values are beneficial for the metabolism. This is because HDL levels are inversely related to cardiovascular risk. Yet, to date, neither of the pharmacological agents raising HDL levels has had a significant effect on cardiovascular mortality and morbidity rates(39).

The treatment of acute IHD has evolved immensely during the last 30 years, from merely relying on bed rest to stepwise progression with the thrombolytic agent streptokinase to finally ending up with percutaneous cardiac interventions (PCIs)(40). In addition to PCI, coronary artery bypass grafts (CABGs) are also chosen in cases where three of the coronary arteries are impaired by atherosclerosis. An Italian research group studied streptokinase in myocardial infarction (GISSI) in more than 10,000 patients(41) and demonstrated that it reduced early mortality in patients with MI.

The Second International Study of Infarct Survival (ISIS-2) showed that the addition of aspirin to patients with MI reduced mortality further(42).

Coronary angioplasty and stenting, together with glycoprotein IIb/IIIb platelet receptor blockers, are the last consolidated breakthroughs which have been achieved so far. Today, with the help of modern technology, the in-hospital mortality rate for acute IHD is estimated at 7%(37).

Surprisingly enough, patients with diagnosed HF have fewer incidences of heart attacks than the rest of the population without HF(43, 44), a finding which may have an important influence on future secondary prevention.

Cardiomyopathy

The description of heart disease based on abnormal functioning and the structure of the myocardial muscle fits into the realm of cardiomyopathy. It is important to note that cardiomyopathy evolves from other conditions in addition to pressure overload and storage/infiltrative disease(45). As a rule it is impossible to discern if these criteria are obeyed when echocardiography or cardiac CT diagnostics are used. However, investigations into

genomics, family history, clinical symptoms and responses to relevant treatment help in making the right diagnosis.

Cardiomyopathy diagnostics are classified according to primary and secondary aetiologies. The former are strictly related to the heart, whereas the latter is related to systemic diseases, including the heart as part of the whole picture. Although this classification is still applied, it has been largely abandoned due to the tenuous line between heart disease and associated comorbidities(46). Generally speaking, cardiomyopathies are distinguished as one of the following: 1) hypertrophic cardiomyopathy (HCM), 2) restrictive cardiomyopathy (RCM), 3) dilated cardiomyopathy (DCM), 4) arrythmogenic right ventricular cardiomyopathy (ARVC) or 5) unclassified.

HCM is defined by left ventricular hypertrophy (LVH)(47), and its prevalence is estimated at 600,000 people in the US alone. Of these, 1% die on an annual basis due to sudden cardiac death. Regarding HCM with known genetic disorders, the sarcomeric subsets are associated with myosin heavy chain 7 (MYH7) and myosin binding protein C3 (MYBPC3) in 80% of cases(48). Despite insights into a considerable amount of the genome underlying HCM, there is only a weak correlation between genotypes and phenotypes, which means that treatment in the majority of cases is unaltered, regardless of the genetic codes unearthed. The gravest and most feared complication of HCM is sudden cardiac death (SCD)(49). Risk factors predicting the outcome of SCD are a family history of SCD, non-sustained ventricular tachycardia (VT), unexplained syncope and left ventricular hypertrophy (LVH)> 30 mm. It should be added that each of these risk factors is a weak predictor. If the risk of SCD is ascertained to exist, the insertion of an implantable cardioverter-defibrillator (ICD) is successful in preventing SCD(50). Overall, the individualised treatment package consists of the following: 1) symptom management, 2) risk stratification for SCD and 3) counselling/screening, incorporating advice to avoid exhausting physical activities and the genetic screening of relatives.

DCM is characterised by left ventricular dilation and dysfunction. Equally, the right ventricle frequently tends to be dilated and dysfunctional, but this is not an assured sign for diagnosis. The disease varies with age and geography, and 25% of cases are associated with inherited autosomal genetic disorders. Autosomal genetic disorders are located in mutations in cytoskeletal and sarcomeric protein genes. Muscular dystrophies, such as Becker's, Duchenne's and x-linked DCM, are examples of x-linked disease(51). DCM can also occur after cardiac infection. In contrast to active or fulminant myocarditis classified as acute inflammatory disorders, often having normally ranged left ventricular size, inflammatory DCM is characterised by chronic inflammatory cells and associated with left ventricular

dilation and reduced LVEF. Discrimination through histology and immunochemistry is therefore compelling in making a DCM diagnosis. An important component of DCM is peripartum cardiomyopathy (PPCM), manifested by signs of cardiac failure during the last months of pregnancy or within five months of delivery(52). The condition is uncorrelated to the mother's number of births, but it is strongly related to gestational hypertension, twin pregnancy and tocolytic therapy. The latter is related to labour repressants, for instance beta-2 agonists such as terbutaline, which are administered to suppress premature labour.

Restrictive cardiomyopathy (RCM) is possibly the least frequent of all the subsets of cardiomyopathies. The word 'restrictive' comes from the failure of the heart muscle to comply with increasing volumes without precipitous rises in pressure(51). It can branch from different preceding conditions, such as end-stage dilated cardiomyopathy (DCM) and HCM, but it can also develop from a primary familial background. An example of the latter is an autosomal dominantly-inherited disease in the Troponin I gene. Systemic progenitors are sarcoidosis, amyloidosis, carcinoid heart disease, scleroderma and anthracycline toxicity.

ARVC is contrary to the mentioned cardiomyopathies defined by the presence of right ventricular myocardium entangled with adipose and fibrous tissue. This transformation is confined to a 'triangle of dysplasia', comprising the right ventricular inflow, outflow and apex. The definition of ARVC is based on right ventricular dysfunction (global or regional), irrespective of left ventricular disease, and has been proven on histological evidence or electrocardiographic abnormalities corresponding with published criteria(53). Although there is a minimal prevalence – estimated at one in every 5000 – ARVC is frequently seen as underlying SCD in young people living in certain European areas. The majority of cases are recognised due to autosomal dominantly-inherited mutations in gene coding for plakophilin 2 as well as related proteins of cardiomyocyte desmosomes.

The group of unclassified cardiomyopathies is heterogeneous and insufficiently characterised. One example is Takotsubo cardiomyopathy, known as apical ballooning syndrome and recognised by transient regional systolic dysfunction confined to the left ventricular apex or the mid-ventricle and verified by absence of obstructive CAD by angiography(54). The syndrome can be seen in the form of angina and promotes electrocardiogram (ECG) changes in the form of T-wave inversion, preceded in some cases by elevations of ST-segments and cardiac enzymes. Symptoms are often connected to emotional and physical stress and appear more frequently in women. Noradrenaline concentrations are elevated in most patients. The function of the left ventricle tends to renormalise over a period varying from days to weeks. The same picture for myocardial dysfunction associated with Takotsubo cardiomyopathy has

been reported in patients with intracranial haemorrhages and other acute cerebral accidents why formulated as neurogenic myocardial stunning.

1.2.5 Comorbidities

Conditions either aggravating HF or simply developing concomitantly are more the rule than the exception. Diseases deserving of mention here are COPD, diabetes, kidney disease, anaemia, hormonal imbalance, muscle weakness and valvular disease. The interplay between HF and concomitant diseases is far from mapped, but the clinical importance of their co-existence is acknowledged. This demands broader and more profound knowledge of doctors in treatments and diagnoses outside their own specialty. Patient management programmes are changing with growing economic frugality and the increasing benefits of dealing comprehensively with multiple diseases.

A clear distinction between respiratory disease and HF can often be confounded by multiple pitfalls hidden in diagnostics tools, amongst which are echocardiography, pulmonary function testing and chest x-rays. One example is enlarged lungs with air trapped in COPD, thus making echocardiographic assessment of cardiac function difficult(55). The great variability in pulmonary tests and a somewhat relaxed attitude to the prescription of inhalers makes concise diagnoses difficult, too.

Respiratory disease mostly diagnosed as COPD is confirmed to aggravate the prognosis of HF(56).

A large observational study in Norway of 4,132 patients found the death rates to be 19% higher in the group with HF and COPD during a mean follow-up of 13.3 years, as compared to the HF group without COPD(57). However, this study exemplified prognostic implications derived from selected heart disease populations, rather than unselected patients with breathlessness, therefore potentially biasing the results in the context of COPD and HF. Possibly worsening the diagnosis of patients with both HF and COPD is the lack of beta-blocker therapy in patients with COPD. Except as a rare side-effect of beta-blockage in asthma patients, beta-blocker-related bronchospasm is a misconception(58); in fact, recent findings suggest that beta-blocker therapy improves COPD management(59).

Evidence relating to diabetes and HF mostly evaluates the diseases from separate points of view, i.e. patients with both diseases and those with diabetes are assessed for the risk of HF. Overall, 5% of the world's population has diabetes, and depending on how effective the

respective health care systems are in preventing and treating the disease, the current number will accelerate disproportionately(60).

Attention to diabetes has largely been drawn to its macro-vascular pathology, which causes CVD and leads to periphery vascular disease, stroke and MI(61). CVD has also been established as the most common killer among diabetics(62). The disease pathway behind macro-vascular disease has been identified as a diabetic effect on endothelial and vascular functions, increasing the potential for thrombosis and vasoconstriction.

Micro-vascular disease, observed for instance within retinopathy, is associated with the development of HF in diabetic patients. Pathways, claimed to underlie both macro-vascular and micro-vascular disease formation, have been linked to the hyperglycaemia-induced overproduction of superoxide by the mitochondrial electron transport chain. This has an activating impact on the deleterious hexosamine pathway, prompting hyperglycaemia-induced cardiomyocyte dysfunction as one of a number of reactions(63). Developing from such links, 'diabetic cardiomyopathy' has become a terminological phrase(64). This variant of HF is observed with preserved and reduced LVEF. The diabetic component has also been described as fatty, sweet and stressed, due to its metabolic abnormalities and cardiac dysfunction(65).

Anti-diabetic drugs in use have increased in order to control the blood sugar. In addition, in order to cause less harmful side-effects such as hypoglycaemia, surprisingly TDZ-based therapies have been connected to HF through a meta-analysis including 8 RCTs involving >37,000 patients(66). Although the underpinning mechanisms remain unknown, it is also concluded that a stricter regimen with lower levels of the glycated haemoglobin (HbA1c) does not favour the incident risk of HF. Doubt has also been raised on another anti-diabetic drug – metformin – which until recently was perceived to be associated with HF incidences. Therefore, it is now prescribed with the prevailing attitude that it is safe regarding the HF risk(67).

Cardio-renal anaemia syndrome

The interactions between HF, chronic kidney disease and anaemia have been termed 'cardio renal anaemia syndrome'. After one of these diseases appears, the two other are likely to follow, thus establishing a vicious cycle. An illustration of interactions between the diseases could start, for instance, with HF impairing kidney perfusion and lead to chronic kidney disease(68), which then causes lower erythropoietin (EPO) production by the interstitial cells in the peritubular capillary bed of the kidney, which in turn lowers bone marrow stimulation

preceding red blood cell production (erythropoiesis). This pattern will finally cause anaemia, which involves oxygen delivery from the lungs and then from the alveoles to the capillaries, where it attaches to red blood cells. Oxygen detachment from the red blood cells happens in muscle or organ tissue capillaries. In order to maintain the demands of the human body in the presence of decreased levels of red blood cells, the failing heart is compelled to work harder, which therefore increases the strain exerted on it. This activates the renin angiotensin aldosterone system (RAAS), hence aggravating HF, and furthermore it leads to water retention, prompting over-hydration.

The treatment of cardio renal anaemia syndrome is primarily based on a beta-blocker and ACE-I strategy, but new insights into the effectiveness of erythropoietin (EPO) administration in addition to the already demonstrated beneficial effect of iron are underway in the Red-HF study(69). Experimental animal studies have reported improved haematocrit, LV function and the induction of angiogenesis(70). One remaining unanswered question in anaemia and HF is the effect of anti-platelets as a deteriorating factor by causing occult bleeding.

Valve disease

Valve disease is mainly considered a disorder on the left side of the heart, and any dysfunction of the aortic and mitral valves accounts for by far the largest proportion of valve disease associated with HF. Making the situation even more complex is that a single accident seldom occurs alone, and it is understood that a diagnosed valve defect can easily be joined by another, or even located in the same valve. The distinction between primary leaflet and functional disease is difficult if HF and valve disease are intertwined; the combined entity of structural valve disease and the syndrome of HF create a double-edged sword. Primary valve disease in the scenario without HF predisposes toward HF due to its potential increasing effect on left ventricular volume, left ventricular hypertrophy and decreasing left ventricular stroke volume (LVEF=stroke volume/left end-diastolic volume)(71). Diametrically, HF remodels the left ventricle, meaning that the valves cannot fit into their frames and functional regurgitation is the end result(72). In the following summary of valve diseases it will not be assessed which of the diseases occurs first. Moreover, although not elaborated on here, ischemic heart diseases also provoke valve disease.

Aortic stenosis is similar to HF and is more frequent in elderly patients, in whom it begins typically after the age of 60. The underlying pathology is mostly associated with calcification of the leaflets, but rheumatic fever due to Streptococcus Pyogenes infection is still a

considerable threat for valve stenosis in non-Western parts of the world(73). The disorder is frequently recognisable by a murmur heard through a stethoscope at the aortic spot on the chest. The murmur appears as a 'second' heart sound. When symptoms of stenosis are present, valve replacement is the only effective therapy available. Eligible patients receive percutaneous valve replacement or open chest surgery. Despite valve replacements, though, the prognosis is still not encouraging. New reports from the FRANCE 2 registry suggest that trans-catheter aortic valve implantation (TAVI) is a reasonable choice in patients not eligible for surgery, and it has a procedural success rate of 96.1%.(74) On the other hand, TAVI and balloon aortic valvuloplasty were compared against each other in the PARTNER trial, through the recruitment non-qualified surgical patients, and found TAVI to reduce deaths and hospitalisation significantly over a follow-up period of two years(75).

New insights into aortic stenosis have established cholesterol, metabolic syndrome, male sex, smoking, hypertension and the metabolic syndrome as the main disease-promoting factors(76). However, initial attempts to reduce aortic stenosis through cholesterol-lowering therapy failed in the SEAS trials, suggesting an urgent rethink of the pathology, prevention and innovation around treatment(77). Furthermore, it should be borne in mind that aortic stenosis sometimes develops as a complication of regurgitation(78).

In addition to aortic stenosis, aortic regurgitation is associated with the same variables that predict aortic stenosis, not to forget the primary disease of the valve resulting in aortic regurgitation. Aortic dysfunction provokes HF progressively as the backward flow increases LV volume and enlarges the muscle mass of the left ventricle, eventually causing LVH. The increased volume will eventually decrease the compliance of the LV manifested by HF. Aortic regurgitation has shown promising responses to ACE-I therapy, but such a medical treatment choice needs to be withheld until confirmed freedom of aortic stenosis is confirmed(79).

Mitral stenosis is most common in Western populations over 60 with associated high comorbidities(80). Its aetiology is similar to aortic stenosis, but this does not mean that the two diseases exist together. A frequent complication attached to the condition is AF, due to the backward flow from the left ventricle which then enlarges the left atrium. This leads to disorganised electrical impulses originating in the pulmonary veins. With respect to treatment, commissurotomy of the leaflets can be achieved through surgery or percutaneous balloon valvuloplasty. The effects of such strategies are mainly successful if the valve area is more than 1.5 cm^2 and coexisting mitral regurgitation is less than severe(81). If the odds of success before intervention are high, valve replacement can be chosen. However, this choice brings

the risk of side effects such as lifelong anti-coagulation therapy or repetitive replacement procedures, as bio-prosthetic valves have a short shelf life.

Mitral regurgitation is a common condition, as up to 80% of people have a backward flow through the mitral valve during leaflet closure. Most are without symptoms, though, and dependent on the underlying mechanisms leading to the regurgitant jet, the prognosis of treatment varies. A rule of thumb is that causal factors should be treated first, meaning that HF should be treated by medication initially, even if regurgitation is confirmed through echocardiography. The amelioration of insufficient closure due to cardiomyopathy or coronary disease treated by drugs or CRT has a remarkably better prognosis than valve-specified treatment due to primary disease(72, 82). Irrespective of the reason behind regurgitation, huge efforts are undertaken to treat valve disease as effectively as possible. A recent study (EVEREST II) compared mitral clips intervention with conventional surgical intervention, in order to investigate if the clip method produced fewer complications than its surgical alternative(83). The conclusion in this RCT was that mitral clips implanted through percutaneous intervention were less effective than surgery. However, percutaneous intervention was associated with superior safety, and clinical outcomes between the interventions were similar.

The tricuspid valves consist of three leaflets in the right side of the heart and serve as a biological device to uniformly pump the blood from the right atrium into the right ventricle. Stenosis of the valves is mainly connected to rheumatoid disease, but other kinds of infections (endocarditis) lead to a narrower orifice between the tricuspid leaflets(84). Regurgitation through the tricuspid valves can also be caused on the right side of the heart by failing function on the left side, which basically is HF. Furthermore, mitral valve disease and pulmonary hypertension can secondarily lead to functional regurgitation(85).

Neuro-humeral imbalance

Neuro-humeral imbalances are immediate responses to HF and are the result of the body trying to compensate for a failing heart. The neuro-humeral axis includes the autonomic nerve system, the RAAS and arginine vasopressin (antidiuretic hormone). Albeit these disorders have been discovered and largely deciphered, HF syndrome still has unmapped hormonal cascades accounting for clinical symptoms in the disease.

Manifested as a mechanism which compensates for the weakness of the heart, rising systemic catecholamines result from the sympathetic nerve system, which is activated due to falling blood pressure and volume overloading. The heart responds by increasing the heart rate and contractility(86). In addition, the sympathetic nerve system provides vasoconstriction, which is illustrated by a rise in blood pressure. Arginine vasopressin stimulation is furthermore conceived to contribute to peripheral vasoconstriction, thus maintaining blood pressure.

The RAAS is demonstrated as an essential factor underlying breathlessness, fatigue and low appetite, which are some of the symptoms found in HF. Equivalently, repercussions attributable to the RAAS can be interpreted as the body's defence against a failing heart. In an attempt to keep a balance between supply and demand, the kidneys start to secrete renin as a result of the falling perfusion to the kidney. Renin converts angiotensinogen (made in the liver) to angiotensin 1 and is then converted to angiotensin 2 by a converting enzyme predominating in the lungs(87). The aftermath of angiotensin 2 is primarily delineated into three deleterious pathways: 1) it contributes to excess systematic vascular resistance, 2) it stimulates catecholamines through sympathetic outflow facilitation and 3) it activates the release of aldosterone (mineralcorticoid) by the adrenal gland, thus provoking salt and fluid retention.

New insights into the complex pathways of neuro-humeral signals are continuously being added to existing understanding. The data suggest that testosterone is a promising therapy for patients with HF(88).

The prevalence of depression among HF patients is high. In addition, the majority of this HF subgroup do not receive relevant treatment for this disease(89), and those suffering from depression have demonstrated increased risks of death and hospital admission(90). For this reason, several attempts have been made to implement non- and medical interventions against depression and anxiety in patients with HF. The upshot of this effort is not immediately

compelling(91); however, it should be noted that most anti-depressive drugs are well tolerated in HF patients, with the exemption of tricyclic antidepressants(92).

1.2.6 Treatment

HF treatments can be subdivided into pharmacological and non-pharmacological therapy. The latter is deciphered in this thesis as 'device therapy and surgery'. Other non-pharmacological therapies, such as smoking cessation, anti-depressive interventions and diet advice, are not elaborated on in this subsection, but they will be mentioned in the cardiac rehabilitation section of this chapter. Interventions such as tele-monitoring and patient management care are also beyond the scope in this thesis. In addition, palliative treatment is not elaborated on either, even though it is a relevant and quickly expanding area, and acute HF treatment is disregarded as well as treatments for the HF comorbidities mentioned above.

Pharmacological treatment

The science of treating and preventing HF with pharmacological drugs is continuously moving. It is important to note that most drugs are only validated in HF patients with LVSD (LVEF ≤ 45%), whereas evidence in the group of HF-PEF patients is sparse but is nevertheless progressing(3).

ACE-Is have been demonstrated in several RCTs to improve survival in HF patients. In the Consensus trial, 253 patients with diagnosed HF were allocated to either enalapril or a placebo.(93) The relative risk (RR) reduction in the drug-assigned group was 27% (P= 0.003) over a mean follow-up of 188 days. A similar benefit of enalapril was demonstrated in the SOLVD-treatment trial (n=2569), where the researchers found an RR reduction of 16% (P=0.004) over a mean follow-up of 41.4%(94).

The ATLAS trial recruited 3,164 patients and showed that lisinopril prompts an RR reduction of 15% (P< 0.001) in the composite outcome of death and HF hospitalisation.(95) Furthermore, three RCTs recruiting patients with LVSD after an acute MI event, but without verification of HF, equally supported the prescription of ACE-Is to HF patients by demonstrating significantly lower death rates in the drug-allocated group. Specifically, these studies were the SAFE, AIRE and TRACE trials investigating the effect of captopril, ramipril and trandolapril, respectively(1, 96, 97).

Angiotensin receptor blockers (ARBs) have until recently been the second choice among most physicians if ACE-Is are not tolerated. However, according to the new guidelines of the European Society of Cardiology (ESC) in HF, aldosterone antagonists are recommended to replace ARBs. Despite the change in ranking of HF drugs, empirical support is well-demonstrated in ARBs, the key trials for which are the valsartan HF trial (VAL-HEFT) and the CHARM study, which investigated the 'add-on' effect of valsartan and candesartan, respectively (98, 99).

Aldosterone antagonists are preferred instead of ARBs, if ACE-Is are not tolerated, due to a higher RR reduction favouring eplerone in the EMPHASIS-HF trial compared to the trials investigating ARBs(100). Besides, ARBs have not shown improved survival chances when added to ACE-Is, which in contrast aldosterone antagonists have demonstrated(101).
The RALES trial allocated 1,663 patients to either spironolactone or a placebo in HF patients with an LVEF of 35% or less. Over an average follow-up time of 24 months an RR reduction in death at 30% ($P< 0.001$) was observed in the treatment group. The enrolled population were all treated with ACE-Is on entry to the trial.

The EMPHASIS-HF randomised 2,737 HF patients while prescribing either a placebo or up to 50 mg eplerone daily. This study design also allocated an aldosterone antagonist to patients already receiving ACE-Is. With a mean follow-up of 21 months, patients assigned to eplerone had an RR reduction of 24% ($P=0.008$).

Beta-blockers are the second mandatory group of medications prescribed for HF treatment. Their immediate use in patients as soon HF diagnosis is verified is due to their anti-remodelling effect on the myocardium and their significant increasing effect on survival. Three pivotal studies emphasising the benefits of beta-blockers are the cardiac insufficiency bisoprolol study (CIBIS-II), carvedilol prospective randomised cumulative survival (COPERNICUS) and the metoprolol CR/XL randomised intervention trial in congestive HF (MERIT-HF)(102-104).

Common to all three studies investigating the effect of bisoprolol (N= 2647), carvidolol (N= 2289) and metoprolol (N= 3991) on the primary outcome of all-cause mortality was a significant RR reduction of 34%. The follow-up times of the trials were similar, varying between 10.4 months and 1.3 years. Regarding LVSD, the inclusion criteria for the COPERNICUS trial was an LVEF less than 25% (severe LVSD). The CIBIS-II and MERIT-HF included HF patients with moderate LVSD, having an LVEF of 35% or less and 40% or less, respectively. However, this variation in LVEF in HF patients did not appear to influence

the benefit of beta-blockers, which possibly explains the recommendation of these drugs in all HF patients with LVSD (LVEF≤ 40%).

The vasodilator combination of hydralazide and isosorbide dinitrate (H-ISDN) is a possibility if ACE-Is and ARBs are not tolerated, especially when considering that the effect of aldosterone antagonists is insufficient. The evidence behind this combination in HF is scarce, as it has only been shown to increase survival in small RCTs of African-Americans(105, 106).

The V-HeFT-I trial randomised 642 men for the administration of a placebo, prazosin or H-ISDN. HF patients randomised to H-ISDN showed a significant RR reduction of 34% at 2 years (P=0.03). The A-HeFT performed similarly to the V-HeFT-I trial, demonstrating a significant RR reduction of 43% (P=0.01) in a population of 1,050 African-Americans. Remarkably, the trial was stopped before time by the steering committee, as the overall mortality rate was observed to be significantly higher in the control group than in the group assigned to H-IDSN.

Digoxin and ivabradine are two drugs targeting the natural pacemakers in the heart, mainly located in the left atria. Therefore, it has been mainly patients with atrial fibrillation (AF) and fast sinus rhythm (SR>60) who have benefitted from the rate control effect of the two drugs. However, as a substantial proportion of AF patients suffer from HF, further investigations have revealed that HF patients might also improve as a result of treatment with digoxin and ivabradine. Even though the largest trial investigating digoxin, which randomised 6,800 HF patients with NYHA class 3 to 4 and placed them on either digoxin or a placebo, did not demonstrate improved overall mortality, the Digitalis Intervention Trial (DIG) established the digoxin reduced overall hospitalisations (absolute risk difference (ARD), 6%; P< 0.001)(107). The benefit shown in this study was also demonstrated in a meta-analysis from 2004(108).

Ivabradine works only on the funny channels in the sinus node; hence the drug does not decrease the heart rate in AF. Therefore, ivabradine is only used for HF patients with sinus rhythm issues. The study leading to its use in HF was the Systolic Heart failure treatment with I_f inhibitor ivabradine Trial (SHIFT), which randomly assigned to 6,588 HF patients either a placebo or ivabradine. The median follow-up was 23 months and showed an RR reduction of 23% in the composite outcome of cardiovascular death and HF hospitalisation (P<0.001).

According to the ESC guidelines for HF treatment, aspirin and statins are not recommended, due to unproven evidence regarding their suitability. First, the use of aspirin has not been

shown to improve survival in HF patients with SR. The latest of the RCTs investigating the issue of evidence in antithrombotic therapy was the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial, which enrolled 2,305 HF patients with a sinus rhythm issue(43). The study concluded that there was no significant difference between patients allocated either aspirin or warfarin.

Second, statins were not shown to decrease all-cause mortality in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) trial(5), which randomly prescribed 5,011 older patients with either Rosuvastatin or a placebo. The overall mortality outcome was established to be non-significant (HR [HR], 0.95; 95% CI, 0.86 to 1.05; P=0.31) over a follow-up period of 32.8 months.

Non-pharmacological treatment

ICDs are implanted in HF patients with the aim of preventing sudden cardiac death (SCD) as the consequence of arrhythmia. According to the most recent ESC guidelines on HF, they are recommended to HF patients with symptomatic and sustained ventricular arrhythmias. This recommendation is mainly based on the Sudden Cardiac Death in Heart Failure Trial (SCD-HeHFT) in which 2,521 HF patients were randomly given an ICD, amiodarone or a placebo(109). The ICD was superior to the placebo and amiodarone and was revealed to have an RR reduction of 23% (P= 0.007) over a median follow-up time of 45.5 months.

Cardiac resynchronization therapy (CRT) has been investigated both in American and European HF patients(71, 110) .Remarkably, it was European HF patients classified to NYHA 3 to 4 classes and having BBB who were shown in the Cardiac Resynchronization in Heart Failure study (Care-HF) to benefit in respect to all-cause mortality. The Care-HF study recruited 814 patients for allocation to either CRT or usual HF care. Over a median follow-up period of 29.4 months, 159 patients died in the CRT group versus 224 patients in the control group (HR, 0.63; 95% CI, 0.51 to 0.77; P<0.001), thus highlighting the efficacy of the treatment.

1.2.7 Aims, objectives and research questions

Important gaps in evidence regarding existing HF therapy are substantial, and it would therefore be unrealistic to confine the whole field to a single PhD thesis. This dearth of evidence is due both to the lack of RCTs substantiating certain treatments and to

undiscovered underlying mechanisms primarily associated with basic science. However, treatments including anti-platelets and statins have never been demonstrated to benefit survival rates or other outcomes in order to establish evidence for regular use. Because these drug treatments are used widely, due to evidence corroborating improved survival in CAD patients, the present thesis will investigate their impact on the survival of HF patients.
The *aim* of this thesis is therefore to investigate the impact of aspirin and statins on all-cause mortality in a HF population enrolled on two EMMACE studies undertaken in 1995 and 2003, respectively. This was planned through propensity scores.

The *primary objective* is to determine the separate impacts of aspirin and statins on all-cause mortality. A *secondary objective* is the combined impact of aspirin and statins versus their non-prescription, while another *secondary objective* is the unadjusted impact of aspirin and statins on HF patients.

The overall *research question*, which is examined in Chapter 4, ask whether aspirin and statins use in HF patients can be defended, similar to their evidence-based use in patients with CAD without HF, or if their use may even be harmful due to certain side-effects.

1.3 Cardiac Rehabilitation

1.3.1 History

Cardiac rehabilitation (CR) is an intervention which aims to prevent patients with CVD from deteriorating further and suffering incidents of heart disease. The main remedies applied in the secondary prevention of CR are exercise, psychological treatments, diet/nutrition advice and lifestyle counselling. Medical treatment is not taken into account in the following part, as it has already been described above. Rehabilitation in modern times is used as an introductory transition from a period of acute illness back into everyday life(111). The concept of rehabilitation in heart disease is that the recipients gain the knowledge and tools necessary to live a normal life alongside their heart disease. The first attempts to discharge patients with heart disease into the outside community under controlled health environments were in the 1940s[112]. Evolving from an exercise framework in the initial versions, CR has gradually been transformed into a set of comprehensive programmes involving psychological-, nutritional-, antismoking-, diabetic-, cholesterol- and lifestyle-related components.

Transferring behavioural and cognitive insights into a layman's perspective of their own disease can be pivotal in the current economic constraints put on health care budgets in most Western societies. The higher engagement and participation of the patients themselves in their disease and associated treatment has been targeted to reduce hospital admissions and unpredicted incidents. Furthermore, it is a strategy for future health care policies to reduce costs without reducing quality, by keeping heart patients in their own homes for as long as possible, where relevant treatment can be undertaken. This is possible through guidance from health care professionals and the patient's own knowledge. An introduction to self-care and health understanding is believed to be essential for CR, and this course usually lasts between 8 and 12 weeks. After CR, further lifelong treatments and observations through tele-monitoring and patient management programmes are used to realise effective secondary prevention(113). These programmes are mainly offered to fragile patients and are used in an attempt to prevent hospital admissions, if the medical condition of the patient is complex.

1.3.2 Components

Exercise is a central part of CR and can either consist of purely aerobic exercise or the combination of aerobic and resistance modules. Aerobic exercise is based on low to moderate intensity cardiovascular exercise as part of endurance training, whereas resistance training

ideally targets a muscle strength stimulus using high intensities. Resistance training matches activities encountered in everyday life.

Psychological interventions address beliefs and misconceptions and try to reduce depression and anxiety in heart patients. It has been established that depression is a significant independent predictor of death and an aggravator of heart disease(114). High incidences of fatal outcomes in patients suffering from psychiatric disease are associated with pro-arrhythmic antipsychotic drugs and the fact that psychiatric disorders are frequently positively linked to risk factors(115, 116). Anxiety, which for instance makes the patient fear not being able to exercise, is an important cause of disability in patients with heart disease. The belief that an active physical life can harm and even lead to heart attacks is in fact a misconception(117). However, it should be added that optimal medical treatment is a necessity for success in exercise.

Depression and anxiety scores are scaled against several benchmarks, making cooperation between investigators and health workers extremely difficult to coordinate. An example of a tool for measuring depression and anxiety is the hospital and depression scale (HADS), which has high sensitivity but low specificity, positive predictive values and high levels of misclassification.(118)

Large trials investigating the effect of interventions on depression, measured against outcomes on death, heart attacks or hospital admission, are sparse. However, there is a tendency to describe the effect of depression in heart patients from post-hoc analyses of trials initially investigating treatments against non-mental disorders. One example is the OPTIMIZE-HF trial involving 48,612 patients with HF admitted to 259 hospitals(119). The trial demonstrated that a history of depression was a significant predictor of a lower likelihood to receive coronary interventions or cardiac devices. Moreover, depression also reduced referrals to outpatient management programmes. Overall, depression was found to remain a significant predictor in a multivariable model calculating the RR of increased hospital admission length and mortality at 60 to 90 days post-discharge.

Despite the lack of robust trials examining the specific treatment effect on psychiatric disorders in heart patients, a well-performed trial investigating the positive effect of the Heart Manual in heart patients was reported in 1992 by Lewin et al.(120). In brief, the Heart Manual was a self-help guide constructed with the aim of reducing psychological distress. The trial randomised 176 patients discharged after an AMI and placed them either on a course of self-help rehabilitation based on the Heart Manual or standard usual care with a placebo manual.

Hospital admissions at six months and psychological adjustment assessed by the hospital anxiety and depression scales at 12 months were both significantly improved in the self-rehabilitation group as compared with the standard usual care group.

Although treating patients with heart disease for depression and other psychological diseases concomitantly is a complex undertaking, evidence for treating both has been established. Drugs found to improve depression are selective reuptake inhibitors (SSRI) and antiepileptic drugs (121, 122). Additionally, cognitive and behavioural treatments are confirmed to ameliorate the conditions of depression and anxiety efficiently(123, 124).

Diet counselling is recommended as part of CR, with the objective being to reduce obesity. Moderate to high body mass indexes (BMIs) and the metabolic syndrome are associated with a serious risk of fatal outcomes in patients with heart disease. Despite this association, doubt has been cast on this notion in the findings of observational studies, whereby heart patients surprisingly improved their survival chances as a result of being overweight – a condition known as the 'obesity paradox'. These findings are very likely the result of unadjusted confounders and the fact that patients are frequently underweight in the terminal part of their life.(125) The obesity paradox can be depicted by a u-shaped curve delineating mortality (y-axis) with a continuous scale on the x-axis of weight(126). The explanation for this phenomenon may be that high mortality from non-cardiac diseases can be observed in the underweight area of the lower end of the x-axis, in contrast to cardiovascular deaths, which are located in the overweight area and equate to large values on the x-axis.

Exercise and nutritional counselling have been demonstrated as being effective in impairing atherosclerosis and decreasing coronary events and hospitalisation. Overall, HF patients, as for all CVD patients, should try not to eat 'unhealthy' foods, but at the same time it is important to realise that HF patients risk nutrient deficiencies. Therefore sufficient calorie intake remains important because micronutrients play a major role in antioxidant defence, which may appear crucial in stopping the pathogenesis of HF(127).

Trials investigating comprehensive interventions related to lifestyle demonstrate convincing results in favour of outcomes in patients assigned to the programmes. By measuring the minimal diameter in the diseased segments of atherosclerosis it is clear that intensive multifactor reduction conducted over four years constrains luminal narrowing in the coronary arteries of CAD patients and decreases hospitalisations for clinical cardiac events, too(128).

Another RCT recruiting 48 patients with moderate to severe CAD reported the feasibility of lifestyle changes with moderate to severe CAD(129). Over a five-year period, the baseline average stenosis decreased by 7.9% (diameter) in the experimental group as compared with relative worsening of 27.7% in the control group. It should be mentioned that the control group made conventional lifestyle changes suggested by their private physician and were equally treated by lipid-lowering drugs, in contrast to the experimental group. A significant difference was also noted between groups in the outcome of cardiac events expressed in the risk of controls at 2.62 times higher than the intervened group (95% [CI], 1.55 to 4.55; $P<0.001$).

It is essential to remark that exercise was an intervention in both of the lifestyle programmes outlined above, and they were indirectly suggested to be an important component in the secondary prevention of atherosclerosis.

1.3.3 Exercise physiology

Exercise is associated with a wide range of physiological effects on the human body. Cardiac, skeletal, vascular, central (hormonal) and periphery adaptations are among the hitherto acknowledged areas benefitting from increased physical activity.

Cardiac adaptations to exercise have been identified to increase cardiac dimensions and stroke volume, respectively(130), which means that the versatile heart can adjust to challenging situations such as climbing a flight of stairs or a hill. Moreover, it has been demonstrated that the afterload of the heart is equally better adapted to the left ventricular function(131). As a result of this interplay, lower resistance in the heart as a distributor of oxygen and nutrients to the organs and muscles has been observed.

Vascular benefits gained from regular exercise are the result of vasodilation. In charge of vasodilation are vasoactive substances such as acetylcholine and nitrogen oxide (NO)(132). It is important to state that vasodilation declines with age, similar to age degeneration elsewhere in the body. Vascular benefits associated with exercise have also been identified in the coronary arteries(133); moreover, peripheral vessels benefit equally as well to exercise due to increased numbers of periphery capillaries providing a greater and improved perfusion, which is similar to the vasodilation effect on coronary arteries.

Skeletal muscle size, which declines with age, is termed ‘sarcopenia’. Additionally, HF patients experience a deranged metabolism in skeletal muscles whereby both muscle bulk and the fibre cross-sectional area are reported to diminish(134). Aerobic exercise and strength interventions have been shown to ameliorate these metabolic derangements most effectively through exercise tests. In addition to the improved perfusion of skeletal muscles, increases in individual fibre areas has also been shown to have an advantageous effect(135).

Central adaptations in the brain associated with exercise have been revealed to prevent neurobiological and some psychiatric diseases. Favourable structural and functional plasticity in the brain and spinal cord have been confirmed through increasing genetic and molecular responses to facilitating neurogenerative, neuroadaptive and neuroprotective pathways(136). Regulatory mechanisms in the brain are linked to beneficial peripheral sympathetic activity, plausibly leading to reductions in heart disease. However, most of these pathways linking favourable effects between the brain, the heart and exercise still need to be delineated further. Central and peripheral adaptations are understood to be crucial in the secondary prevention of CVD. The endocrine organs play a key role in these beneficial effects, but they are far from the only organs involved. The central reactive oxygen species (ROS) superoxide anion O_2^-, stimulated by angiotensin II, shows regulatory autonomic effects through the central nervous system (CNS). A cerebral decrease in O_2^- leads to reduced sympathetic output in animal models of HF as opposed to an increase in O_2^- enhancing the output(137). Evidence for interval training shows a marked positive impact on oxidative stress(138). The association between exercise, insulin sensitivity, glycaemic control and the incidence of diabetes has bolstered new arguments for an active lifestyle. Studies in patients with diabetes and cardiovascular disease have emphasised favourable survival outcomes associated with physical activity.(139) The impaired metabolism of carbohydrates in skeletal muscles and adipose tissue is one reason identified to cause insulin resistance, impaired insulin secretion and ultimately hyperglycaemia.(140, 141) Conversely, physical activity confers glucose regulation through skeletal muscle activity such as improved non- and insulin-signalling kinetics, raised myoglobin and raised concentrations of enzymes serving the glucose metabolism(142). Other useful results from exercise have been linked to structural changes in the skeletal muscles and systematic influences through alleviation in comorbid conditions such as hypertension and dyslipidaemia.

1.3.4 Delivery and format

Predominantly, CR is delivered through two separate formats with various modifications. The first variation is exercise programmes based on physical activity alone. Modifications to such programmes will mainly vary between aerobic exercise alone or the combination of both aerobic and anaerobic exercise. The second main variation is CR based on multiple components such as lifestyle advice as well as psychological, diet and health education. In addition to these health-promoting modules, exercise is still the fundamental element of the programmes. Modifiers are therefore also aerobic exercise alone or the combination of aerobic and anaerobic exercise. The exercise component, which can vary in each type of programme, usually involves cycling, walking or swimming. Furthermore, the length and frequency of the exercise varies as well as the location – at home, in the community or at hospital.

1.3.5 Evidence

In general, the existing evidence on exercise-based CR is robust in patients with CAD without HF, but it is more elusive in HF patients despite the common pathology of CAD. Outcomes shown to improve through exercise in CAD patients are mortality, health-related quality of life (HRQoL), hospital admissions and exercise capacities. Concerning HF patients the picture is less clear, but exercise capacities and HRQoL are significantly enhanced in meta-analyses.

The low incidences of adverse events reported in trials and registers convincingly underscores the safety of exercise. For instance, in a French registry produced by the Functional Evaluation and Cardiac Rehabilitation Working Group of the French Society of Cardiology, a total of 25,420 patients were assessed over a one-year period in 65 separate CR centres to establish whether any serious event occurred inside a time interval of one hour following a stress test or exercise session(143). Overall, 20 severe cardiac events were recorded. Of these, five were related to exercise testing and 15 were related to exercise training. Translated into an event rate, this was one per 8,484 exercise stress tests, or one per 49,565 patient hours of exercise training. The HF-ACTION RCT trial, which recruited 2,331 patients at 83 centres, found that 37 patients (37/1159) experienced a serious event that required hospitalisation during 36 sessions of supervised training(144). This number is compared to 22 patients (22/1172) with similar episodes in a placebo group.

Exercise interventions are therefore supported by broad evidence and can be performed safely in HF patients.

1.3.6 Financial review

Cost-effectiveness analysis (CEA) is performed broadly in health economics, and most treatments offered by the NHS for cardiac diseases have to undergo such an analysis(145, 146). The cost- effectiveness (CE) ratio is appreciated as the proportion of the difference between the investigated treatment and standard care as the nominator versus the difference in health effect in the denominator. In an attempt to avoid terminological intangibleness, it will only be mentioned that the CE ratio above can be subcategorised to the subset of cost-utility analyses (CUA), whereby the denominator contains differences between quality adjusted life years (QULYs) in the groups assigned to the investigated treatment and standard care.(147) It should be taken into consideration that the CE ratio is not always a positive number, but depends rather on the benefits of treatments.

Among the most important and largest trial of exercise programs in HF patients, the HF-ACTION trial was evaluated for its economic details. Shortly to summarize the trial, of 2331 patients, 1159 patients were assigned to 36 supervised sessions of exercise training followed by home based exercise. Exercise equipment was brought home to all patients, who were assigned for the exercise training group. A pre-specified aim of 5 sessions a week was posed. During a median follow-up of 2.5 years, 65% in the exercise group and 68% in the group receiving standard care died or were hospitalised for any reason. Costs associated with the intervention and control group were a priori designed to consist of expenses for medical resources, for instance hospitalisation costs during the trial, protocol driven costs in form of educational resources, tests, procedures and study visits required by the protocol. In addition were costs for exercise training, including expenses for supervised exercise training through personal and fixed facility costs, and home-based exercise costs, including equipment and the personnel to undertake reminder calls to promote adherence, and finally the estimated costs of the time the patients were spending in relation to the exercise programme.

The outcome of these financial evaluations had miscellaneous messages. First, total direct medical costs per participant in the exercise group were estimated at $50,857 versus $56,177 in the standard care group (95% CI for difference, $-12,755 to $1,547; P= 0.10). Secondary costs of exercise training were estimated at $1,006 compared to an estimated $5,018 in costs of patient time. Finally, the CUA showed an estimated mean undiscounted QALY of 2.02 in

the exercise group (n= 1150 compared to 1.99 in the usual care group (n= 1158) (95% CI for the difference, -0.06 to 0.11).
In conclusion, the economic evaluations showed little difference in medical resources, but the important point was that the cost of the exercise intervention was relatively cheap compared with the other costs associated with HF in the health care system.

Followed up over 15.5 years, the cost-effectiveness analysis by Belardinelli et al. investigated the effect of a 14-month exercise programme randomised to 110 HF patients attending exercise classes 2-3 times a week(148, 149). The study provided long-term insights into the cost effectiveness of exercise programmes. The cost-effectiveness ratio for long-term exercise in patients was ascertained at $1,773/life year when adjustments for the costs of hospitalisation, exercise training, wage losses due to exercise training and an annual discount of 3% were added.

1.3.7 Aims, objectives and research questions

HF is a leading cause of hospital expenses in the Western world. Several of its aetiologies are lifestyle-orientated. As health care costs become more varied following broader treatment possibilities, any savings in the budget to circumvent restrictions in treatment possibilities are needed. In addition to classic cuts in hospital stays, the secondary prevention of cardiovascular events by the patients themselves is strongly suggested as a valuable strategy(150). The evidence underlying this strategy, however, is not unilaterally convincing.

Very few lifestyle studies have been undertaken in HF patients, as they are time-consuming, expensive and demand the time of staff. Even though survival chances and hospital admissions are reduced by lifestyle changes incorporated into CR, it is not yet certain what effects can be expected in HF outcomes. Another area where knowledge is incomplete is the study of whether solely aerobic exercise or the combination of aerobic and resistance exercise yield different clinical outcomes.

The lack of establishment in CR referral, enrolment and adherence in HF patients is also a question raising concern in the UK and elsewhere. Furthermore, long-term follow-ups of exercise capacities have not been reviewed yet through synthesised effect measures in meta-analyses.

The *aim* of Chapter 2 is to investigate CR referrals on all-cause mortality.

The *primary objective* in Chapter 2 is to identify the association between CR referral and all-cause mortality in patients with MI, adjusted by multivariable analysis of the EMMACE studies.

A *secondary objective* is to investigate the association between CR referral and HF patients. In addition, another *secondary objective* is to investigate variables significantly predicting CR referral.

The *research question* posed in Chapter 2 involves examining whether there were any differences in long-term mortality between CAD patients and patients with CAD and HF enrolled in the EMMACE studies.

The *aim* of Chapter 3 is to undertake meta-analyses on the outcomes of mortality, hospital admissions and exercise capacities in HF patients randomised to exercise-based CR and adjusted by contemporary treatments through the period 1999 until 2010.

The primary objective in Chapter 3 is to assess long-term mortality, hospital admissions and the exercise capacities of peak oxygenation uptake (PVO_2), exercise time, the 6-minute walk test and exercise power (watts) in HF patients during a minimum follow-up of six months through meta-analyses. *Secondary objectives* are examinations of heterogeneity, baseline characteristics and investigations into the subgroup of patients with HF and preserved ejection fraction (HF-PEF).

The research question constructed in Chapter 3 asks whether HF patients benefit from improved survival, less hospital admissions and better exercise capacities in a similar way to patients with CAD but without HF.

Chapter 2– CR referral after a myocardial infarction

2.1 Introduction

Alongside improved treatments in both the acute and preventive phases of cardiovascular disease, the number of survivors is increasing(151), which means that patients who have had a heart attack or have been diagnosed with HF have the potential to live many years after the event. However, this potential is only realised if the individual patient prevents their existing heart disease from deteriorating.

Cardiac rehabilitation (CR) has been shown to be an efficient remedy inside secondary prevention, specifically in patients suffering a myocardial infarction (MI). The evidence is bolstered through experimental and observational studies. The primary treatment benefits achieved by CR are lower overall mortality and hospital admissions. Hence, international guidelines in cardiology strongly recommend CR as an integrated part of recovery in the period shortly after hospital discharge(152). Although HF patients are also recommended CR, the evidence underpinning their referral is not as clear as for patients with only coronary artery disease (CAD)(8).

In order to pave the way for secondary prevention through CR, the first step is to refer the patients. The most common location for CR referral is in hospital, but primary and tertiary sectors also have the ability to refer for CR. Despite support from leading health societies and the provision of sufficient funding, registers reveal a low number of patients completing CR programmes(153). Several reasons explain this anomaly. First, health staff fail to refer large numbers of patients. Second, some patients live far away from the CR centre and therefore find it difficult to travel long distances each time they have to attend a CR session. Third, patients misconceive the importance of attending CR as an active part of their treatment. This can in some cases be associated with ethnic minorities and their language skills, making it difficult for them to understand secondary prevention(154).

The *aim* of the following chapter is first to evaluate the impact of CR referral on the long-term prognosis in patients admitted with acute myocardial infarction stratified by two separate cohorts followed in the EMMACE-I and II studies. The *primary objective* is long-term mortality in patients admitted to hospital with acute MI. A *secondary objective* is to evaluate

the influence of CR referral on mortality in HF patients. Another *secondary objective* is to assess independent predictors for CR referral. The *research question* of this chapter compares mortalities in patients with CAD versus a subgroup with both CAD and HF.

2.2 Methods

2.2.1 Study design

Two identically designed cohort studies, named the Evaluation of Methods and Management of Acute Coronary Events (EMMACE)-I and II, were used in the following chapter and chapter 4. The cohorts were recorded on each side of the millennium, as the EMMACE-I study began in 1995, whereas the EMMACE-II was initiated in 2005. The studies examined the outcome of death in consecutively admitted patients, who were eligible if they had confirmed acute coronary syndrome (ACS), in adjacent hospitals in Yorkshire, UK. Patient recruitment lasted for three months in 1995 in the EMMACE-I study and for six months in 2003 in the EMMACE-II study. Characteristics of patients, discharge variables and all-cause mortality during hospital admission were collected. Furthermore, all-cause mortality was followed up to 15 years after recruitment.

Data gathering was performed after each patient had given fully informed consent in written form, which had to be approved by the appropriate regional and research Ethics Committees, in accordance with the Declaration of Helsinki. Qualified participants in both studies were identified through clinical codes, coronary care registers and biochemistry laboratory cardiac biomarker assay databases. Patients were enrolled in the study irrespective of complete data, in which case their medical records were used for further data collection. The UK Office of National Statistics provided long-term mortality data, which was censored on 23rd September 2010.

2.2.2 Study patients and assessments

Only patients diagnosed with acute MI were included in the analyses. Overall, 20 hospitals in West Yorkshire contributed to the data collection. Diagnosis of acute MI in the EMMACE studies was identified according to any two of the WHO criteria: chest pain, electrocardiographic changes or a 100% increase in a single myocardial enzyme(155). Cardiac biomarkers between the studies changed in the period overlapping the data collections: creatinine phosphate kinase (CPK), lactate dehydrogenase (LDH) and serum glutamic oxalate transaminase (SGOT) and creatinine kinase myocardial band (CKMB) were

used in 1995, while cardiac troponin I and CKMB were used in 2003(9, 156). Data providing the clinical coding of acute MI, medical history, medication and clinical measurements were assessed from the patients' medical records.

Invasive cardiology consisted of reperfusion during the hospital stay and was defined as primary PCI or thrombolysis. Revascularisation was defined as coronary artery bypass grafting (CABG) or PCI. The difference between 'primary PCI' and 'PCI' is that the former has to be completed within 12 hours after symptoms' present themselves in acute MIs through ST-elevations (STEMI) on an ECG. If missed (missed STEMI), the term PCI can be applied for the intervention and it is no longer acute.

Ischaemic heart disease (IHD) comprised at least one of the following three indicators: previous MI, angina or revascularisation. Specialist cardiology input was defined as a Cardiologist leading the management of the patient during hospital admission. Referral for CR was assessed as recorded on discharge. The follow-up ranged from a minimum of 14 and six years in the EMMACE-I and II studies, respectively.

2.2.3 Outcomes

The primary outcome was all-cause mortality from the time of discharge until 23th September 2010 in all patients diagnosed with acute MI in the EMMACE studies. A post-hoc analysis was undertaken to evaluate the effect of CR referral on the outcome. CR referral was defined as a secondary outcome along with its associated determinants. Furthermore, any peaks in the primary outcome were treated as an additional secondary outcome.

2.2.4 Statistics

Formal baseline characteristics were calculated as absolute numbers (%) or medians with interquartile ranges (IQRs). A comparison of continuous variables was made with the Kruskal Wallis test, and the Pearson's Chi-square test was used for discrete values. P-values less or equal to 0.05 indicated significance.

Kaplan Meier plots illustrated cumulative survival among patient groups (unadjusted), and the log rank test was used for the comparison between them. One-year mortalities were also calculated as a cumulative failure with an associated 95% CI. The RR of death was defined as HRs determined from multivariable Cox proportional hazard models.

To assure that follow-up time periods were identical in the EMMACE studies, each of them was constrained to 90 months' follow-up time.

Selection of variables

Pre-specified variables in the models took account of epidemiology, comorbidities, risk-factors and treatment effects related to sex, age, chronic HF, diabetes mellitus, chronic obstructive pulmonary disease (COPD), ST deviation, heart rate (HR), systolic blood pressure (SBP), cardiac arrest, revascularisation, reperfusion, medication prescribed on discharge – including ACE-inhibitors, beta-blockers, statins, anti-platelet agents – and the admitting Cardiologist. The main motivation underlying the selection of variables was based on similarities in the two EMMACE studies(9). In addition, these post-hoc analyses had limited freedom regarding pre-specified possible confounders, literally meaning that only variables appearing in both EMMACE datasets could be included. AF and clopidogrel were examples of variables not collected in both decades. There was a well-founded reason behind the lack of clopidogrel data in 1995, though, because it was not licenced before 2003.

Age and sex have been appointed essential roles in disease models in the contemporary era of rational medicine(157). Therefore, the inclusion of both of these factors was a natural choice. Age is a strong causal factor for biologic degeneration of the human organism, and the only way to preclude the variable in a model would be to assure that participants were of the same age(158). Adjustments for gender are important due to differences in disease disposition and expected lifespans for women and men. For instance, men are known to have a higher incidence of cardiovascular disease (CVD) than women, who in contrast have a greater prevalence of CVD than men, due to their higher average life expectancy. This discrepancy is often resolved by constraining studies to either women or men(159).

Diabetes, COPD and HF were chosen as covariates for the multivariable analyses. Diabetes is an important comorbidity because in addition, as an independent predictor of mortality, it plays a central role in the pathology of CVD. Similarly, HF is a robust marker for all-cause death and mirrors the severity of the IHD, although HF can evolve without IHD and therefore pre-exists prior to the event of ACS in the EMMACE studies(160). Similarly, COPD forecasts bleak prognoses and causes about a quarter of hospital admissions in A&Es(161). Indirectly, it reveals smoking history and therefore frequently coexists with CVD, thus aggravating the overall prognosis(162).

The risk factors (ST deviation, HR, SBP and cardiac arrest) of the mini-GRACE risk score were used to adjust the six-month survival rate(163), in order to re-establish equipoise amongst patients during hospital admission. A cardiac enzyme increase at the time of acute MIs is related to the prognosis(164). Because cardiac enzymes were unavailable as a unified measurement, they became a confounder during the two EMMACE studies(165, 166).

Essential medication applied in the adjustment were anti-platelets, including aspirin and clopidogrel, beta-blockers, statins and ACEIs. The latter included ACE-inhibitors and angiotensin receptor blockers (ARBs). The status of medication was recorded on discharge. Other treatment parameters were reperfusion, revascularisation and Cardiologist input.
The models were divided into separate decades to avoid a treatment year effect. In Appendix 2.1, a log file shows how the variables were incorporated into a Cox proportional regression model in the Stata program. Assumptions of the proportionality and functionality of the covariates were tested through inflation of variance, Schoenfeld residuals and Martingale residuals(167). Breaks in linearity were corrected by restricted cubic splines(168). The robustness of the models was investigated through the specification link test for single-equation models. Interactions were pre-specified between CR referral and the following: age, SBP, COPD, HF and diabetes. In the case of a verified interaction, the relevant variables were modified or withheld from the model in order to eliminate the interaction. Left censoring of varying intervals in the first 12 months in the models was deployed to assess time variance of the covariates.

Logistic regression was performed to calculate the odds ratios (ORs) of CR referral by incorporating the same variables as the survival model, and it was used to compute a propensity score estimating CR referral through the components of the mini-GRACE risk score: age, HR, SBP, electrocardiographic ST-segment deviation and cardiac arrest at hospitalisation.(163)

Additionally, the modified GRACE score of the included patients was calculated from their six-month mortality in order to risk-stratify. The variables were identical to those in the mini-GRACE risk score applied to CR referral. Post estimates of the logistic regression models were tested through the Hosmer and Lemeshow goodness of fit with a group number of 10. P-values less than 0.05 indicated evidence of a lack of fit. An assessment of the pairwise interactions between all the variables was performed, if the fit was low.

2.2.5 Missing values

The validity of clinical studies is threatened by missing values. A neat definition of missing data was recently formulated as "values that are not available and that would be meaningful for analysis if they were observed"(169). Limited recommendations on how to address the problem of missing data make this area particularly difficult. The following subsection reviews approaches based on integrated models, whilst the last part of the section explains and justifies the integrated models chosen for this thesis.

Missing data cause insecurity in conclusions made on the basis of non- and parametric analyses. Frequently, observational data are reported as incomplete. Explaining missing figures in non-experimental data are their large size, the retrospective collection of variables, the post-hoc determination of which variables should be recorded and smaller resources in these studies compared with multi-centre randomised controlled trials (RCTs). In contrast to observational studies, RCTs are frequently supported by the prosperous pharmaceutical industry or national health research funds. Nevertheless, observational data provide a closer real-world glimpse of disease prevalence. The latter is converse to RCTs, in which data trial investigators and steering committees restrict data gathering.

The nature of missing data has been classified according to Rubin et al. and varies from missing not at random (MNAR) and missing at random (MAR), to missing completely at random (MCAR)(170). When data are MNAR, the underlying failure to record a given variable has to be related to the variable itself. An example is a patient selected for trial participation. During the collection of baseline characteristics, missing measurements are explained by the patient's withdrawal prompted by kidney failure. The missing glomerular filtration rate (GFR) is therefore not missing at random but as a result of its decreasing size, indicating aggravating kidney disease. Otherwise, if kidney disease is known, a low GFR is predictable, which changes the classification to MAR. In general, when missing values are associated with other recorded variables, the MAR terminology is appropriate. MCAR is stated in cases where the underlying cause of the missing values is interpreted as irrelevant to the outcome of the analysis; for example, a blood sample is accidently destroyed in the lab before analysis.

Dealing with missing data

At first glance, missing data can be ignored in any analysis. Such an approach is called a 'complete case analysis', where missing data are literally ignored. Such a way of dealing with the data reduces the number of participants in the calculations, as a subject is expelled from the model as soon as a variable is unavailable, for instance in a survival analysis. The consequences of using complete cases may weaken the final analysis and result in type 1 errors, which means that a truly significant effect of an intervention may be translated as being ineffective(171). Another possibility is that the investigated intervention is inferred to be more effective, which equates to an overestimation (type 2 error). Eventually, the missing numbers may not influence the outcome.

The different methods employed to replace missing numbers can utilise, for instance, the mean, linear regressions or simulations of the existing data. The growing attitude towards dealing with missing values involves replacing all missing variables, as this approach provides a more robust outcome in data analyses compared to using complete cases. Simulations are regularly used in MIs. The replacement of missing data through regression models, using complete data to predict missing values, is a rapidly emerging method. One frequent condition in the assessment of missing data values is that the imputing model (regression model) is richer in variables than the model used for analysing the outcome. Such scenarios are built on ignitability in statistical terms(172). MIs follow three steps. The first consists of imputing the missing data, the second involves analysing the outcome using a complete data technique and the third step yields the overall outcome by combining uncertainty in the data and the uncertainty of the missing values.

Multiple imputations by chained equations

Stata provides MIs by chained equations (ICE), which is one of the MI subclasses. ICE applies univariate regression imputations, in contrast to regression switching used in multivariate imputation, which is another established type of MI. The justification of ICE is not as theoretically sound as MIs based on multivariate normalisation (MVN) distribution; however, the method performs well in the practical setting. Contrary to the lack of multiple dimensions in its distribution, missing values of counts and categorical variables can be understood more easily by employing this method (ICE). The MVN model is not constrained to 0's and 1's fitting a binary outcome(173). Mathematically, this does not have an important

influence on the calculations, but it is hard to grasp for users without a mathematical background. ICE may be less advantageous when imputed predictors are continuous, which is opposite to binary outcomes. Secondly, the less advantageous sides of ICE are tediousness when the number of variables is high.

The outcome, irrespective of the analysis, is recommended to be included in the imputation model(174). In the relevant case of Cox hazard regression, the cumulative survival model of Nelson-Aalen can be incorporated to comply with this theory. Concerning longitudinal studies, the wide shape of data has to be preserved during the imputation process instead of longitudinal shape, which is used for the analysis.

Reasons for preferring ICE over the MVN method, which is also available in Stata, include the already mentioned fewer assumptions behind the model and the higher accuracy in approximating missing binary data.

Missing data in CR referral were evaluated for any association with the chosen covariates from the survival and propensity score models. If MAR was likely, missing data were imputed univariately according to the ICE methods developed by Royston et al. and incorporated a cumulative baseline hazard function by Nelson-Aalen (170, 174).

2.2.6 Computer programs and databases

Stata 12.1

Stata version 12.1, developed by StataCorp, was used for all the statistical data analyses in this thesis, which consisted of summary statistics, survival functions, linear regression, propensity functions, MIs and meta-analyses. Applied syntaxes for each chapter can be seen in the Appendix.

PubMed

Predominantly, PubMed was used as a tool to retrieve articles and associated references. It is a database accessible through the webpage http://www.ncbi.nlm.nih.gov/pubmed/ and includes more than 22 million citations from the biomedical literature from sources such as MEDLINE, life science journals and online books. Recent citations, even those from approximately the last two decades, are as a rule linked directly to full-link texts from

PubMed Central or publishers' websites. The user-friendliness of the database is excellent and it can be used by both laymen and health care professionals. The advantages of using the program are numerous. First, one is able to store up to 500 citations for 8 hours on the 'Clipboard'. Furthermore, after setting up an account, which is also a free resource, one can keep as many citations as needed for an unlimited period. Second, several data search functions are feasible, for instance medical subject heading (MeSH) searches based on pre-specified terms and Boolean operators (AND, OR and NOT). A simple search example could be "Heart failure and gender". Additionally, the database has a large memory, which recognises the names of studies from the past, important associations and causalities between clinical variables, interventions and outcomes. Third, filters can be designed in multiple permutations in order to assure more specific results for searches. An example is the limitation of searches to RCTs restricted to human beings during the years 1990 to 2012.
It should also be mentioned that PubMed is just one of several functions offered by the US National Library of Medicine's National Institute of Health.

References

Endnote 5.0 was used to store and distribute all the references in this thesis. In addition to the abstracts for the meta-analyses provided by the search machines in MEDLINE, CENTRAL, EMBASE, CINAHL and PsycINFO, the PubMed database gained insight into abstracts covering research subjects in internal medicine. Finally, core medical journals were approached through the search portals of the University of York. If the university did not subscribe to relevant journals, the library at the University of York could request the items through the British Library. If abstracts or journals were written in a foreign language such as Russian, Polish, Mandarin, Italian or French, personal contact with the author was undertaken in order to copy the original paper. However, none of the attempts to contact authors of English and foreign nationalities was successful in my attempt to garner supplementary information.

2.2.7 Peer reviews

In order to practice presentations of the results and to receive critique from an international forum, posters were submitted at international and national congresses. Poster presentations at the conferences arranged by the ESC of Heart Failure in Berlin 2010 and Belgrade 2012 were created. Furthermore, poster presentation at the British Cardiovascular Society in Manchester 2011 was made, as well as at the European Society of Cardiology in Paris 2011, although the author was not in attendance on this occasion.

Essential results of key chapters in the thesis were submitted in article format to journals relating to HF and cardiology. At the time of submitting the thesis, a single publication was completed at the European Journal of Preventive Cardiology(175).

2.3 Results

2.3.1 Study Participants

Overall, 2,196 and 2,055 patients were diagnosed with acute MI in the EMMACE-I and II studies in 1995 and 2003, respectively (Table 3.1). Out of each study population, 984 (74%) and 1,256 (64%) were referred for cardiac rehabilitation (CR) over the two decades, ($P \leq 0.05$). It was noted that missing values in the referred population in the EMMACE-I study were almost 40% compared to 4% in the EMMACE-II study.

There were no significant differences in age, sex or smoking between the groups. Concerning comorbidities verified on discharge time, HF was more frequently observed in the EMMACE-I study compared to the EMMACE-II. Otherwise, lifestyle diseases, such as hypertension and hyperlipidaemia, were more richly represented in the EMMACE-II study. When diagnostic and clinical measurements were taken into account, the risk classification after acute MI through Killip class and HR were significantly higher in the EMMACE-I study. In contrast, SBP measurements were higher in the EMMACE-II study(176).

The prescription of guideline-recommended treatment for cardiovascular disease (CVD) was in general more represented in the EMMACE-II study compared with the EMMACE-I. Examples of medications significantly more frequently prescribed in 2003 were statins, ACEIs and beta-blockers.

Similarly, the intravascular procedure through revascularisation was more frequently performed in 2003, in contrast to reperfusion being applied more in 1995. The former covered coronary artery bypass grafts (CABGs) and percutaneous coronary interventions (PCI), where the latter included primary PCI. The choice between the two procedures, both with the aim of improving circulation in oxygen-deprived areas of the heart muscle (angina and/or ischemia), depends on how acutely the patient's symptoms evolve. This is combined with the estimated odds for the oxygen-deprived heart muscle regaining its previous function. If the symptoms of pain are associated with a protracted history equivalent to stable angina, CABG and PTCA will be undertaken and planned ahead of time, even though CABG can be acute, too(177). Otherwise, if the symptoms of chest pain are acute and co-existent with ST-electrocardiographic (ECG) elevations and elevated myocardial enzymes, the diagnosis of acute MI is likely, in which case the patient will therefore be offered primary PCI. The estimated time from when the pain starts to the insertion of a catheter into the patient has to be within 12 hours.

The distinction between types of acute MI demonstrated that the ST-elevation myocardial infarction (STEMI) subgroup was more represented in 1995 compared to 2003 (47% vs. 33%).

Propensity scores using the clinical prognostic measurement of the mini-GRACE score, predicting six-month mortality and the likelihood of CR referral, were both greater in the 1995 population(166). The EMMACE-II study revealed that patients were more frequently influenced by Cardiologist input during hospital admission compared to the EMMACE-I study. Concerning prognosis, the outcomes of one-year mortality and cardiac arrest were higher in 1995 (Table 3.1).

Table 2.1. Baseline characters in the EMMACE-I and II studies

Characteristics	EMMACE-I, 1995 (n= 2196)	EMMACE-II, 2003 (n= 2055)
Missing CR referral data, n (%)	872 (39.7)	80 (3.9)
Referred for CR, n (%)	986 (74)*	1256 (64)
Median (IQR) age, years	72 (62 to 79)	71 (62 to 79)
Female sex, n (%)	865 (39)	737 (36)
Current smokers, n (%)	542 (28)	589 (31)
Hypertension, n (%)	633 (29)*	867 (43)
Diabetes mellitus, n (%)	283 (13)	348 (17)
Chronic obstructive pulmonary disease, n (%)	320 (15)	328 (16)
Heart Failure, n (%)	1142 (52)*	672 (33)
Hyperlipidaemia, n (%)	156 (7)*	678 (35)
Ischaemic heart disease, n (%)	1019 (46)	985 (48)
Cerebrovascular disease, n (%)	213 (10)	232 (11)
Median (IQR) systolic BP[§], mmHG	140 (120 -160)*	141 (120 -160)
Median (IQR) heart rate, bpm	80 (68-100)*	80 (66 -96)
ST-elevation myocardial infarction, n (%)	957 (47)*	670 (33)
Killip-Class 1, n (%)	1045 (49)*	1469 (71)
Class 2 to 4, n (%)	1096 (51)	568 (28)
Cardiac arrest, n (%)	450 (21)*	199 (10)
Median (IQR)[π] modified-GRACE risk score, per unit	42.4 (14.1-80.6)*	15.7 (3.5-44.2)
Median (IQR)[π] propensity for CR	73.8 (58.4-85.5)*	67.7 (55.6-78.1)
Reperfusion, n (%)	920 (42)*	511 (25)
Revascularisation, n (%)	43 (2)*	291 (14)
Specialist cardiology input, n (%)	786 (37)*	959 (47)
Anti-platelet agent on discharge, n (%)	1429 (86)	1751 (86)
Statin on discharge, n (%)	138 (8)*	1640 (82)
ACE-inhibitor on discharge, n (%)	629 (38)*	1298 (65)
Beta-blocker on discharge, n (%)	696 (42)*	1345 (67)
One-year mortality rate[α] (95% CI[¶])	0.32 (0.30-0.34)*	0.21 (0.20-0.23)

[§] BP: blood pressure; *Indicates a significant difference between means or proportions with a p-value less than or equal to 0.05; [π] Built on heart rate, systolic blood pressure, cardiac arrest and ST-deviations; [α]Based on a cumulative hazard assumption given percentage values, e.g. 0.12 equals 12 %; CI: confidence interval[¶].

2.3.2 CR referral

In 1995

In 1995, CR-referred patients were more likely to be younger smoking men compared with their non-referred counterparts (Table 3.2). Prescription of anti-platelets, statins and beta-blockers were all prescribed at higher proportions in CR-referred patients compared to non-referred patients. Being CR-referred also meant that patients were more inclined to receive reperfusion and Cardiologist input during their admission.

The CR-referred proportion of the EMMACE-I study had fewer comorbidities, such as HF, IHD and cerebrovascular disease (CVD), than their non-referred counterpart, but they did have significantly higher numbers of hyperlipidaemia. Clinical measurements assessed both HR and Killip-class as being lower in CR-referred patients.

Diagnostic and prognostic insights demonstrated STEMIs to be more frequent, with the mini-GRACE score predicting six-month mortality and one-year mortality to be higher in the referred patients.

In 2003

In 2003, CR-referred patients agreed with the 1995 CR-referred population in being more likely to be young smoking men. Prescribed guidelines for recommended medication associated with ACS were significantly better represented in the CR-referred population. The higher prescription of statins and beta-blockers was found in the non-referred patients in 2003 compared with their parallels in 1995.

Clinical assessments of Killip-classes concurred with the 1995 data as being higher for the non-referred cohort. SBP was similarly lower in the CR-referred patients.

Cardiologist input and invasive treatments were all significantly associated with CR referral in 2003. Patients without a history of IHD and COPD more often received CR referral than patients with these illnesses. Contradictory to the 1995 cohort, patients with established HF in 2003 were more likely to be CR-referred compared to patients without HF.

In terms of prognosis for the EMMACE-II population, the magnitudes of the one-year mortality and propensity scores based on the mini GRACE score were both smaller in the CR-referred group than in the non-referred group. Cardiac arrests were equally seen more frequently in the non-referred population in 2003, compared to the referred population in 2003 and to their non-referred counterparts in 1995. However, caution should be applied to any interpretations of these comparisons between decades, as a large number of patients with missing CR referral values in 1995 suffered a cardiac arrest. Patients with a STEMI diagnosis in 2003 were more likely, along with the 1995 cohort, to be CR referrals.

Table 2.2. Baseline characteristics of non- and CR-referred patients

Characteristics	EMMACE-1, 1995		EMMACE-2, 2003	
	Referred for CR (n= 986)	Not referred for CR (n= 338)	Referred for CR (n= 1256)	Not referred for CR (n= 719)
Missing values for CR referral, n (%)	872 (39.7)		80 (3.9)	
Median (IQR) age, years	66.1 (57.5- 73.6)*§	75.1 (67.5- 82.2)	69 (57.0- 77.0)*	76 (66.0- 82.0)
Female sex, n (%)	296 (30.0)*	161 (47.6)§	404 (32.2)*	296 (41.1)
Current Smokers, n (%)	385 (40.8)*§	74 (26.2)	434 (36.1)*	138 (21.4)
Hypertension, n (%)	284 (28.8)§	99 (29.3)§	523 (42.6)	306 (44.2)
Diabetes mellitus, n (%)	103 (10.5)§	44 (13.0)§	193 (15.5)	131 (18.5)
Chronic obstructive airways disease, n (%)	120 (12.2)	55 (16.3)	184 (14.8)*	132 (18.5)
Chronic heart failure, n (%)	389 (39.5)*	192 (56.8)§	466 (37.1)*	187 (26.0)
Hyperlipidaemia, n (%)	87 (8.9)*§	28 (8.3)§	402 (34.1)	247 (36.4)
Ischaemic heart disease, n (%)	374 (38.0)*	185 (54.7)§	487 (38.8)*	448 (62.5)
Cerebrovascular disease, n (%)	59 (6.0)*§	50 (14.8)	111 (8.9)	113 (15.9)
Systolic BP, median (IQR), mmHg	140 (122-160)	142 (121-160)	142 (123-160)*	140 (118-161)
Heart rate, median (IQR), bpm	79.5 (64.0- 90.0)*	84.0 (72.0-101.0)	77 (65.0-92.0)	84 (69.5-100.0)
ST-elevation myocardial infarction, n (%)	527 (55.6)*§	111 (33.8)§	513 (41.0)*	145 (20.2)

Killip-Class 1, n (%)	582 (60.2) *§	150 (45.3)§	969 (77.2)*	447 (62.2)
Class 2 to 4, n (%)	378 (38.2)	181 (61.8)	279 (22.2)	267 (37.1)
Cardiac arrest, n (%)	90 (9.1)§	40 (11.9)§	52 (4.1)*	147 (20.5)
Modified-GRACE risk score$^{\rho}$, median (IQR)$^{\pi}$	21.8 (6.5-47.9)*§	59.8 (27.7-83.1)§	10.8 (2.5-31.1)*	32.5(8.4-73.9)
Propensity score for CR$^{\rho}$, median (IQR) $^{\pi}$	81.6 (90.2-71.7)*§	67.2 (79.1-52.6)§	72.5 (81.3- 60.7)*	60.2 (42.6-70.4)
Reperfusion, n (%)	576 (58.4)*§	93 (27.5)§	431 (34.2)*	76 (10.9)
Revascularisation, n (%)	21 (2.1)§	3 (0.9)§	215 (17.2)*	58 (8.1)
Specialist cardiology input, n (%)	471 (49.0)*	94 (29.1)§	626 (50.1)*	285 (39.9)§
Anti-platelet agent, n (%)	863 (90.2)*	232 (80.8)§	1157 (92.2)*	527 (73.8)
Statin, n (%)	95 (9.9)*§	16 (5.6)§	1132 (90.8)*	442 (64.4)
ACE-inhibitor, n (%)	344 (36.0)§	113 (39.2)	942 (75.5)*	300 (43.7)
Beta-blocker, n (%)	499 (52.1)*§	72 (25.1)§	914 (73.4)*	377 (55.0)
one-year mortality (95% CI)$^{\alpha}$	0.11 (0.10 to 0.14)*	0.30 (0.25 to 0.35)§	0.12 (0.10 to 0.14)*	0.41(0.37 to 0.44)

* Indicates statistical significance when comparing CR and non-CR-referred patients in the same year with a P-value ≤ 0.05; § means statistical significance when comparing the effect between 1995 and 2003 within equal groups (either CR or non- CR-referred) with a P -value of ≤ 0.05; π: For each point increase. α: based on a cumulative hazard assumption given in percentage values, e.g. 0.11 equals 11%; $^{\rho}$ Built on heart rate, systolic blood pressure, cardiac arrest and ST deviation.

2.3.3 Propensity for CR referral

The number of predictors for CR referral between the decades of the EMMACE studies increased, but in general the variables associated with CR referral changed. In 1995, CR referral was negatively associated with age, while the other epidemiological variable of male sex had a borderline positive influence on the process, with a lower limit of the confidence interval almost greater than 1 (95% [CI], 0.98 to 1.93) – see Table 3.3. Reperfusion during admissions for acute MI and the prescription of beta-blockers on discharge were two other significant positive factors for CR referral in the EMMACE-I study.

In 2003, both invasive- and non-invasive-related treatment predictors significantly increased the risk of being CR-referred. Reperfusion and revascularisation showed that the odds ratios of being referred were 4.11 and 1.50, respectively (OR, 4.11; 95% [CI], 2.96 to 5.71 and OR, 1.50; 95% [CI], 1.05 to 2.17). Statins (OR, 2.52), ACE- I (OR, 2.39) and anti- platelet therapy (OR, 1.47) were also all positive predictors for CR referral in the EMMACE- 2 study (Table 3.3).

Of all the comorbid conditions, HF caused the CR referral variable to soar significantly in contrast to diabetes, which had the opposite effect (OR for HF, 2.19; 95% [CI], 1.70 to 2.84; vs. OR for diabetes, 0.73; 95% [CI], 0.54 to 0.99). The mini-GRACE score, constructed to predict death within six months of the patients being admitted with acute MI, was a strong negative predictor of CR referral (OR for mini-GRACE, 0.17; 95% [CI], 0.10 to 0.31), but only in 2003.

Sensitivity

The goodness of fit tests according to Hosmer-Lemeshow for 10 groups was not significant in either of the EMMACE studies (1995, P= 0.90 vs. 2003, P= 0.25), indicating a good fit between the predicted and fitted model values. Despite the high level of missing values regarding CR referral in 1995 (39.7%), it was decided not to undertake imputations for the CR referral propensity score, as it was not a primary endpoint in the studies.

Table 2.3. Adjusted odds ratios (95% CI) for predictors of referral for CR in 1995 and 2003

Study	EMMACE 1, 1995			EMMACE 2, 2003		
Variable	Odds ratio 95% CI	Z-score	P-value	Odds ratio 95% CI	Z-score	P-value
Age	0.96 (0.94-0.99)	-2.84	0.004	1.01 (1.00-1.03)	1.80	0.07
Sex	1.38 (0.98-1.93)	1.87	0.06	1.07 (0.84-1.36)	0.51	0.61
Admitting Cardiologist	1.34 (0.95-1.90)	1.69	0.09	0.89 (0.70-1.13)	-0.97	0.33
Statin	1.12 (0.57-2.18)	0.32	0.75	2.52 (1.82-3.42)	5.57	<0.001
ACE-I	1.01 (0.71-1.45)	0.07	0.95	2.39 (1.89-3.02)	7.24	<0.001
Beta-blocker	1.72 (1.15-2.58)	2.66	0.008	1.10 (0.84-1.46)	0.70	0.48
Anti-platelets	1.03 (0.65-1.64)	0.13	0.90	1.47 (1.04-2.08)	2.16	0.03

HF	0.86	-0.78	0.44	2.19	5.99	<0.001
	(0.59-1.26)			(1.70-2.84)		
COPD	1.18	0.73	0.47	1.07	0.39	0.70
	(0.75-1.85)			(0.77-1.48)		
Diabetes	0.94	-0.26	0.79	0.73	-2.06	0.04
	(0.59-1.50)			(0.54-0.99)		
Mini-GRACE*	0.60	-1.12	0.26	0.17	-5.78	<0.001
	(0.24-1.47)			(0.10-0.31)		
Reperfusion	3.12	6.57	<0.001	4.11	8.45	<0.001
	(2.22-4.39)			(2.96-5.71)		
Revascularisation	1.86	0.80	0.43	1.50	2.21	0.03
	(0.40-8.60)			(1.05-2.17)		

HF: Heart failure; COPD: Chronic obstructive pulmonary disease; GRACE: Global Registry of Acute Cardiac Events;

* Based on propensity of death at six-months adjusted for ST deviations, systolic BP, heart rate, cardiac arrest and age; The goodness of fit tests according to Hosmer-Lemeshow for a group of 10 were insignificant in both 1995, p=0.90, and 2003, p=0.25.

2.3.4 Missing data of CR referral

Missing data on CR referral were more than 10 times more frequent in the EMMACE-I study compared to the EMMACE-II cohort (N= 872 vs. N= 80). Patient histories of HF diagnosis, abandoned beta-blockers and statins prescriptions, less use of reperfusion, male sex, no admitting Cardiologist, a higher mini-GRACE score indicating a worse prognosis, a lower propensity score for CR referral and higher age were all significantly associated with missing data on CR referral in 1995 (Table 3.4).

In 2003, fewer variables were associated with the missing data on CR referral. Significantly related to the absence of a CR referral value were male sex and lower proportions of invasive reperfusion and revascularisation treatment. In comparison to the EMMACE-I study the influence of some variables changed to have a reverse effect. For instance, the mini-GRACE risk score was lower and the amounts of patients admitted by Cardiologists was higher in the patient group missing CR referral data in 2003.

Table 2.4. Missing values for CR data

Cohorts	**EMMACE 1, 1995**		**EMMACE 2, 2003**	
Associations	Missing CR	P-value	Missing CR	P-value
	N= 872		N= 80	
HF	496	<0.001	19	0.08
No HF	261		61	
COPD	130	0.02	12	0.89
No COPD	624		65	
Diabetes	118	0.003	24	0.001
No diabetes	636		55	
Cardiac arrest	270	<0.001	0	0.003
No cardiac arrest	488		80	
Anti-platelet	309	0.001	67	0.65
No anti-platelets	75		13	
Beta-blocker	116	<0.001	54	0.35
No beta-blocker	267		21	
Ace-I	161	0.06	56	0.06
No Ace-Is	221		19	
Statins	22	0.05	66	0.15
No statins	360		9	
Revascularisation	19	0.54	18	0.01

No revascularisation	849		56	
Reperfusion	235	<0.001	4	<0.001
No reperfusion	523		73	
Sex (Male)	412	<0.001	43	0.05
Female	346		37	
Admitting Cardiologist	208	<0.001	48	0.01
No admitting cardiologist	524		30	
Mini-GRACE (missing)	64.9 (675)	<0.001	0.19 (73)	0.01
Complete	36.4 (1189)		0.28 (1843)	
Propensity for Rehab (missing)	63.0 (675)	<0.001	67.4 (73)	0.16
Complete	75.8 (1189)		64.4 (1843)	
Age (missing)	74.9 (754)	<0.001	68.4 (77)	0.47
Complete	67.5 (1246)		69.5 (1858)	

The missing CR counts the number or calculates the mean of missing values for CR referral for each variable. The P-value indicates a significant difference between the means or proportions of missing CR referrals in the relevant variable. HF: Heart failure; COPD: Chronic obstructive pulmonary disease; ACE-I: Angiotensin-converting-enzyme inhibitor; GRACE: Global Registry of Acute Cardiac Events.

2.3.5 Mortality

"One-year" mortalities

At one year, the cumulative mortality rates in the EMMACE-I and -II studies were 32% and 21%, respectively (OR, 1.49; 95% CI, 1.29 to 1.71; P<0.001) (Table 3.1). CR referral on discharge showed that referred patients had significantly lower odds of death than those not referred in 1995 (OR, 0.34; 95% [CI], 0.24 to 0.46; P< 0.001) and in 2003 (OR, 0.19; 95% [CI], 0.15 to 0.23; P< 0.001). When the one-year cumulative odds for mortality in CR-referred patients were compared between the two EMMACE studies, there was no significant difference (not shown).

If only HF patients in the EMMACE studies had been followed, 1,034 (52%) would have been discharged with HF in 1995 compared to 672 (33%) in 2003. Of the HF patients during the first year, 473 (46%) died in the EMMACE-I cohort versus 153 (23%) in the EMMACE-II cohort. A smaller proportion of HF patients (68%) were referred to CR in 1995 than in 2003 (71%). Non-referred HF patients lived significantly shorter amounts of time than their referred counterparts, both in 1995 and 2003 (OR for death when referred in 1995, 0.34; 95% [CI], 0.23 to 0.51; P=0.001 vs. OR in 2003, 0.15; 95% [CI], 0.10 to 0.23; P=0.001). Between the decades, a comparison of the one-year mortality odds for CR-referred HF patients equally reveals significantly higher odds of dying in 1995 compared to 2003 (OR, 1.60, 95% [CI], 1.09 to 2.35; P= 0.02).

Long-term mortalities

Survivors at the 90-month follow-up were 649 (30%) and 1,122 (55%) in the EMMACE-I and -II studies, respectively. The median survival time was not measurable in both decades for the CR-referred patients within the first 90 months (Figure 3.1) because in 2003 it was greater than 90 months. The median survival times for non-referred patients were 48.3 and 32.0 months in the EMMACE-I and -II studies, respectively. Among CR-referred patients the magnitude increased to 168.5 months in 1995. Figure 3.1 depicts the proportion which survived, stratified by year and CR referral status. Significant unadjusted survival differences between CR-referred compared to non-referred patients were observed in both 1995 and 2003 (log-rank test; P< 0.001 for 1995 and 2003). A comparison of the impact of CR referral between the two decades, using unadjusted analysis, did not show a significant effect (P= 0.58).

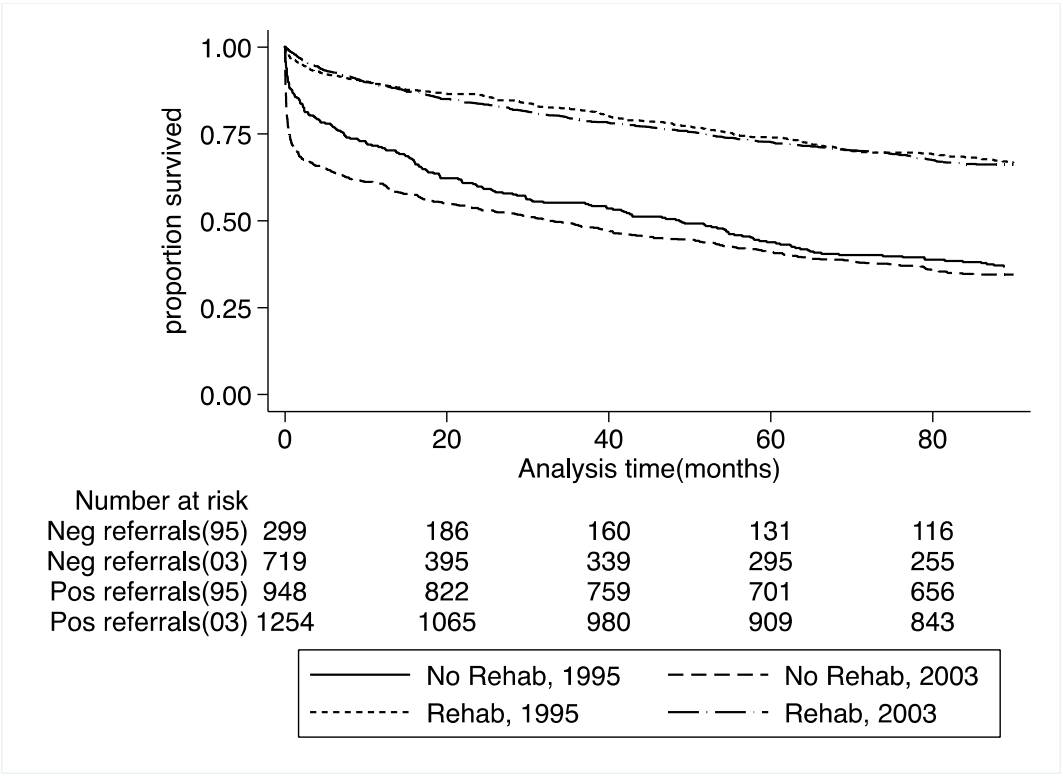


Figure 2.1. Kaplan-Meier survival estimates for patients hospitalised in 1995 and 2003 with an acute myocardial infarction, stratified by referral for CR; Rehab: CR referred; No Rehab: Not CR referred; Neg referral; Not CR referred; Pos referrals: CR referred.

Reflecting changes in the relative risks of dying throughout the two decades, the hazards ratios (HRs) for death during a follow-up of 0 to 90 months were 0.99 (95% CI, 0.78 to 1.25; P= 0.91) in 1995 and 0.57 (95% CI, 0.49 to 0.67; P< 0.001) in 2003 – see Table 3.5.

Table 2.5. Mortalities associated with CR referral, obtained from Cox proportional HRs (95% CI)

Modelling strategy	*EMMACE 1, 1995*		*EMMACE 2, 2003*	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Univariable with exit at 90 months	0.39 (0.33-0.47)	<0.001	0.35 (0.30-0.40)	<0.001
Complete model* with exit at 90 months	0.99 (0.78-1.25)	0.91	0.57 (0.49-0.67)	<0.001
Multiple imputations (0-90 months)	0.78 (0.65-0.95)	0.01	0.57 (0.49-0.67)	<0.001
Entry at 3 months (3-90 months)	1.00 (0.78-1.20)	0.97	0.78 (0.64-0.94)	0.01
Multiple imputation with entry at 3 months (3-90 months)	0.90 (0.70- 1.17)	0.44	0.80 (0.66-0.96)	0.02

* Including the variables of age, sex, COPD, HF, diabetes, beta- blocker, ACE-I, statin, anti-platelets, revascularisation, reperfusion, ST deviations, heart-rate, SBP, cardiac arrest and the admitting Cardiologist.

Estimations of breaks in the assumptions posed in the survival models

Violations of statistical assumptions specified in the Cox proportional hazard regression model can render unreliable the final interpretation of the relative risk of death for any binary and continuous variables. The following shows a few examples of how the integrity of the models was secured through investigations of linearity, proportionality and additivity of the HRs calculated in the Cox model. Variations in the inflation of individual covariates and overall model fits were also assessed.

Linearity, or the functional form of age in the EMMACE-I study, was assessed through martingale residuals (see Figure 3.2). Age was also a predictor in the survival model.

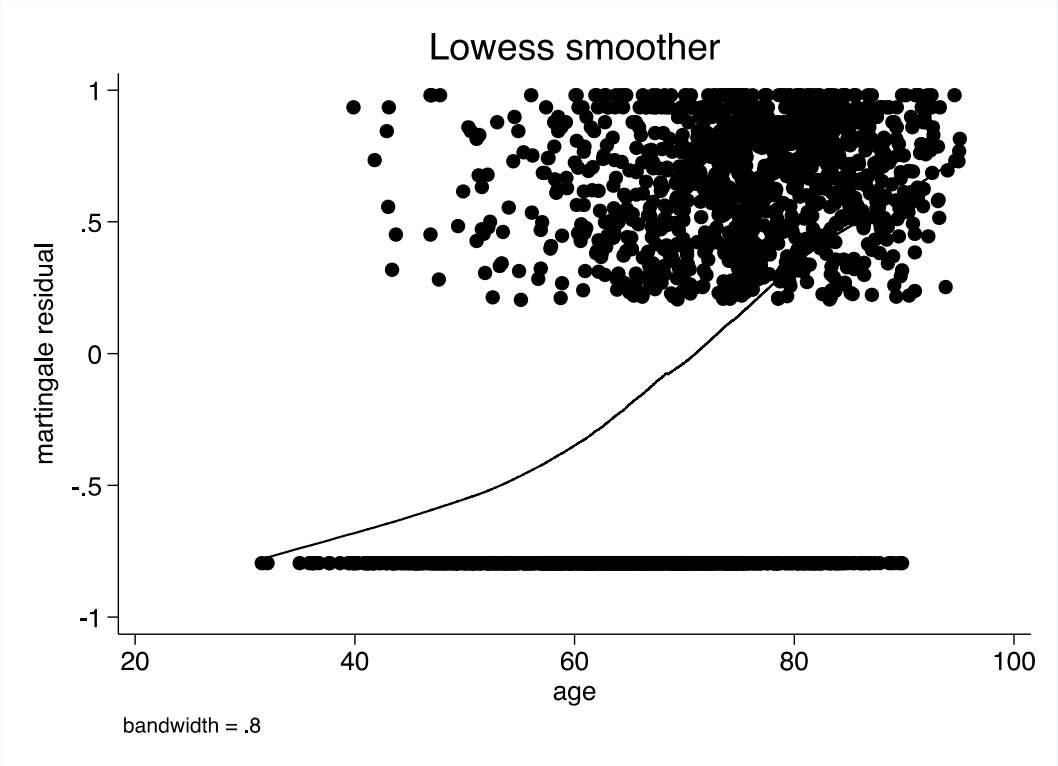


Figure 2.2. Lowness smoothing plot of martingale residuals corresponding to the age of the patients.

The graph above indicates non-linearity, a finding deduced from the varying sizes of residuals, which under linearity are close to zero. One way to allow non-linearity is through the mk-spline function, which was undertaken for age. Successively, a comparison of two Cox models incorporating all pre-specified variables, but differing by having age as a linear variable or mk-spline, was undertaken. The idea was then to observe the effect of the format of age on the HR of CR referral; it did not have a remarkable effect on the HR for CR referral

(HR for CR referral ‘model with mk-spline variables’, 1.00; 95% [CI], 0.79 to 1.27; P= 0.996 vs. HR for CR referral ‘model with age’, 1.00; 95% [CI], 0.79 to 1.26; P= 0.97), if one or the other was chosen. It was therefore decided to retain age as a linear variable.

Proportionality was examined through Schoenfeld’s residuals, revealing all the variables required to obey the assumptions of proportionality (Table 3.6). One example illustrated in Table 3.6 is the log-log survival plot comparing CR-referred versus non-referred patients (see Figure 3.3). Even though the two plots were not completely proportional, they were nevertheless acceptable. The assessment of non-proportionality was achieved on the varying distance between the two graphs. During perfect proportionality their distance should be equivalent over the whole follow-up period.

Table 2.6. Investigation of proportionality in Cox's model

Variables	*Rho*	*Chi2*	*Df*	*P-Value (Chi2)*
CR referral	0.06	1.67	1	0.20
Sex	0.04	0.81	1	0.37
Revascularisation	-0.06	1.31	1	0.25
Reperfusion	-0.06	1.77	1	0.18
Diabetes	-0.02	0.15	1	0.70
Anti-platelets therapy	0.01	0.03	1	0.86
Beta- blocker	0.07	2.15	1	0.14
ACE- I	0.06	1.62	1	0.20
Statin	-0.09	3.66	1	0.06
COPD	0.002	0.00	1	0.97
HF	<-0.001	0.00	1	0.99
Admitting Cardiologist	<0.001	0.00	1	0.99
Age	0.09	3.35	1	0.07
Global test	NA	14.69	13	0.33

ACE-I: Angiotensin-converting-enzyme inhibitor; COPD: Chronic obstructive pulmonary disease; HF: Heart failure NA, Non-applicable. If the Rho values were insignificant (P≤ 0.05) a break of proportionality was suggested.

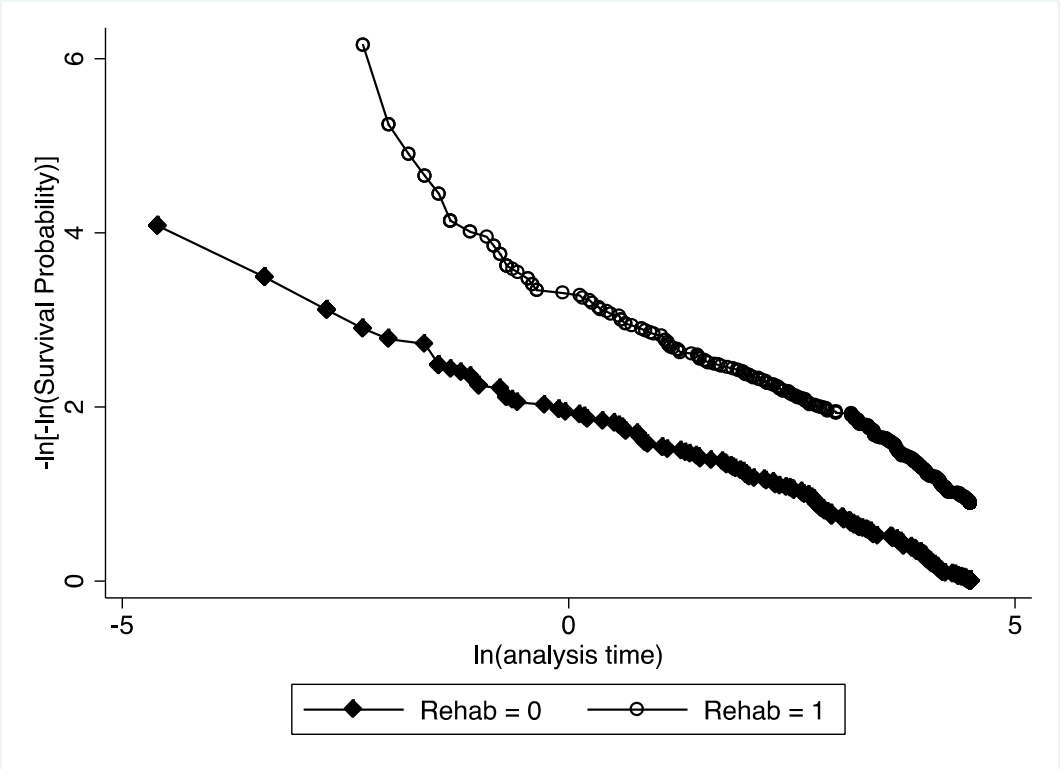


Figure 2.3. Log-log plot of survival compared to the CR-referred and non-referred populations, which also illustrated proportionality; Rehab=0: Not CR referred; Rehab=1: CR referred.

Assessing whether parameters were additive in the Cox proportional hazard model was achieved by examining selected combinations of interactions. One finding of a significant interaction was between the year of the EMMACE study and the CR referral variable (P< 0.001). Other combinations of interactions investigated were between CR referral and the variables age, SBP, COPD, CHF and diabetes. They were all non-significant, except for age, which showed a significant interaction in 1995 (P = 0.05). However, this particular interaction was left out for two reasons. First, inclusion of the interaction term in 1995 had an immense effect on the hazard ratio (HR) of CR referral, which seemed more the result of the non-linearity of age. Second, the large numbers of missing values for CR referral in 1995 could have contributed to the interaction due to selection bias.

COPD also demonstrated interaction with CR referral in 1995 in the survival model. Overall, it was concluded that separating data from each EMMACE study would prevent violation of the additive assumption in Cox's model. The survival models assessing the CR referral effect on death were for that reason distinguished according to data from 1995 and 2003, but with a common follow-up until September 2010.

Variances in inflation (VIF) were investigated, in order to assess whether any of the variables in the two EMMACE models pointed towards multi-collinearity. This was not the case, though, as the mean VIF values were 1.20 and 1.21 in 1995 and 2003, which is close enough to the golden standard of 1.00 to be acceptable. Neither of the variables had VIF variables greater than 1.55.

Eventually, the link test was undertaken for each model in an attempt to assess the fit of the model. Both models had reasonable fits, a finding interpreted from the p-values of the square of their predictions. Link tests were expected to be non-significant, which was indeed the case (P= 0.07 & P= 0.33).

Estimates of time-dependency on the effect of CR referral through Schoenfeld's residuals were assessed during the first three months. In both decades great differences in the HRs of CR referral in line with time were observed. In 1995, CR referral became a non-significant negative factor for survival during the first two months (HRs> 1.00), in contrast to 2003, where the relative risk of CR referral became a significantly strong positive factor for survival (HRs< 1.00) during the first three months.

HRs in the left truncated follow-up: three to 90 months

When both models were left truncated for the first three months, the HR for CR referral in 1995 had no significant impact on survival (HR, 1.00; 95% [CI], 0.78 to 1.20; P= 0.97), in contrast to the slightly changed, but still significant, HR for CR referral in 2003 improving survival (HR, 0.78; 95% [CI], 0.64 to 0.94; 0.01).

2.3.6 Heart failure patients

Overall, HF patients had a significantly lower chance of surviving at 90 months compared with patients without HF in both decades in the EMMACE studies (P< 0.001) (Figure 3.5). When the patient population was cut down to only HF patients, the impact of CR referral did not alter remarkably compared to the results calculated from the entire cohort. In 1995, when a follow-up period from three months to 90 months was contemplated, CR referral was not a significant independent variable for decreased survival (HR, 1.12; 95% [CI], 0.80 to 1.56; P= 0.52). Similar to the whole cohort in the EMMACE-II study, CR referral for HF patients was

an independent factor for reduced RR of death, estimated at 42% (HR, 0.58; 95% [CI], 0.42 to 0.81; P= 0.001) in the follow-up period of three to 90 months.

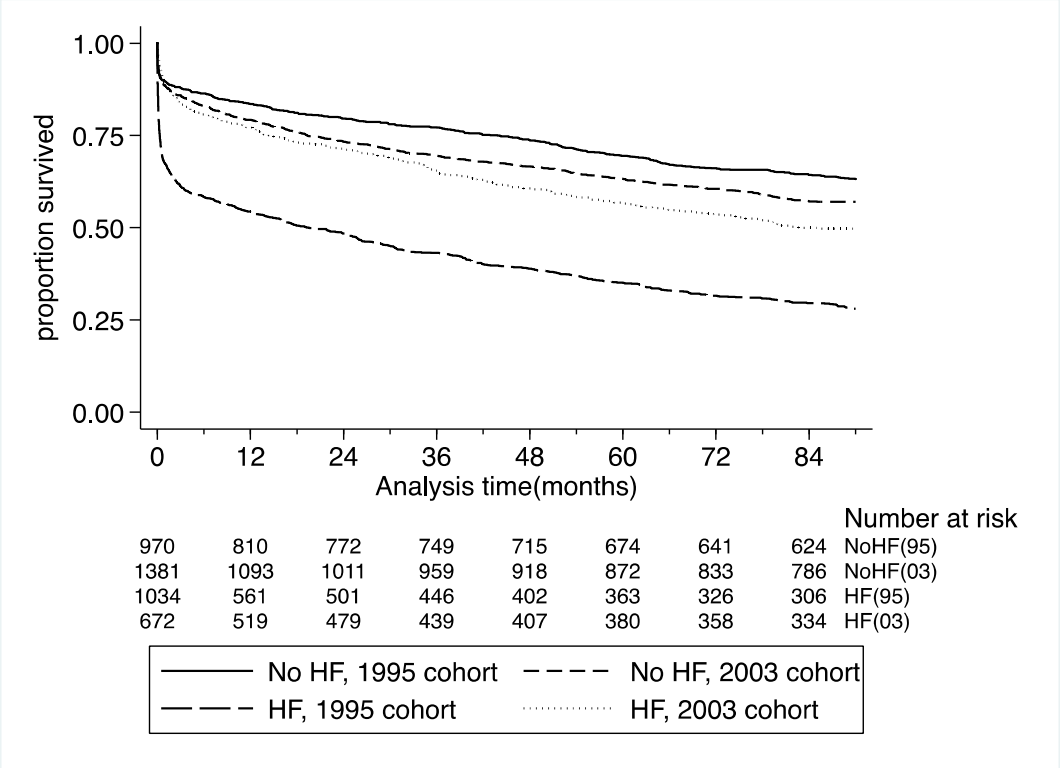


Figure 2.4. Kaplan Meier curves comparing patients with IHD and HF diagnosis versus patients with IHD alone for time to death; HF: Heart failure.

2.3.7 Multiple imputations

When multiple imputations (MIs) were performed for the whole EMMACE population of 1995, the CR referral for HR approached significant effects. When the follow-up period covered the period 0 to 90 months, CR referral became even more of a significant predictor of increased survival (HR, 0.78; 95% [CI], 0.65 to 0.95; P= 0.01). This was not the case when the follow-up ranged from three to 90 months (Table 3.5). However, the HR was still suggesting a beneficial effect of CR referral on discharge at 95% [CI], which had a larger likelihood below 1 than above 1 (95% [CI], 0.70 to 1.17; P= 0.44).

If CR referral was not imputed, missing numbers increased immensely. CR referral was the variable with the most missing values in 1995, but it was still a significant predictor of reduced mortality in the follow-up for 0 to 90 months in a model where it was the only variable not imputed (HR, 0.81; 95% [CI], 0.66 to 1.00; P= 0.048). The estimated survival

effect of CR referral decreased when the same scenario was conducted in the truncated model (HR, 0.95; 95% [CI], 0.75 to 1.21; P=0.67).

In both the unrestrained follow-up and the truncated model in 2003, imputation of CR referral demonstrated that it had a reducing effect on long-term mortality. The imputed results were almost identical to the non-imputed models (Table 3.5). With respect to the MIs performed without CR referral among the imputed variables, the picture did not change much compared to the model imputing CR referral. In the complete follow-up, RR reduction stood at 43% (HR for 0 to 90 months, 0.57; 95% [CI], 0.49 to 0.66; P<0.001) but plummeted to 21% in the truncated model (HR for 3 to 90 months, 0.79; 95% [CI], 0.65 to 0.95; P=0.01).

2.4 Discussion

2.4.1 Summary

Overall, the results show that the benefits of CR were similar in patients with CAD compared with their integrated subpopulation suffering from HF and CAD, assessed from a pre-specified survival model censored at three and 90 months.

During the eight years between the EMMACE-I and -II studies several changes were observed in the baseline variables recorded during hospital admission time. Regarding competing diseases, hypertension and hyperlipidaemia were significantly more frequent in the EMMACE-II study, contrary to HF and STEMIs, which were both significantly higher in the EMMACE-I study. Risk factors such as higher Killip-class, cardiac arrest and the modified mini-GRACE score were all more prevalent and higher in the EMMACE-I study. With the exception of reperfusion, which was used more frequently in the EMMACE-I study, revascularisation and Cardiologists' treatment plans were seen more often in the EMMACE-II study. Furthermore, guideline-recommended treatments through statins, ACEIs and beta-blockers were all more prescribed in the EMMACE-II study, too.

Both the absolute numbers and independent predictors for CR referral changed between the two decades of the EMMACE studies. In 1995, 986 (74%), and 1,256 (64%) in 2003, were CR-referred. It is important to keep in mind that missing CR referral data in 1995 accounted for almost 40% of observations compared to less than 4% in 2003.

Concerning independent predictors for CR referral, the trend of characteristics shifted between the two cohorts. In 1995 age was the only negative factor, whereas beta-blockers and reperfusion were positive factors. Reperfusion was also a positive factor in 2003, equal to HF, anti-platelets, statins and ACEIs. Conversely, diabetes and the modified GRACE score were both negative factors in 2003.

2.4.2 Strength of the study

Real-world data versus RCTs and meta-analyses

Traditionally, RCTs examining the effect sizes of interventions are linked to clinical evidence; observational studies are less accurate in their estimations of effect sizes. These treatment effects will often be volatile compared to those found in RCTs(178). Patient selection is another term used in both RCTs and observational studies. Regarding RCTs, patient selection means the inclination of investigators to recruit younger patients with little comorbidity. In observational studies, patient selection covers the trend prescribing some form of intervention but only to a certain group of patients, and they are frequently dependent on risk factors and comorbidities. Edward Hannan cited a number of criteria to look for when assessing the outcomes of RCTs and observational studies(179). As an overall statement he concluded that the distinction between RCTs and observational studies is less important, but he did underscore the quality of a database as being crucial. The second criterion to look for when estimating the usefulness of a treatment is whether the recruited patients in a study are the same patients who in a real-world situation would be likely to receive the treatment. The third criterion requires the researcher to assess whether the outcomes of a study are clinically meaningful, while the fourth involves determining whether the size and generalisability of a database encompass statistical power and whether the results can be referred to other clinical settings. The fifth criterion identifies the strategy and assesses its appropriateness. Finally, the follow-up period is assessed for its relevance; for instance, it may seem less important to evaluate the long-term effects of acute intervention rather than 30 days' survival. In the following, these criteria will be evaluated as part of a critique of observational studies and RCTs.

Observational data in the EMMACE studies had several methodological advantages. First, it has been seen very rarely before that identical observations of clinical, epidemiological and pathological variables have been repeatedly measured across two consecutive decades. Another advantage was that the EMMACE studies were both multicentre studies, having seldom been conducted in the area of secondary prevention.

Presumably, the Framingham studies are the only pre-existing examples similar to the EMMACE studies(180). The most obvious difference between the EMMACE and the

Framingham studies is their different geographical location, which means that epidemiological and environmental confounders make it hard to draw direct comparisons between European and American cohorts. Nevertheless, it appears fair to generalise the many mechanistic findings uncovered in the Framingham studies against the European model.

In contrast to the RCT methodology, which often recruits multinational centres, data collection from the same geographical region is assumed to be advantageous. Through this method, unmeasured confounders between different geographical regions can be avoided, even though differences may persist between central learning hospitals and district hospitals in peripheral regional areas.

In addition to keeping data collection in a geographically confined area, the long-term follow-up of both cohorts was another positive aspect of the studies. The possibility of intra- and inter-cohort comparisons in the time span between admission and the endpoint in the follow-up provided a variety of possibilities, which specifically allowed for differentiating the time course of the CR referral effect on mortality. As the analyses indicated that a large proportion of patients died during the first three months, and given the fact that CR is not meant to have an acute life-saving function, left-censoring at three months was decided upon for this study. Overall, it is believed that this initial cut-off in the follow-up provided robustness for the analyses by removing unmeasured confounders, namely patients with high risk factors and comorbidities dying during the period. Corrections of unmeasured confounders through statistical adjustment are a field full of landmines. Christenfeld et al. suggest how to avoid wrestling with confounders by selecting patients without large variations in the area of interest(181). In heart research, this could be achieved through the recruitment of patients with similar health statuses, for instance by NYHA class.

Missing data analysis

The missing data analysis performed for the ICE MIs was definitely a strength in the studies(182). Taking into account the missing values did not influence the outcomes of CR referral considerably when the analysis was censored before three months and after 90 months, independent of the study year.

Conversely, when the censoring was removed before three months (0 to 90 months) in 1995, the ICE MIs had a turning point effect on the CR referral HR. This meant it moved from not being a significant independent decreasing factor for mortality to a beneficial event after the

missing data were imputed. This implies that given a large number of missing data, as in the 1995 cohort of the CR referral variable, it is not advisable to draw final conclusions about the data without MIs.

In 2003, the MIs did not change the HR of CR referral significantly when censoring before three months was removed. In other words, censoring had a greater effect on the CR referral HR than MI in 2003.

2.4.3 Limitations of the study

No causality

The fact that the EMMACE studies were based on observations and not on randomised allocations of CR referral meant that it was not possible to state causal associations. Thus, it is important to keep in mind that any relationship found between mortality and CR was only a plausible affiliation. In order to clarify causal relationships between CR referral and mortality, an RCT is necessary.

Unmeasured confounders

An evident shortcoming of the analysis was that enrolment and the completion of CR data were not recorded. Although excused from the pre-specification of data collection to hospital admission time, enrolment and completion would have added abundant information to the CR referral variable. The fact that the HRs for CR referral were revealed to be time-dependent in both studies meant that unmeasured confounders could have had a disturbing influence on the outcome.

The reason underlying the positive finding of CR referral on mortality may at the same time reveal a shortcoming of the analysis. The exposure definition of CR in the EMMACE studies encompassed only referral on discharge post MI where a substantial part of the growing evidence of CR includes referral, enrolment and completion in the outcomes. This may explain why the majority of contemporary studies investigating CR has little or no impact on mortality in patients with IHD with or without HF. Contemporary studies of CR stand therefore in contrast with the results found here.

Potential physical activity after discharge, independent of CR attendance, is another unmeasured confounder. Despite the fact that physical activity measures are often biased by

the study participants' own ideals, it would nonetheless have illuminated the long-term effect of CR referral and, indirectly, adherence to a healthy lifestyle. Other essential covariates which could be considered for a priori data collection in a cardiovascular study are LVEF, NT-proBNP and cancer diagnoses.

Patient selection for CR referral was another potential weakness of the EMMACE studies. Two different mechanisms were suggested. First, the mini-GRACE score, estimating the risks for six-month mortality, was significantly higher in both decades in patients not CR-referred compared to their referred counterparts. Second, another mechanism examined patients dying during the admission period, who were then automatically recorded as non-CR-referred or perhaps missing. This creates an odd scenario, seen from the perspective that the patient never had a fair chance of receiving a referral. In conclusion, the higher frequency of comorbidities and unfavourable risk scores in patients not referred suggests that patient selection was an essential part of the decision-making process in CR referral.

Time-dependent technological changes make adjustments between the two EMMACE studies difficult. A remarkable change was the ischemic myocardial markers used in the diagnosis of acute MI. Unfortunately, the separate myocardial markers used in each decade were unavailable for further adjustment; therefore, the improvement in specificity and sensitivity associated with the diagnosis of acute MI was non-measureable(156, 183). Finally, faster diagnoses led to quicker treatment and resulted in better outcomes. These steps underlying medical decision-making remain unmeasured confounders.

Missing data

In general, most of the variables recorded in the EMMACE studies had missing values below 5%. However, in the case of CR referral, a missing percentage of 40% was observed in 1995 compared to 4% in 2003. The high number for the CR referral variable in 1995 may be associated with various explanations. Given the higher mortality rate in 1995 compared to 2003, larger numbers of patients were likely to be deceased at the time of CR referral. This does not excuse the lack of CR referral documentation, but it does seem a plausible underlying reason.

Less focus on the area of secondary prevention and CR referral in 1995 can also underpin the greater number of missing values. Correspondingly, the greater focus on secondary prevention and CR during the eight years between the EMMACE studies might have led to more extensive documentation in the patient notes on CR referral.

Incremental, specialised treatments by Cardiologists during the decade between the studies might also explain the higher reporting of CR referral in 2003. This might possibly also explain that fewer patients with an acute MI were treated as outliers on clinically inappropriate wards in 2003. A higher level of treatment expertise in 2003 is therefore likely to have prompted more attention to CR referral. Results from the Myocardial Ischemia National Audit Project (MINAP) register, investigating the care of CAD after 2003, suggested however that less than 50% of admitted patients with ACS benefitted from a consultant in cardiology(151).

The conditions of being either missing completely at random (MCAR) or missing at random (MAR) are prerequisites for validating the replacement of missing values by MIs(184). In the context of the EMMACE studies it is questionable whether this was the case for the EMMACE-I study. Closer observation of the missing CR referral data in 1995 reveals an association with HF, the lower prescription of guideline-recommended medication, fewer reperfusions, older ages, a higher proportion of the male sex, a lower degree of admitting cardiologists, a higher mini-GRACE score and a lower propensity score for CR referral compared to patients with complete CR referral information (Table 4). This finding can be generalised to the distinction of a poorer clinical condition in patients with missing CR referral data; nonetheless, it is not likely that a single variable was the reason behind the missing CR referral data. Consequently, the performances of MIs can still be defended. An example of a breach of the MAR's condition is for instance when patients with cardiac arrest are missing CR referral data.

Overall, the fact that there were fewer missing data in 2003 than in 1995 is associated with the significantly improved treatment of acute MI, resulting in lower mortality. The higher survival rate was indirectly related to a better clinical condition observed through fewer HF patients and a lower Killip class in the EMMACE-II study compared to the EMMACE-I. It is hypothesised that general improvements in the health of patients between the studies may have led to the absolute higher CR referral rate in 2003.

2.4.4 Previous literature

Similar to the EMMACE studies, Brown et al. investigated CR referral among 72,817 patients on discharge after an MI, a PCI or a CABG event between January 2000 and September

2007(185). Overall, 56% were referred for CR. Similar to the EMMACE studies, older age and the presence of comorbidities were associated with decreased CR referral.
More extensively, Suaya et al. assessed mortality among 601,099 Medicare patients who were hospitalised for coronary disease or treated through cardiac revascularisation procedures(153). Of these patients, only 12.2% attended CR. Brown et al. also found risk reductions of 34% in patients attending CR compared with matched non-attenders over a five-year period. Furthermore, the number of sessions completed was associated significantly with survival during five years.

In addition to observing the referral and enrolment of patients with CVD, Canadian researchers have also investigated how to optimise these crucial facets of the rehabilitation process. In a prospective controlled trial, a Canadian research group clustered hospitals into one of four referral strategies: usual care, automatic, through health care liaison or combined automatic and liaison referral(186). The combination of automatic and liaison referral showed the highest CR use (odds ratio 8.41) followed by the automatic strategy (odds ratio 3.27).

2.5 Conclusion

In conclusion, CR referral had a significant improving effect on all-cause mortality in the EMMACE-II study, but not in the EMMACE-I, when identical multivariable analyses were performed. In order to reduce the time-dependency of the CR referral variable and associated instability in the analyses, left-censoring at three months was incorporated into the analysis. In this setting CR referral reduced mortality by 22% (P=0.01) in the EMMACE-II study, but it remained neutral in the EMMACE-I parallel. Sensitivity analysis taking regard of missing values did not change the outcome effect of CR referral in the truncated follow-up. Moreover, reducing the study populations to purely HF patients did not affect the independency of CR referral as a survival predictor in the EMMACE-II study. A comparison of baseline characteristics between the two EMMACE studies revealed a decrease in risk factors and an increase in the treatment level of acute MI during the eight years between the studies.

Chapter 3 – Contemporary meta-analysis assessing exercise interventions in HF patients

3.1 Introduction

Past attempts to establish the role of exercise-based CR in HF patients have partly failed(144). Meta-analyses have frequently been performed to generate synthesised effect sizes in the endpoints of all-cause deaths and hospital admissions(8), which can be explained through the lack of well-powered prospective clinical studies investigating the area. As a result of conflicting evidence, the funding of exercise-based CR has not been efficiently outsourced(187). As a result, many HF patients have missed out on a golden opportunity to achieve a healthy lifestyle. Furthermore, the lack of multifaceted secondary prevention may lead to an unfavourable prognosis for some HF patients(188).

Despite their broad data searches and well-designed strategies, previous meta-analyses, including the Cochrane Systematic reviews investigating exercise-based CR in HF patients, have not applied a subgroup analysis of contemporary treatment assessments. An approach with an unrestricted timeframe could cause an interaction between the year of study and the exercise intervention. For instance, on the one hand it can be speculated that HF patients two decades ago may have benefited more from regular exercise compared to current patients who receive a higher level of invasive and pharmacological treatments. On the other hand, current HF patients may be in a better physical condition compared to patients treated before the modern era of medicine. Therefore, they are potentially more compliant to exercise programmes and may consequently achieve better outcomes.

The most efficient format of exercise-based CR is another unanswered question in secondary prevention of HF. Yet, paradoxical results have been reported in the comparison between comprehensive and solely exercise-based CR programmes. Whether resistance or aerobic exercise training determines outcomes, or if a better exercise outcome is achieved through the fusion of the two, remains unknown(189).

Intuitively, key outcomes of exercise-based CR are related to adherence to the exercise programme(190), and existing meta-analyses have rarely investigated patients' commitment to regular exercise(191), which could be due to a lack of RCTs reporting in the field.

In light of these sparsely investigated areas in existing meta-analyses, the aim of this chapter is to update a systematic review of exercise in HF patients. The primary objectives are to investigate outcomes of all-cause deaths, hospital admissions and the exercise capacities of exercise time, the 6-MWT, PVO_2 and exercise power through meta-analyses, including RCTs with patients with HF randomised to exercise training with a minimum follow-up of six months in the period between January 1999 and August 2010. Secondary objectives are to establish the association between the primary objectives and contemporary treatments, baseline characteristics, the HF-PEF subset, exercise mode, adherence, the CR format and long-term insights into exercise measures. The research question, which I attempt to answer, asks whether contemporary time adjustments influence the outcomes of mortality, hospital admissions and exercise capacities during a minimum follow-up of six months, as such a question has not been investigated in previous systematic reviews.

3.2 Background

Chapter 1 reviewed the definition and nature of HF, which for many patients culminates in breathlessness associated with mild exertion. This section will summarise the development of exercise interventions which aim to increase fitness in HF patients and are demonstrated through less breathlessness during exercise.

3.2.1 Description of the intervention and how it works

Exercise-based CR programmes designed for HF patients vary between hospital-, community- and home-based CR. Frequently, the community and home-based CR programmes are natural extensions of the hospital-based programmes.

In general, two types of exercise for HF patients are put into practice: endurance and muscular strength training. The former is also described as cardiovascular training or aerobic exercise, whereas muscular strength training is known as resistance training. Typically, aerobic training is performed with 60-70% of the maximum individual capacity for a minimum period of 30 minutes, whereas resistance training is built on a higher workload (60-100%) but is usually confined to 8-12 repetitions of a specific exercise repeated in a series of

three(192). Until recently, exercise modes for HF patients were confined to aerobic training, but this has changed more and more toward a combination of both resistance and aerobic training, as recommended by the American Heart Association (AHA) (193, 194).

Pathways to achieving healthy fat metabolism during aerobic exercise are plentiful, including walking, running, swimming and cycling used in the majority of programmes(195). Resistance training, performed in a large number of methods, varies according to the targeted muscle groups. A simple example of calisthenics exercise is leg squatting repeated 10 times and in three sets.

Mechanisms proven to benefit the cardiovascular circulation and functional capacity are demonstrated in several experimental settings.

Reduced periphery resistance caused by vasodilation is one benefit achieved through combined aerobic and resistance training. The underlying mechanism is shown to be based on nitric oxide (NO) processes(196). Furthermore, the aerobic exercise-induced activation of neural pathways stimulates the parasympathetic tone of the autonomic nerve system(197). The clinical result of these cascades is both lower blood pressure and HR, thus decreasing the risk of fatal events and mortality.

Resistance and aerobic exercise have also been established to impede left ventricular remodelling, which involves structural changes in a failing heart and leads to a lower functional capacity in HF patients(198, 199). Remodelling change is defined by decreased LVEF and larger geometric measurements of the left ventricle and atrium. Monitoring of the condition is mainly done through echocardiography and magnetic resonance images (MRIs).

Neuro-endocrinological pathways, leading to a high NT-proBNP and reduced insulin sensitivity, are examples of HF-induced hormonal dysfunction and are associated with the increased frequency of death. Resistance and aerobic training have indicated in observational studies beneficial lower values of NT-proBNP and increased insulin sensitivity(200, 201). Reduced skeletal muscle mass is linked to the HF syndrome, which can compromise a patient's ability to exercise(202). Moderate to high intensity resistance training is shown to enhance muscular mass and function, and it is associated with functional capacity, independence and QoL (quality of life).

Comprehensive CR programmes are based on broad treatment aims. From a simple point of view they are composed of components which are suggested to benefit HF patients. Examples

of interventions used in comprehensive CR programmes – in addition to exercise – are health, diet and psychological counselling and the management of drug treatment. Comprehensive CR programmes compared with exercise-based CR do not present convincing results. This may be explained by the fact that even if a patient is not offered comprehensive CR, its broad treatment components are likely to be available from other sources in the treatment sector(128).

3.2.2 Evidence from the past

Four recent systematic reviews indicate exercise-based CR to be beneficial for HF patients, but they also highlight pitfalls within the evidence. More detailed investigations are therefore necessary in this instance.

Cochrane Systematic review

The most recent systematic review (Davies et al.) of the Cochrane Collaboration did not find that exercise-based CR either increased survival or reduced hospital readmission in HF patients, or that there was an improvement in the long term(8). However, the meta-analysis of QoL limited to Minnesota living with HF (MLWHF) revealed a significant mean difference favouring the training group. The strength of the meta-analysis was the broad search performed, in that it collected an initial 11,561 studies. Nevertheless, the final studies selected for the meta-analysis did not recruit HF-PEF patients and the BNPs were gathered neither as an outcome nor as a covariate.

Moreover, the review did not evaluate the effect of physical training on exercise capacities from long-term perspectives, even though they recognised that the existing findings from Rees et al. in the existing Cochrane review had only established a blend of short- and long-term benefits of exercise(10). It is also unknown whether comprehensive formats or exercise modes were independent for successful outcomes.

The ExTraMATCH study

The exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH), by Piepoli in 2004, was the first example of a meta-analysis incorporating RCTs and showing significant reductions in the key outcomes of all-cause mortality and hospital readmissions(203). Overall, 801 patients were included, with a mean follow-up time of 705 days. The virtue of the study was the author's access to individual follow-up time data in each trial, which made the data analysis more accurate and extensive. The observation period covered from 1990 to 2002. This choice of period may have biased the results, though, due to changes in the quality of HF care in this epoch, suggesting that only part of the included patients benefitted from beta-blockers and ACE-Is prescription as well as invasive treatments. Another caveat was also that MEDLINE was the only database used for the search strategy. As such, the ExtraMATCH study could have been more informative and valid if the authors had undertaken a sensitivity analysis to compare HF-PEF and HF-REF patients. However, sparsely available empirical data in this area excuses the lack of such analysis.

A systematic review of moderate to high resistance training in HF patients

Moderate to high-level resistance training has not yet been proven in systematic reviews of HF patients to have an independent effect on the outcomes of death, hospital admission or exercise capacities. A recent systematic review by Spruit et al. did not suggest any independent effects of moderate to high resistance training, either on exercise capacities or QoL(189). This was concluded when moderate to high resistance training was compared as a single intervention with a physically inactive control group in four out of 10 included articles. A total of five articles compared the combination of moderate to high resistance training and endurance training with endurance training alone and did not find any differences here, either. Similar findings were found in the broad comparisons between endurance training vs. high to moderate resistance training vs. the combination of endurance and resistance training vs. usual care controls, which was based on a single study. In addition, the systematic review was not able to demonstrate any significant effect of resistance training in HF patients, but it was noted that the internal validity of the outcomes was low. This was concluded by the fact that only one study out of the ten was an RCT, which indicates low causality. Moreover, the mean score on the Delphi list was poor, which implies that the methodological quality was low(204, 205).

Home-based exercise in HF patients

The meta-analysis by Hwang et al. was undertaken in an attempt to evaluate home-based exercise programmes with usual care in HF patients(206). Their primary findings were measured through exercise capacities of the 6-MWT, exercise time and PVO_2.

All three outcome measures were established to improve significantly in the home-based exercise interventions compared with the usual care (weighted mean difference (WMD) of 6-MWT, 30.41 m; 95% CI, 6.13 to 54.68; P = 0.01), (WMD of exercise time, 1.94 min; 95% CI, 0.89 to 2.98; P<0.001), & (WMD of PVO_2, 2.86 ml/kg; 95% CI, 1.43 to 4.29; P < 0.001). The significant benefits of home-based exercise programmes were suggested as not only a single intervention but also as a follow-up intervention after centre-based exercise programmes. The latter intervention aimed to prevent the abrupt discontinuation of exercise and to provide adherence to an active lifestyle. A limitation of the meta-analysis by Hwang et al. was the heterogeneity of the included trials. However, reducing the analysis to trials based solely on home-based exercise, by excluding trials based on the combination of centre- and home-based exercise programmes, did not change the effect trend.

Despite the fact that a total of four meta-analyses, excluding patients with HF-PEF, did not distinguish between short- and long-term effects in exercise capacities, they may nevertheless have broad validity(8, 203, 206, 207), as they demonstrated that home-based exercise programmes improved exercise capacities compared to usual care in HF patients in three separate exercise measures. The potential impact on exercise adherence after a centre-based programme may be challenged through a trial randomising patients to a home-based exercise programme versus a placebo following centre-based CR.

Overall, the evidence found by the above summarised systematic reviews of the relationship between exercise-based CR and outcomes of mortality, hospital admission and exercise capacities in HF patients remains unclear from a contemporary, long-term perspective. Until now, systematic reviews have not investigated the relation between LVEF, NT-proBNP, exercise mode, any adjustments for planned admissions and the effect of exercise-based CR.

3.2.3 Rationale for this review

The necessity for this systematic review is explained by the need to acquire new knowledge concerning the outcomes of deaths, hospital admissions and exercise capacities in HF patients attending exercise-based CR. As such, it is hoped that this review will contribute to a better understanding of treatment regimes for an increasing population with the clinical syndrome of HF and at the same time highlight potential health care costs and the benefits for this patient group at a time of unprecedented pressure to reduce expenditure and save money. Currently, the HF patients group is both under-diagnosed and under-treated, and therefore these areas deserve to be focused upon(24).

As mentioned in the background chapter, in the UK alone the total annual cost of HF to the NHS is around £716 million, or around 1.8% of the total UK NHS budget. About 70% of the costs of HF patients are attributable to hospital admissions(15). Cost benefit analyses in exercise-based CR have been investigated very little to date(208); nevertheless, because the cost price of an exercise-based CR intervention is relatively low compared with unplanned emergency admissions, they may have a broad utility either in their current or a modified form.

New insights into the benefits of exercise-based CR in HF patients could increase CR referral and enrolment, which together will hopefully increase QoL and life expectancy in this patient group.

3.3 Aim and objectives

Please see 3.1 Introduction.

3.4 Methods

3.4.1 Criteria

Study types

Only RCTs were included, because they are considered to provide the most accurate evidence in treatment comparisons. Of these, only designs comprising parallel groups, including cross-over trials with a minimum six months' follow-up from the start date of the study, were assessed. There had to be a minimum of one control group without increased activity according to their usual level, which meant that trials comparing two separate types of exercise without a control group were not taken into consideration.

Participants

All adults (≥18 years) with diagnosed HF, either due to ischemic or non-ischemic cardiomyopathy, were considered. HF diagnosis in the selected studies had to correspond with the criteria set out by the ESC, which are symptoms typical of HF, signs of fluid retention (e.g. pulmonary congestion) and objective evidence of a structural or functional abnormality of the heart at rest(14). A distinction was made between ischemic and non-ischemic aetiology, which were categorised by DCM and ischemic cardiomyopathy (ICM). For sensitivity analysis, all studies including fusions of patients with CAD, with and without HF, were investigated. One prerequisite was that they reported 95% CI of the LVEF overlapping with LVSD or proportions of HF patients in the trial.

Trials were excluded if they had recruited patients who had had a heart-transplant (HTX), required dialysis or had attended exercise-based CR in the past.

Interventions

The CR interventions included in the review were either based exclusively on exercise training or were part of comprehensive CR. The word 'comprehensive' was appreciated as describing multifaceted programmes, for example those composed of psychological, diet and/or health education components. The nature of the exercise training was based on aerobic and resistance modules. According to the exercise mode, neither of the studies was based

solely on resistance training. Post-hoc analysis disclosed that water-based training was not part of any of the training programmes, while cycling accounted for 61%. However, high proportions of cycling, walking or running were still part of most of these training programmes. Due to the difficulties of separating cycling in the training programmes, meta-regression assessing the difference between walking/running and cycling was not undertaken. There were no pre-specified limitations to the exercise location to indicate whether training was performed on land or in water. All studies applying functional electrical stimulation to the muscles, in order to imitate physical activity, were excluded.

3.4.2 Outcome measures

Primary outcomes

All-cause mortality and hospital readmissions were the two separate pre-hoc primary outcomes. The reason for the broad perspectives in the outcomes, although not combined, is that deterioration in heart failure can be manifested often as non-cardiac diseases, for instance anaemia and kidney disease. Therefore, specific HF-related endpoints were abandoned because they demand a hierarchical classification, which is difficult in systematic reviews due to heterogeneity in trials.

Secondary outcomes

Measurements of exercise capacity (Chapter 5) in the form of PVO_2, exercise time, exercise power (watts) and the 6-MWT were the secondary outcomes. They were all evaluated earlier, but not with the minimum six-month follow-up period(10). The effects of NT-proBNP, HF-PEF, exercise mode, planned hospital readmissions and LVEF on the primary and secondary outcomes were assessed.

3.4.3 Search strategies

Electronic searches

Searches were undertaken through the Medline, CENTRAL, EMBASE, CINAHL and PsycINFO databases for the period between January 1999 and August 2010. This timeframe was chosen due to the time of publications in the last Cochrane systematic review of exercise training in CAD and HF patients and their respective overlap(7, 8). Search terms were built on the same categories as the Cochrane reviews, but they were slightly modified; see Appendix 4.1.

Other resources

Studies from the last Cochrane systematic reviews were compared with the search results from the databases, and if not identical a decision was made whether to include them. Practically, this meant that studies including exercise capacities were included from the Rees et al. study, while those with mortality and readmission were retrieved from Davies et al.(8, 10).

3.4.4 Data collection and analysis

Study selection

Certain studies were not selected because it was not possible to access them through the University of York's subscriptions to databases. They included studies with a follow-up less than six months, without reporting 95% CI of the mean LVEF or mean LVEF and standard deviations (SD) in the case mix of HF and non-HF patients. The lack of a specific comparison between exercise training and usual care also prompted exclusion. There were no constraints on the published language, but papers published in Chinese, Polish, Russian or Italian were inaccessible. This persisted after attempting to make contact with the respective authors of the non-English papers by email.

Data extraction

Only full articles were retrieved for data extraction, which meant that conference abstracts were excluded. Independent of endpoint types and outcomes, comparisons were made between controls and patients attending the intervention. Continuous outcome data were recorded as means, standard errors (SE) and SDs and finally calculated to WMD and associated 95% CI. To assess the relative risk (RR) ratio of discrete outcome data, the numbers of deaths, survivors and sample sizes for controls and patients attending the interventions were recorded. Covariates used to describe baseline characteristics were collected, namely type and year of CR (comprehensive or not), recruitment site, mean age, gender, follow-up time in months, LVEF, NYHA class, proportion of IHD, frequency of weekly exercise (>2 times a week or not), length of the exercise programme in months and pharmacological treatment covering ACE-Is, beta-blockers, digoxin, anti-platelets, statins and diuretics. The exercise capacities mentioned as secondary outcomes were also assessed. Covariates from the baseline were the same variables used in the meta-regression, irrespective

of heterogeneity being present or not. Endnote, version X5, was used to assemble the chosen articles.

Risk of bias

Types of reporting biases were illustrated by the following definitions taken from the Cochrane handbook for systematic reviews of interventions: adequate sequence generation, allocation concealment, blinding of subjective outcomes, blinding of mortality, incomplete outcome data addressed (long-term, > 6 months), free of selective reporting and free of other biases; see Appendix 4.2(209). Briefly, the meaning of adequate sequence generation is the quality of the randomisation of the trial. Allocation concealment refers to double blinding of patient allocation to the trial arms, which means that both patients and trial investigators at the recruitment time are unaware of which treatment the patient will receive. The 'blinding' of patient outcomes means that the researchers have no knowledge about the treatment allocation at the time of data collection. Ways of dealing with incomplete data were also investigated; for instance, the intention to treat is a well-recognised tool in this respect. This is based on the inclusion of all patients initially randomised in the final analysis, irrespective of their study participation. This method demands that the patient's endpoint at the end of the trial is known, which can be difficult in some cases. The examination of selective reporting is an approach used to link the endpoints stated in the methods with actual results reported in the results section. Finally, other biases could be, for instance, imbalances in baseline values.

Statistics

Baseline variables were the CR programme, epidemiologic data, follow-up time, clinical measurements such as LVEF, prescribed medication and history of IHD. Continuous and discrete variables were calculated as means or proportions, respectively, and they were weighted by the sample size of each study. A range of the minimum and maximum values of the above covariates was reported in the summary of baseline statistics. RR was calculated as an effect measure for binary outcomes, where the WMD was performed for continuous outcomes of exercise capacities in the meta-analysis. Irrespective of outcome type, sample size weights were applied in the forest plots. Heterogeneity was assessed by the heterogeneity index (I^2), which reflects the proportion of the variance leading to real differences in the effect size(210). The index is based on the heterogeneity statistic with degrees of freedom (DF), and it is calculated by the ratio of true heterogeneity to total variance across the observed effect estimates. Galbraith plots, which are scatter plots for each z-statistic against the reciprocal value of the standard error, and also identify trials outside the pooled 95% CI estimate(211), were also depicted in order to assess heterogeneity. Galbraith plots can also be regarded as an

alternative to forest plots. The fixed effect model was used for analysis without significant heterogeneity, where both fixed and random effects models were used when the heterogeneity of the endpoint was confirmed. The random effects model was performed in line with DerSimonian et al.(212).

Meta-regressions are similar to multiple regressions in that they assess the linear relationship between covariates (independent variables) and a dependent variable. The only difference is that meta-regression apply covariates at the study level rather than at the subject level, and the dependent variable is the effect size rather than an individual score(213). The meta-regressions were performed in order to explore heterogeneity through univariable analysis. Funnel plots illustrated possible publication biases in the case of dissymmetry in the plot of effect size against sample size. Sensitivity analyses are reported to compare studies with/without 100% HF patients. The standard deviation was computed from the interquartile range (IQR) when not reported by a normal approximation. STATA version 11.2 was used for all calculations.

3.5 Results

Of the 14,875 studies (Appendix 4.3) which were identified through the pre-specified database search, 2,238 records were removed due to duplication. After screening the remaining 12,637 abstracts, 163 full-text articles were selected as eligible. Finally, 16 studies were incorporated in the meta-analysis for the PVO_2, 11 studies for exercise time, 12 studies for 6-MWT, 11 studies for exercise power, 10 for hospital admission and 18 studies for mortality (Table 4.1).

3.5.1 Mortality

Baseline

Of the 21 studies reporting on mortality, 18 were included in the meta-analysis. Two of these had no deaths at all during their follow-ups and were therefore excluded; see Figure 4.1 (214, 215). Comprehensive CR was part of the intervention offered in 14% of the trials retrieved from the databases. The mean time length of exercise intervention was 21.4 months, and 88% of the patients in the intervention group planned to exercise more than two times a week. The follow-up time for a trial was on average 29.7 months and varied between six and 72 months.

The average trial size enrolled 1,458 patients with a mean age of 61.2 (range, 54.0 to 80.5) years. They had a mean LVEF of 25.9% (range, 23.5 to 41.0), and a proportion of 57% (range, 0.16 to 0.85) confirmed diagnosed CAD. The combination of resistance and aerobic training was seen in 84% of interventions compared to aerobic training alone in the remaining studies (16%).

ACE-Is (88%) and diuretics (84%) were the most frequently prescribed medications among the studies. The remaining investigated drugs, encompassing beta-blockers, digoxin, anti-platelets and statins, were prescribed for about half of the patients in each study. Doses of background drugs were in general not available and were therefore reported as dichotomous variables.

Table 3.1. Baseline characteristics. Studies including mortality

Variables	**Mortality,** **Mean** **(Range) (No. of studies)** **N= 18**
Epidemiology	
Age (mean), years	61.2 (54.0-80.5) (17)
Women, proportion	0.24 (0- 0.45) (9)
IHD, proportion	0.57 (0.16- 0.85) (14)
Study characteristics	
Sample size (mean), participants	1458 (21-2331) (18)
Recruitment in-hospital, proportion	0.04 (0-1) (17)
Comprehensive, proportion	0.14 (0-1) (18)
Follow-up time (mean), months	29.7 (6-72) (18)
Exercise duration (mean), months	21.4 (1-30) (18)
≥3 times/week, proportion	0.88 (0-1) (18)
Combined aerobic and strength training, proportion	0.84 (0-1) (17)
Adherence, proportion	0.66 (0.44-0.94) (13)
Clinical tests	
Baseline exercise capacity (mean), NA	NA
NYHA- Class II-III, proportion	0.98 (0.82-1) (12)
LVEF (mean),%	25.9 (23.5-41.0) (14)
Medications	
ACE-I, proportion	0.92 (0.64-1) (11)
Beta-blockers, proportion	0.80 (0.12-0.95) (10)
Digoxin, proportion	0.47 (0.21-0.68) (10)
Anti-platelets, proportion	0.46 (0.40-0.55) (2)
Statins, proportion	0.47 (0.34-0.54) (4)
Diuretics, proportion	0.80 (0.50-0.94) (10)

IHD, Ischemic heart disease; LVEF, Left ventricular ejection fraction; NYHA: New York Heart association Functional Classification; () shows the number of studies used in the calculations; NA, Non-applicable; ACE-I, Angiotensin-converting enzyme, but also included were angiotensin-type 2 receptor blockers.

Effect of the intervention

The influence of exercise training on all-cause mortality was non-significant; see Figure 4.1. The RR ratio of exercise training showed a limited beneficial effect on survival, with an overall value of 0.89 (95% CI, 0.79 to 1.03; P= 0.13, see Table 4.2). Heterogeneity was low, with a percentage of chi-squared statistics not explained by variations within the studies (I^2) equal to 0.0 (P= 0.79).

Table 3.2. Outcomes of mortality and hospital admission

Primary objectives of mortality and hospital admission*		
Outcomes	≤ 12 months	unadjusted
Mortality- RR ratio	0.95 (0.63- 1.42)	0.89 (0.78- 1.03)
Hospital admission- RR ratio	0.69 (0.53- 0.91)§	0.73 (0.58- 0.91)§

RR, relative risk.

¶ P ≤ 0.05

§ P ≤ 0.01

*** P < 0.001**

Heterogeneity

The LVEF did not seem to correlate with mortality, which may be explained by the lack of heterogeneity, but the LVEF had a skewed distribution, as only two of the included studies included HF-PEF patients. Another diagnostic factor for HF, NT-proBNP was similarly measured in two studies.

A Galbraith plot was designed to localise any trials that might causing heterogeneity; see Figure 4.2. The trial by Belardinelli et al. was located at the lower limit of the 95% CI, suggesting that it did indeed cause heterogeneity.

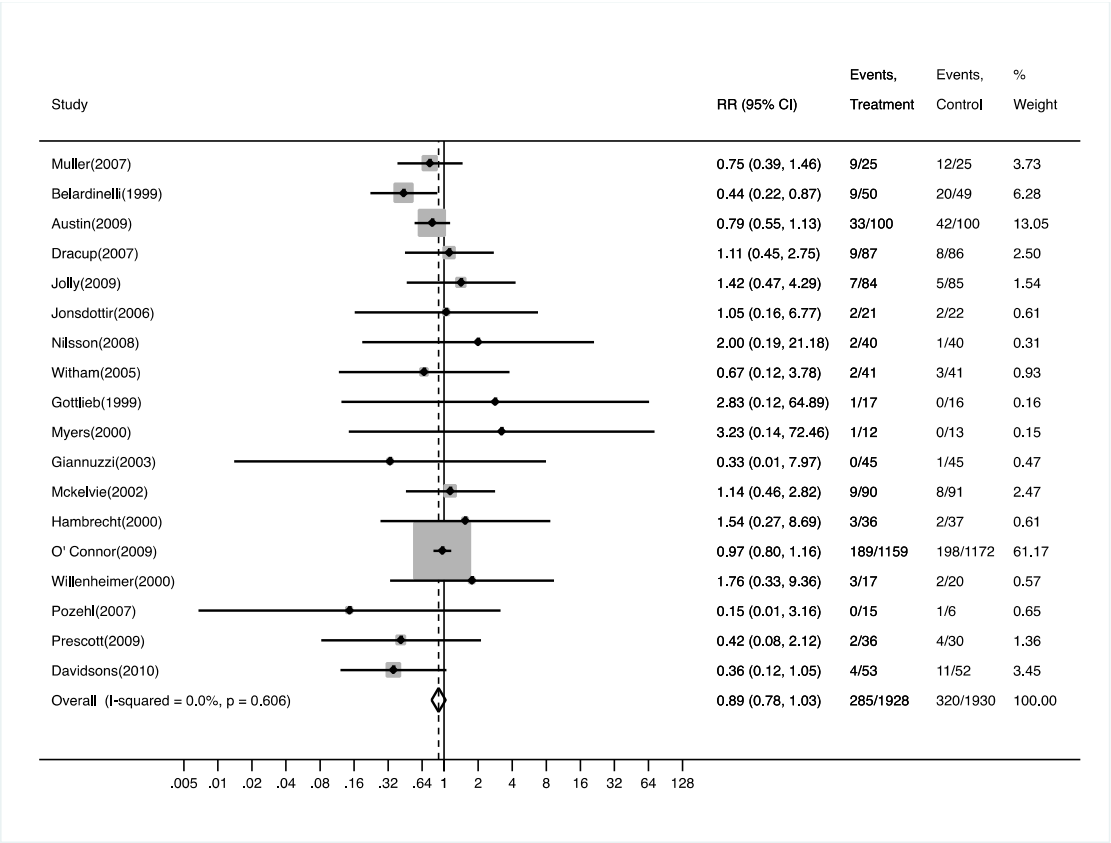


Figure 3.1. Forest plot. The exercise effect on mortality**;** The sizes of the squares (grey) are proportional to the weight of each study's sample size; The diamond shows the overall 95% CI (Confidence interval); RR: Relative risk reduction; % Weight; Weight calculated from the percentage of the study compared to the population of the pooled study population.

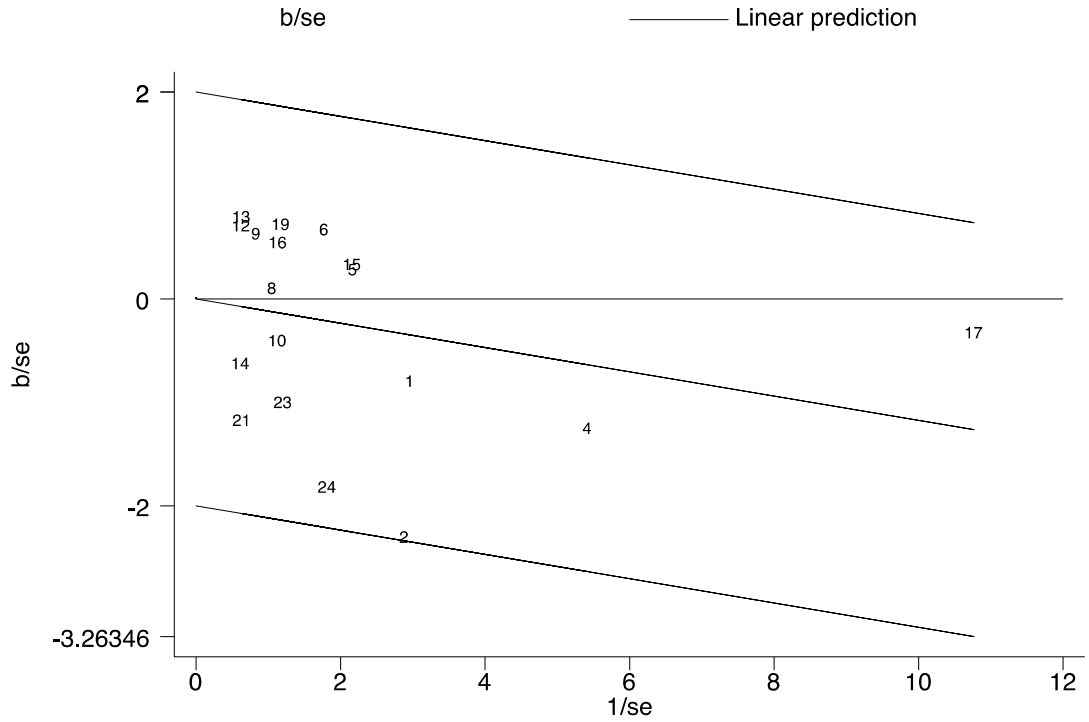


Figure 3.2. Galbraith plot. Illustrates the ratio of the natural logarithm of the RR divided by its standard error (z-statistics) versus the reciprocal of the standard errors (x-axis).

Bias

A funnel plot suggested that there were no publication biases among the selected studies, as their distributions showed almost identical stratification to positive and negative exercise effects, respectively (Figure 4.3). A sensitivity analysis was undertaken, including studies with a case mix of HF and CAD patients, which modified the outcome slightly (RR, 0.88; 95% CI, 0.77 to 1.01; P= 0.07) (Appendix 4.4). Heterogeneity according this model was consistently 0.0%.

The quality of reporting biases in the trials was in general poor; see Appendix 4.2 Only the trials by O'Connor et al. and Witham et al. reported extensively on matters of sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome data and selective outcome reporting.

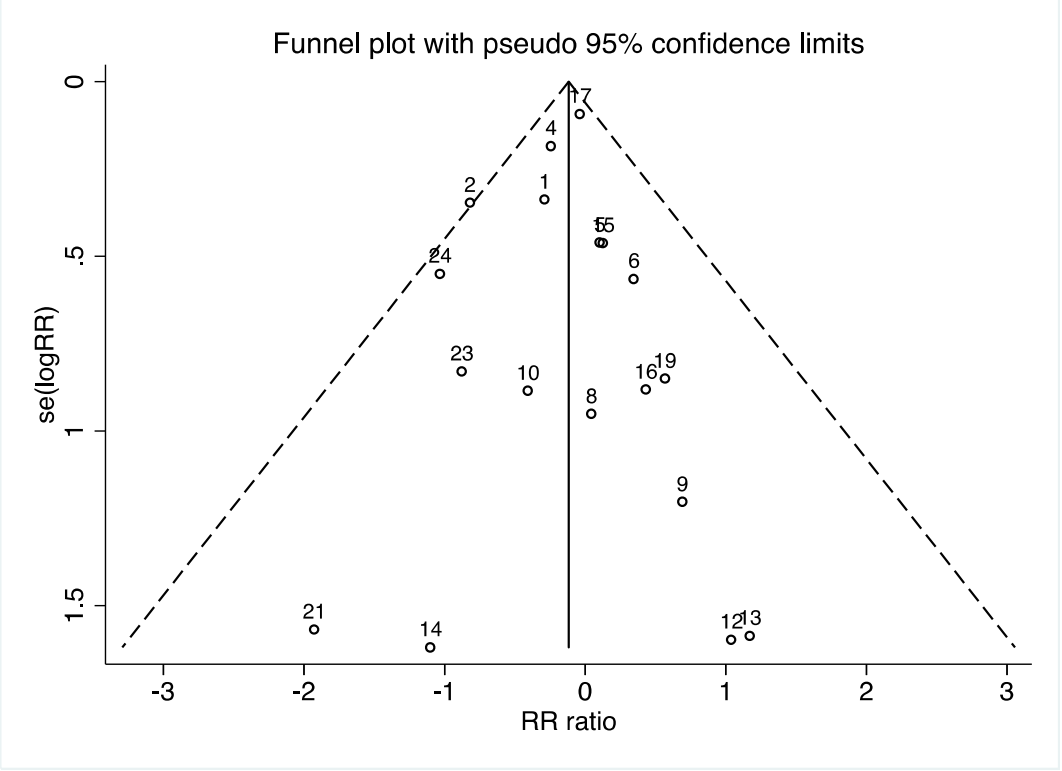


Figure 3.3. Funnel plot. The standard error of the natural logarithm of the RR ratio depicted versus the RR ratio in studies measuring mortality.

3.5.2 Hospital Readmissions

Baseline

Five studies out of the 16 in total were excluded due to the mix cases of both HF and non-HF in their patient samples or the reporting of hospital readmissions as numeric values. Repeated recordings of hospital admissions meant that the same patient was admitted more than once(216-218). As such, only the first admission for each patient was included in the meta-analysis. Comprehensive programmes were seen in 36% of the selected trials (Table 4.3). The time length of the exercise programmes was on average 7.9 months (range, 2 to 12), and out of these 94% had a minimum of three exercises scheduled weekly. The exercise interventions were followed up over 35.9 months (range, 6 to 48) on average, calculated from the randomisation start.

The sample size had a mean of 1,616 patients (range, 25 to 2330). The age of each patient was typically 60.4 years (range, 53.9 to 71.8). In all, 75% of the patients had had a diagnosis of IHD in the past, and the overall mean LVEF was 26.8% (range, 24.8 to 43.0). The prescription of medication was similar to the analysis of mortality, with the most frequent prescriptions being ACE-Is (89%) and diuretics (78%). Statin prescriptions were less frequently represented by 40% compared to treatments with beta-blockers, anti-platelets and digoxin, which were observed in 85%, 55% and 45% of cases, respectively.

Table 3.3. Baseline characteristics. Studies including hospitalisation

Variables	**Mean (Range) (No. of studies) N= 11**
Epidemiology	
Age (mean), years	60.4 (53.9- 71.8) (11)
Women, proportion	0.36 (0-0.64) (6)
IHD, proportion	0.75 (0.44-1) (9)
Study characteristics	
Sample size (mean), participants	1616 (25-2330) (11)
Recruitment in hospital, proportion	0.07 (0-1) (11)
Comprehensive, proportion	0.36 (0-1) (11)
Follow-up time (mean), months	35.9 (6-48) (11)
Exercise duration (mean), months	7.9 (2-12) (10)
≥3 times/week, proportion	0.94 (0-1) (11)
Combined aerobic and strength training, proportion	0.64 (0-1) (9)
Adherence, proportion	0.67 (0.44-1) (8)
Clinical tests	
Baseline exercise capacity (mean), NA	NA
NYHA II-III, proportion	0.98 (0.82-1) (8)
LVEF (mean) %	26.8 (24.8-43.0) (8)
Medications	
ACE-I, proportion	0.89 (0.74-1) (6)
Beta-blockers, proportion	0.85 (0.21-0.95) (6)
Digoxin, proportion	0.45 (0.11-0.68) (5)
Anti-platelets, proportion	0.55 (0.40-0.75) (3)
Statins, proportion	0.40 (0.29-0.48) (4)
Diuretics, proportion	0.78 (0.31-0.98) (7)

IHD, Ischemic heart disease; LVEF, Left ventricular ejection fraction; NYHA: New York Heart association Functional Classification; () shows the number of studies used in the calculations; NA, Non-applicable; ACE-I, Angiotensin-converting enzyme, but also included were angiotensin-type 2 receptor blockers.

Effect of the intervention

There was a significant reduction in admissions as a result of the exercise intervention effect (P= 0.006); see Figure 4.4. The RR ratio between patients attending exercise and physical inactive controls was 0.73 (95% CI, 0.58 to 0.91; P=0.006), while heterogeneity was moderate (I^2= 48.8%), thus justifying the use of the random effect model.

The effect of exercise moved remarkably lower when the fixed effect model was used, in spite of moderate heterogeneity (RR, 0.90; 95% CI, 0.83 to 0.97; P= 0.005).

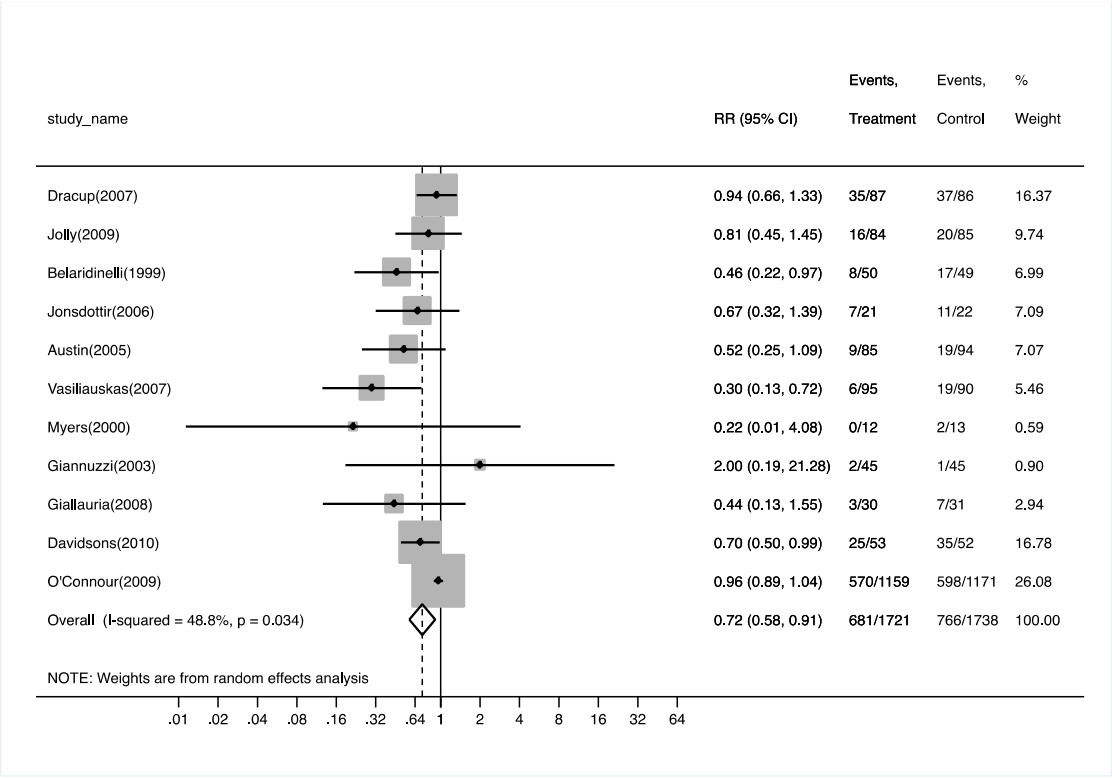


Figure 3.4. Forest plot. The exercise effect on hospital admission (random effect model); The sizes of the squares (grey) are proportional to the weight of each study's sample size; The diamond shows the overall 95% CI (Confidence interval); 95% CI: 95% Confidence interval; RR: Relative risk reduction; % Weight; Weight calculated from the percentage of the study compared to the population of the pooled study population.

Heterogeneity

A Galbraith plot was undertaken to reveal studies creating heterogeneity; see Figure 4.5. Only the study by Vasiliauskas et al. lay outside the limits of the 95% CI, which demonstrated the overall low heterogeneity. Planned hospitalisations were identified in four of the trials, but they did not change the direction of the outcome when only these were taken into account (RR, 0.78; 95% CI, 0.63 to 0.97; P<0.001). Only two studies, by Jonsdottir et al. and Gialluria et al., measured NT-proBNP. The former also included HF-PEF patients. The application of cycling in the exercise programmes was common, but the distinction between walking and cycling, or a combination thereof, was not feasible. Hence, this categorisation was not incorporated into a meta-regressions model. Due to the moderate amount of heterogeneity in the analysis, meta-regressions were applied to investigate any associations between the outcome and the baseline variables (Table 4.5). The meta-regressions found both LVEF and IHD to be significantly negatively associated with hospital admission, which meant that increasing values for both reduced hospitalisations. Conversely, the aerobic and strength exercise mode and follow-up time both increased hospital admission significantly.

Table 3.4. Univariable meta-regressions. Statistical associations between baseline variables and the event of hospitalisation.

Variables	**Hospital admission, exponential coefficient Exponential coefficients (95% CI)**
Age (mean), years	1.00 (0.96- 1.04)
Women, proportion	0.17 (0.014-2.04)
IHD, proportion	0.16 (0.05-0.48)*
Sample size (mean), participants	1.00 (1.00-1.00)
Recruitment in-hospital, proportion	0.85 (0.46-1.57)
Comprehensive, proportion	0.91 (0.51-1.62)
Follow-up time (mean), months	11.5 (4.4- 18.6)*
Exercise duration (mean), months	1.03 (0.96-1.11)
≥3 times/week, proportion	1.28 (0.61-2.69)
Combined aerobic and strength training, proportion	2.12 (1.06-4.20)*
Adherence, proportion	-0.93 (-2.42-0.57)
Baseline exercise capacity (mean), NA	NA
NYHA II-III, proportion	1.59 (0.002-1040)
LVEF (mean) %	0.95 (0.92-0.99)*
ACE-I, proportion	0.11 (<0.001- 141.2)
Beta-blockers, proportion	2.14 (0.42-10.9)
Digoxin, proportion	6.29 (0.16- 249.3)
Anti-platelets, proportion	0.032 (<0.001- >1000)
Statins, proportion	54.9 (<0.001- >1000)
Diuretics, proportion	4.02 (0.43-37.9)

¶ P ≤ 0.05; § P ≤ 0.01; * P ≤ 0.001; 95% CI: 95% Confidence interval;
IHD, Ischemic heart disease; LVEF, Left ventricular ejection fraction; NYHA: New York Heart association Functional Classification; () shows the number of studies used in the calculations; NA, Non-applicable; ACE-I, Angiotensin-converting enzyme, but also included were angiotensin-type 2 receptor blockers.

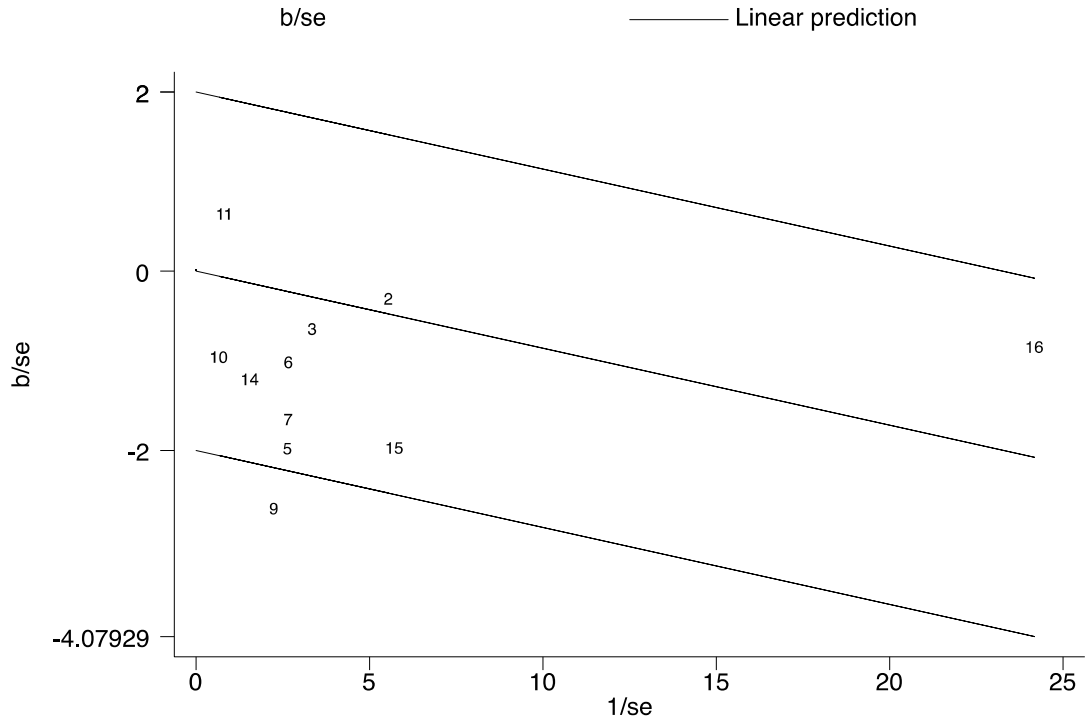


Figure 3.5. Galbraith plot. The ratio of the RR log of the first hospitalisation divided by its standard error versus the reciprocal of the standard errors.

Bias

Publication bias was investigated through a funnel plot; see Figure 4.6. There was no symmetry between studies in each direction of the mean RR ratio of exercise training versus usual treatment. Rather, there was a trend to publish studies with a negative RR log, implicitly showing exercise interventions to reduce hospital interventions.

A sensitivity analysis was undertaken to estimate differences in exercise training in trials recruiting heterogeneous groups of non-HF and HF patients, but all having CAD (Appendix 4.3). The overall effect was unchanged by including these studies (RR, 0.71; 95% CI, 0.59 to 0.87; P=0.001). Heterogeneity of the average effect was slightly greater in the sensitivity analysis (I^2= 57.7%; P= 0.004). The studies included in the meta-analysis all reported biases poorly, thus casting doubt on the internal validity of the trials (Appendix 4.2).

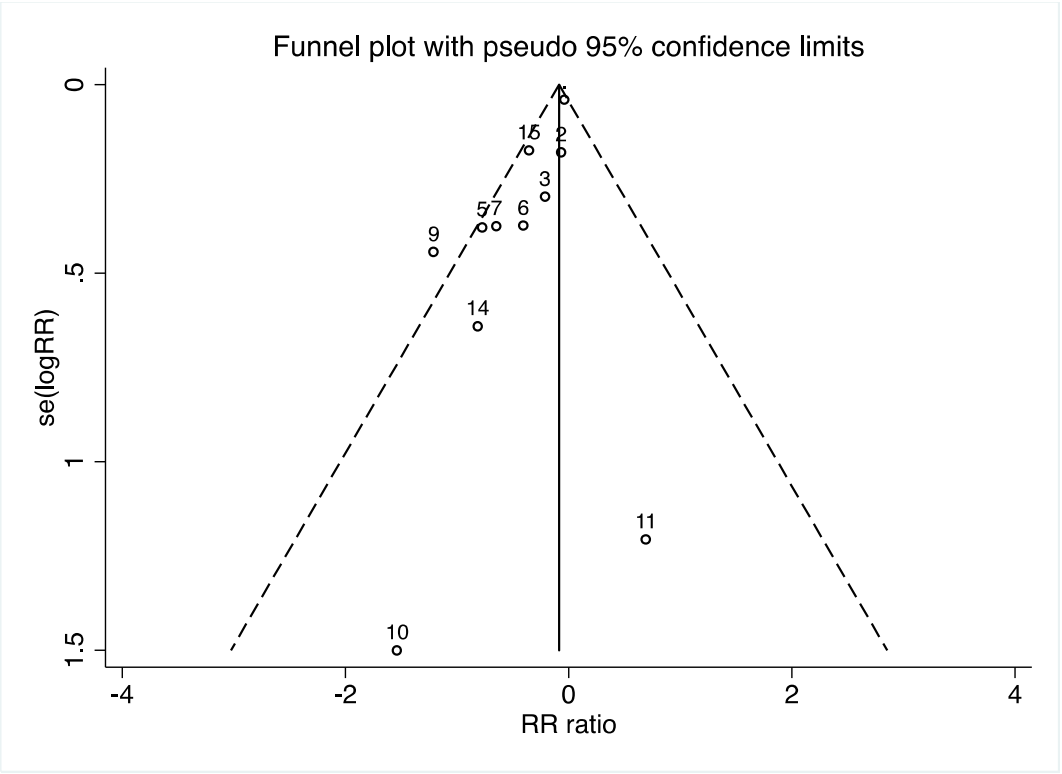


Figure 3.6. Funnel plot. Publications of hospital admissions for HF patients, depicting the standard error of the RR ratio (log) versus the RR ratio.

3.5.3 Six-Minute Walk Test (6-MWT)

Baseline

Of the search results take from five different databases, 12 studies investigating the exercise training effect in HF patients measured through the 6-MWT were extracted. The HF-Action study was excluded from the preliminary analysis, as the standard deviations and means of the participants had to be extrapolated from medians and interquartile ranges, which required making the assumption the the underlying distribution was normally deviated.

The characteristics of the studies were as follows. The studies had a mean sample size of 150 patients, ranging from 33 to 200 (Table 5.1), who had a mean age of 65.1 (range, 53.9 to 80.5), and 33% were women. Comprehensiveness in the CR programmes was seen in 41% of the trials, the mean exercise duration was 8.2 months (range, 3 to 14) and the average follow-up time was 10.6 months (range, 6 to 18). Seventy per cent of the trials had a minimum of exercise three times a week in the intervention group.

The pooled patient population had a mean LVEF of 31.3% (range, 23.5 to 43.0) and 72% (range, 0.41 to 1.00) of these had IHD. The mean 6-min-walk distance at baseline was 368 metres, varying from 213 to 484 metres. It should be mentioned that two studies from the US most likely experienced distance conversion mistakes in their 6-min-walks, as they claimed distances of 1250 m to 1500 m were achieved during six minutes(219, 220). After comparison with another study from the US, the distances were decided to be in feet and were converted by a factor of 0.3048 m/feet.(221) Patient-prescribed medication was not reported well for most HF-medications. ACE-Is (90%) and diuretics (79%) were the most prescribed drugs, and although reported diligently, BBs were only prescribed to 54% of the cohort.

Table 3.5. Baseline characteristics. Studies including the 6-MWT

Variables	**6-MWT, Mean (Range) (No. of studies) N= 12**
Epidemiology	
Age (mean), years	65.1 (53.9-80.5) (11)
Women, proportion	0.33 (0.19-0.57) (9)
IHD, proportion	0.72 (0.41-1) (10)
Study characteristics	
Sample size (mean), participants	150 (33-200) (11)
Recruitment in-hospital, proportion	0.12 (0-1) (10)
Comprehensive, proportion	0.41 (0-1) (11)
Follow-up time (mean), months	10.6 (6-18) (11)
Exercise duration (mean), months	8.2 (3-14) (11)
≥3 times/week, proportion	0.70 (0-1) (11)
Combined aerobic and strength training, proportion	0.84 (0-1) (11)
Adherence, proportion	0.75 (0.44-0.94) (11)
Clinical tests	
Baseline exercise capacity (mean), 6-MWT	368 (213-484) (11)
NYHA II-III, proportion	0.97 (0.90-1) (9)
LVEF (mean) %	31.3 (23.5-43.0) (11)
Medications	
ACE-I, proportion	0.90 (0.74-0.98) (10)
Beta-blockers, proportion	0.54 (0.20-0.93) (10)
Digoxin, proportion	0.43 (0.11-0.68) (7)
Anti-platelets, proportion	0.57 (0.40-0.75) (3)
Statins, proportion	0.45 (0.29-0.79) (4)
Diuretics, proportion	0.79 (0.31-0.94) (9)

6-MWT: six-minute walk test; IHD, Ischemic heart disease; LVEF, Left ventricular ejection fraction; NYHA: New York Heart association Functional Classification; () shows the number of studies used in the calculations; NA, Non-applicable; ACE-I, Angiotensin-converting enzyme, but also included were angiotensin-type 2 receptor blockers.

Effect of the intervention

The fixed effect model revealed high heterogeneity from the heterogeneity index (I^2 = 97.1%). A random effect model, in line with DerSimonian and Laird, was then constructed (Figure 5.1).(212) A significant effect of exercise training was found when the comparison between the intervention and control group was undertaken. The weighted mean difference (WMD) was 41.58 m (95% confidence interval CI, 5.00 to 78.17; P=0.03) in the random effect model, which differed from the 90.21 m (95% CI, 84.02 to 96.40, P<0.001) found in the fixed effect model.

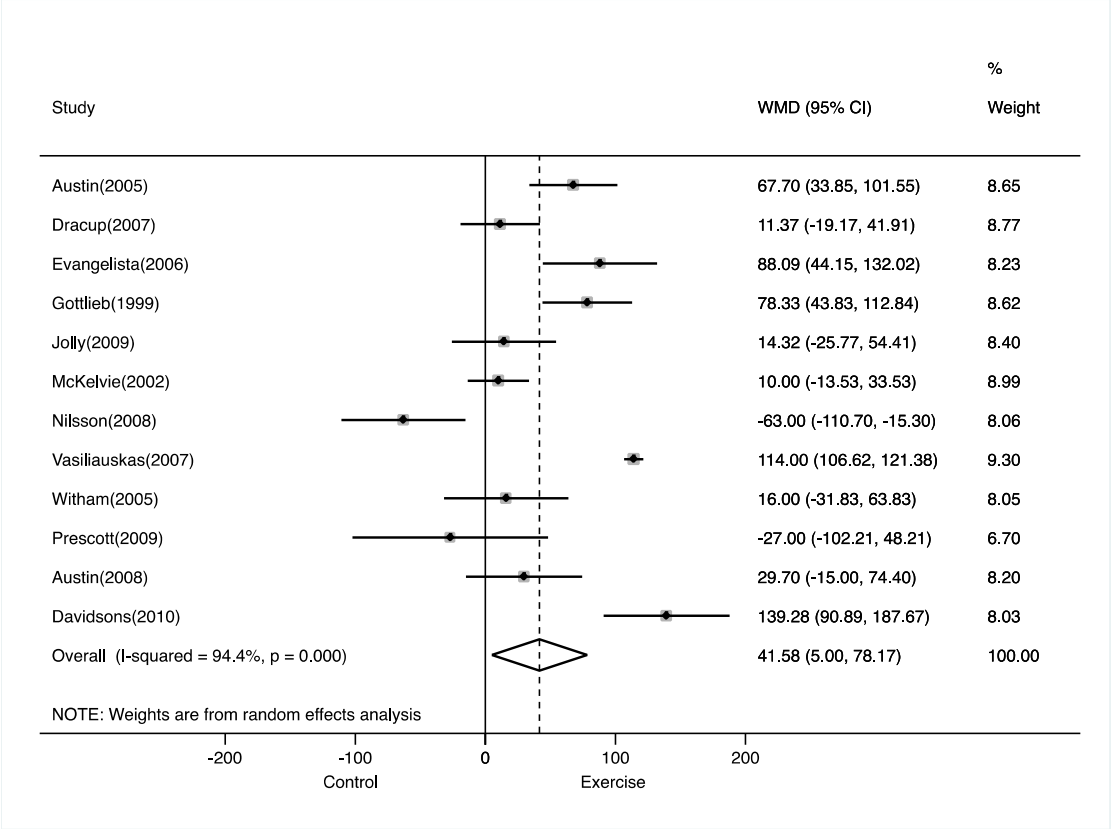


Figure 3.7. Forest plot. The exercise effect on the 6-MWT**;** The sizes of the squares (grey) are proportional to the weight of each study's sample size; The diamond shows the overall 95% CI (Confidence interval); WMD: Weighted mean difference; % Weight; Weight calculated from the percentage of the study compared to the population of the pooled study population.

Table 3.6. Univariable meta-regressions of baseline characteristics and the 6-MWT

Variables	6- MWT, coefficient (95% CI)
Age (mean), years	-1.2 (-6.8- 4.4)
Women, proportion	236.9 (-116.4- 590.3)
IHD, proportion	3.9 (-211.9- 220.0)
Sample size (mean), participants	126.2 (85.5- 166.9)*
Recruitment in-hospital, proportion	104.6 (-28.7-237.9)
Comprehensive, proportion	0.09 (-7.0- 7.2)
Follow-up time (mean), months	11.5 (4.4- 18.6)§
Exercise duration (mean), months	-7.9 (-17.2- 1.3)
≥3 times/week, proportion	62.7 (-6.7- 132.0)
Combined aerobic and strength training, proportion	NA
Adherence, proportion	97.8 (-80.3-275.9)
Baseline exercise capacity (mean), 6-MWT	-0.001 (-0.01- 0.01)
NYHA II-III, proportion	479.8 (-998.0-1958)
LVEF (mean) %	2.6 (-5.7- 10.8)
ACE-I, proportion	-1.06 (-12.44- 14.57)
Beta-blockers, proportion	-0.81 (-4.51- 2.68)
Digoxin, proportion	-2.23 (-7.23- 2.77)
Anti-platelets, proportion	7.76 (-13.3- 28.8)
Statins, proportion	-4.68 (-16.6- 7.26)
Diuretics, proportion	-3.53 (-8.52- 1.45)

¶ P ≤ 0.05; § P ≤ 0.01; * P ≤ 0.001; 95% CI: 95% Confidence interval;
IHD, Ischemic heart disease; LVEF, Left ventricular ejection fraction; NYHA: New York Heart association Functional Classification; () shows the number of studies used in the calculations; NA, Non-applicable; ACE-I, Angiotensin-converting enzyme, but also included were angiotensin-type 2 receptor blockers.

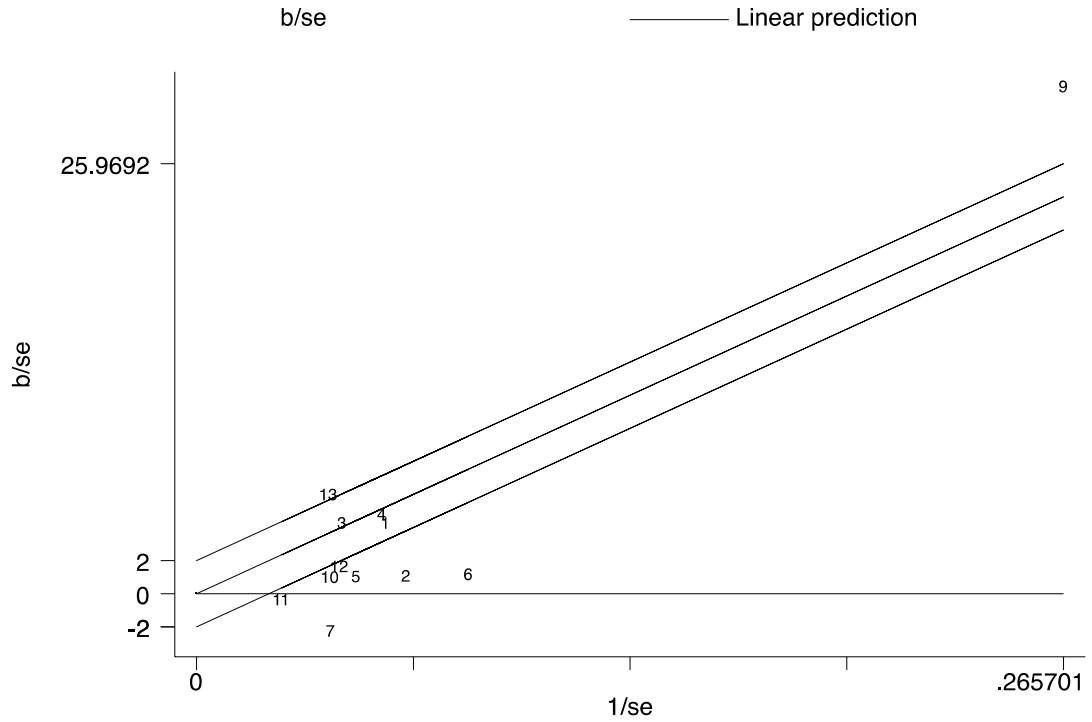


Figure 3.8. Galbraith plot. The WMD (Weighted mean difference) divided by its standard error versus the reciprocal of the standard error studies of the 6-MWT.

Heterogeneity

Meta-regression was undertaken to investigate baseline covariates, potentially explaining the high amount of heterogeneity (94.4%) (Table 5.2). For the 6-MWT follow-up measurements, meta-regression revealed positive univariate linear relations between the pooled outcome, sample size and the follow-up time (P= 0.01 & P< 0.001).

In order to assess studies with heterogeneity, a Galbraith plot was designed (Figure 5.2) which revealed that all studies except three were located more than 2.0 units outside of the true effect. The studies within the 95% CI were those by Davidsons et al., Evangelista et al. and Gottlieb et al.

A meta-funnel plot investigated possible publication bias (Figure 5.3).
More than half of the studies were situated outside the pseudo 95% CI limits, indicating dissymmetry between studies on each side of the pooled mean effect. A sensitivity analysis was undertaken, including the HF-action study (Appendix 4.3). This was possible because a normal approximation was calculated for the medians and interquartile ranges reported in

peer-reviewed papers. A random effect model showed a significant WMD of 37.39 (95% CI, -0.49 to 75.28; P= 0.05), while heterogeneity was unchanged and high (I^2= 97.7%).

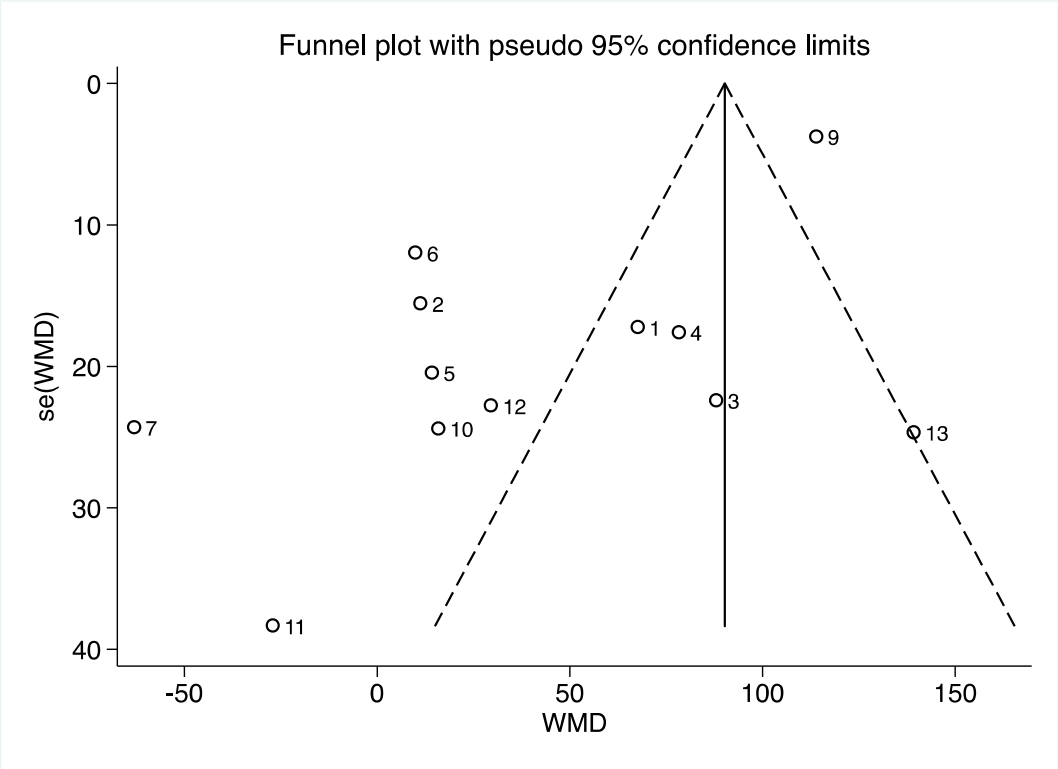


Figure 3.9. Funnel plot. Studies measuring the 6-MWT illustrating the standard error of the WMD (Weighted mean difference) versus the WMD.

3.5.4 Exercise time

Baseline

The data search provided 13 RCT studies. Of these, two were excluded due to their failure to report the necessary parameters incorporated in the meta-analysis(144, 222)
Comprehensiveness was seen in 20% of the exercise interventions, and the average length of the latter was 5.9 months with a mean follow-up time of 12.8 months (Table 5.3). Eighty-one per cent of the studies planned exercise training at a minimum of three times weekly.
The average number of patients in a trial was 95 with a mean age of 59.9 years (range, 51.5 to 70.2). Only 8% of the study participants were women. IHD was diagnosed in 70% (range, 16 to 100) of the pooled population, which had an LVEF of 32% (range, 22% to 43%). At the baseline, the average exercise time was presumed to be 8.8 minutes (range, 5.5 to 18.4) for any patient, either from the intervention or the control group. Medications were prescribed similarly to the other exercise outcomes, showing that 94% and 68% took ACE-Is and diuretics, respectively.

Table 3.7. Baseline characteristics. Studies including the exercise time test.

Variables	**Exercise time, Mean (Range) (No. of studies) N= 11**
Epidemiology	
Age (mean), years	59.9 (51.5-70.2) (11)
Women, proportion	0.08 (0.00-0.21) (7)
IHD, proportion	0.70 (0.16-1) (7)
Study characteristics	
Sample size (mean), patients	95 (24-185) (11)
Recruitment in-hospital, proportion	0.12 (0-1) (10)
Comprehensive, proportion	0.20 (0-1) (11)
Follow-up time (mean), months	12.8 (6-72) (11)
Exercise duration (mean), months	5.9 (1-14) (11)
≥3 times/week, proportion	0.81 (0-1) (11)
Combined aerobic and strength training, proportion	0.48 (0-1) (11)
Adherence, proportion	0.88 (0.55-1) (9)
Clinical tests	
Baseline exercise capacity (mean), Exercise time	8.8 (5.5-18.4) (11)
NYHA II-III, proportion	1 (1) (6)
LVEF (mean) %	32.0 (22.0-43.0) (10)
Medications	
ACE-I, proportion	0.94 (0.91-1) (10)
Beta-blockers, proportion	0.54 (0.07-0.93) (8)
Digoxin, proportion	0.41 (0.11-0.91) (9)
Anti-platelets, proportion	0.75 (0.75) (1)
Statins, proportion	0.37 (0.29-0.79) (3)
Diuretics, proportion	0.68 (0.30-1.00) (10)

IHD, Ischemic heart disease; LVEF, Left ventricular ejection fraction; NYHA: New York Heart association Functional Classification; () shows the number of studies used in the calculations; NA, Non-applicable; ACE-I, Angiotensin-converting enzyme, but also included were angiotensin-type 2 receptor blockers; * Only one trial reported on the the anti-platelet prescription (Vasiliaukas et al.).

Effect of the intervention

A moderate level of heterogeneity was found from an index including the chi-squared statistics (I^2= 82.6%), which is why a random effect model was chosen to compute the pooled effect of exercise interventions on exercise time (Figure 5.4). The exercise effect expressed by exercise time was 2.96 minutes (95% CI, 1.83 to 4.09; P<0.001), therefore favouring exercise intervention and which indicated a significant difference between the controls and patients undergoing the intervention.

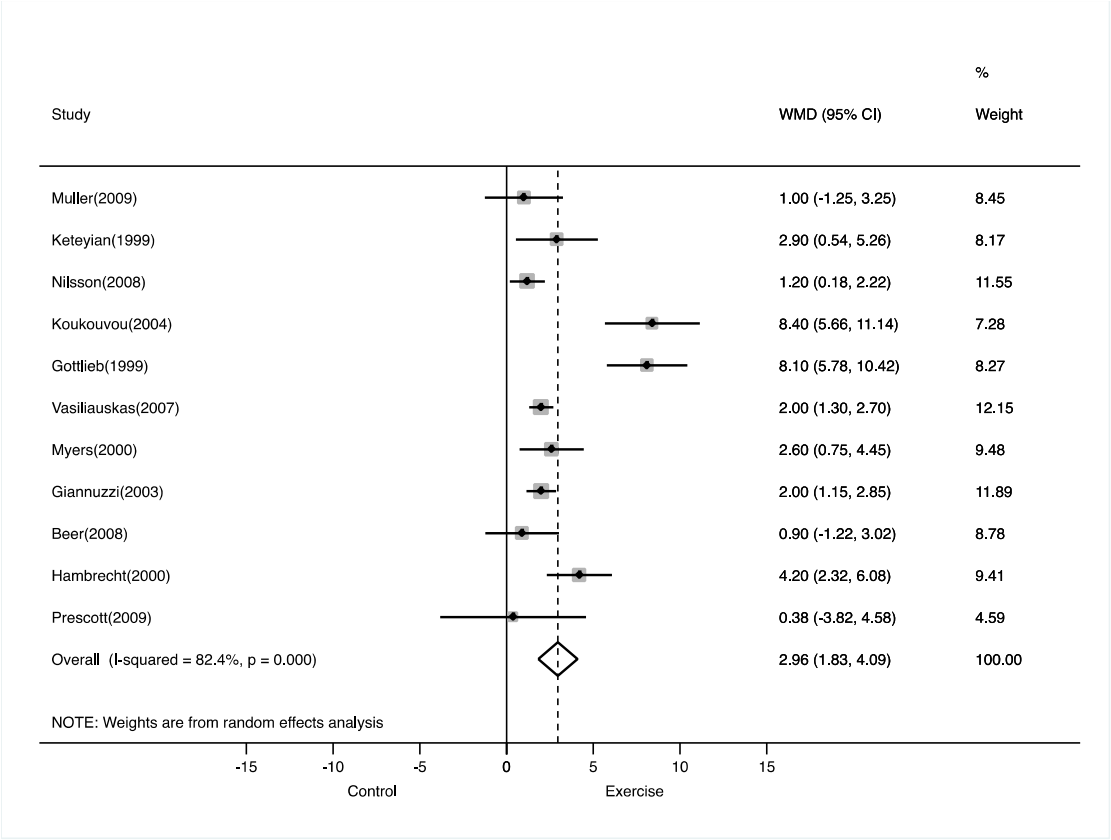


Figure 3.10. Forest plot. Illustrating exercise effect on exercise time. The size of the squares (grey) are proportional to the weight of each study's sample size; The diamond shows the overall 95% CI (Confidence interval); WMD: Weighted mean difference; % Weight; Weight calculated from the percentage of the study compared to the population of the pooled study population.

Regression of the pre-hoc designed covariates in a univariable model did not convincingly explain heterogeneity (Table 5.4). However, the high level of heterogeneity was partly explained by a positive relation between the baseline value of exercise time and its follow-up measurement by a value of 0.4, i.e. the higher baseline measurement of exercise time resulted in higher follow-up measurements.

The Galbraith plot indicated that two studies resided outside the 95% CI, which happened to be the studies of Koukoukou et al. and Gottlieb et al. (Figure 5.6)(221, 223). The two studies

basically confirm the forest plot from the much larger weighted mean difference between the intervention and the control group.

Table 3.8. Meta-regressions. Statistical associations between baseline characteristics and the exercise time test (minutes)

Variables	**Exercise time, coefficient (95% CI)**
Age (mean), years	-0.05 (-0.4- 0.3)
Women, proportion	-13.2 (-38.7- 12.2)
IHD, proportion	-0.08 (-11.6- 11.4)
Sample size (mean), participants	-0.01 (-0.05- 0.03)
Recruitment in-hospital, proportion	1.10 (-5.78-7.97)
Comprehensive, proportion	-2.0 (-6.0- 2.0)
Follow-up time (mean), months	-0.05 (-0.1- 0.05)
Exercise duration (mean), months	0.1 (-0.5- 0.8)
≥3 times/week, proportion	-2.5 (-2.2- 7.4)
Combined aerobic and strength training, proportion	0.4 (-3.5- 4.2)
Adherence, proportion	-7.82 (-13.4-(-2.2))§
Baseline exercise capacity (mean), Exercise time	0.4 (0.04-0.9)¶
NYHA II-III, proportion	NA
LVEF (mean) %	-0.1 (-0.4- 0.2)
ACE-I, proportion	23.9 (-27.4- 75.3)
Beta-blockers, proportion	-1.9 (-4.1- 0.3)
Digoxin, proportion	1.7 (-1.2- 4.6)
Anti-platelets, proportion	NA
Statins, proportion	-2.9 (-55.9- 50.1)
Diuretics, proportion	2.1 (-5.6- 9.8)

¶ P ≤ 0.05; § P ≤ 0.01; * P ≤ 0.001; 95% CI: 95% Confidence interval;
IHD, Ischemic heart disease; LVEF, Left ventricular ejection fraction; NYHA: New York Heart association Functional Classification; () shows the number of studies used in the calculations; NA, Non-applicable; ACE-I, Angiotensin-converting enzyme, but also included were angiotensin-type 2 receptor blockers.

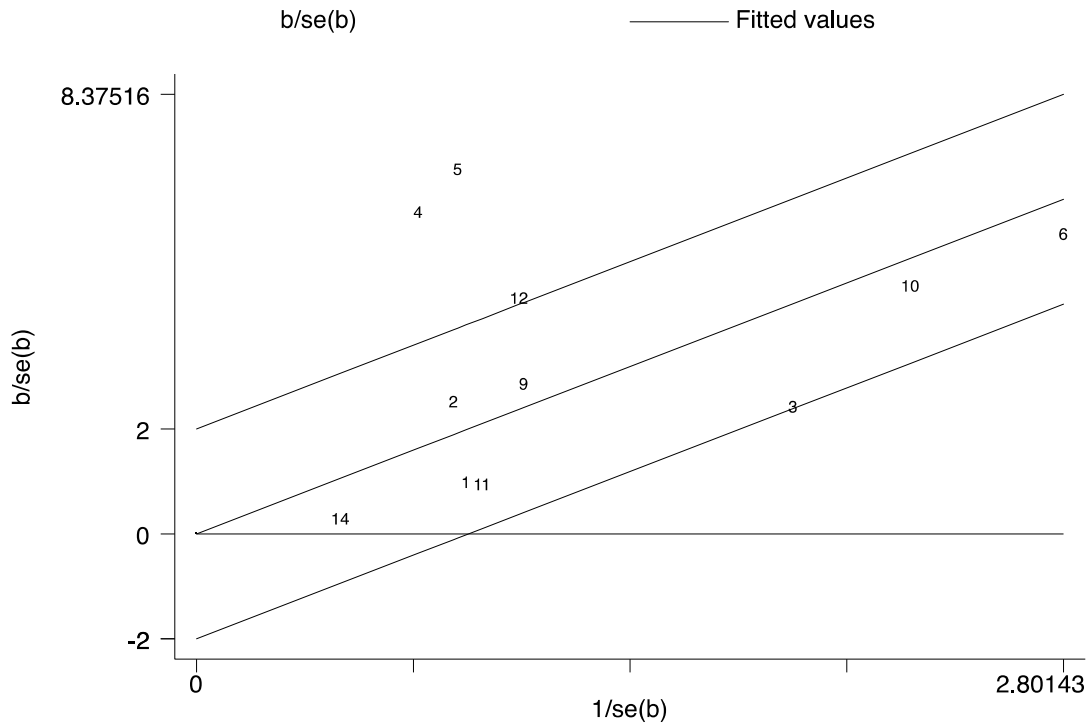


Figure 3.11. Galbraith plot. The WMD (Weighted mean difference) divided by its standard error versus the reciprocal of the standard error in studies of exercise time.

Heterogeneity

The funnel plot revealed symmetry in the studies on both sides of the overall mean (Figure 5.6). The outliers were the same two studies observed to lie outside the 95% CI in the Galbraith plot(221, 223). A sensitivity analysis was undertaken and included the HF-action trial showing a WMD equal to 2.72 (95% CI, 1.72 to 3.70; P<0.001). Overall heterogeneity was slightly decreased to 74.8% (P<0.001).

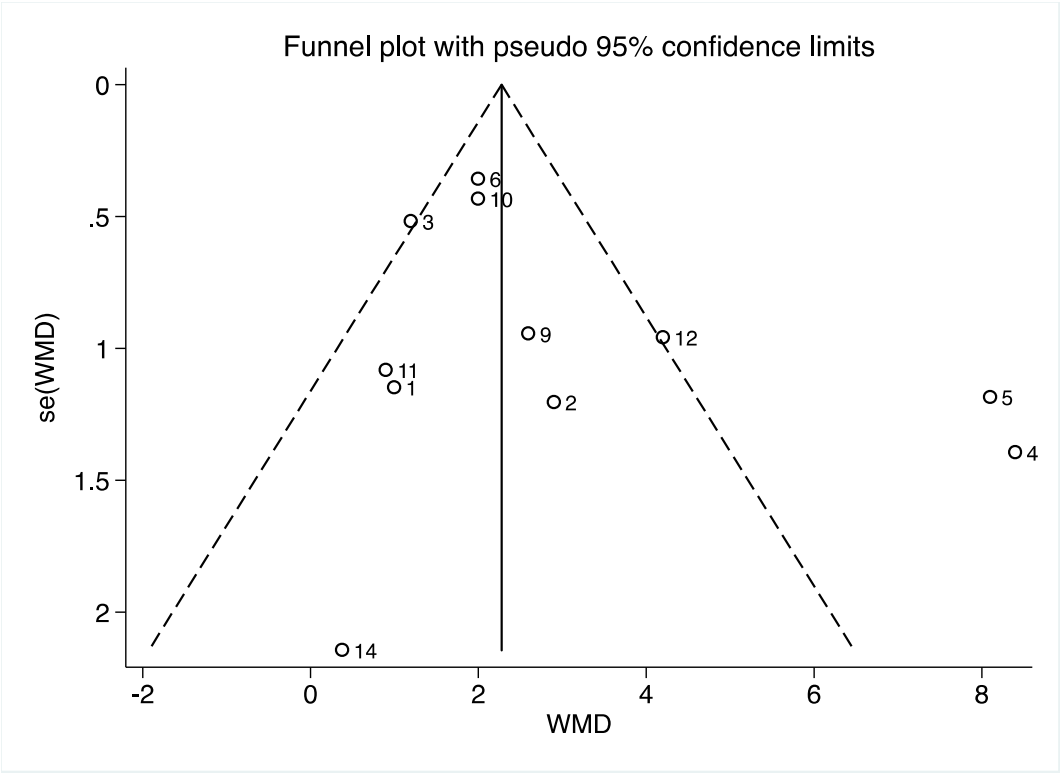


Figure 3.12. Funnel plot. The standard error of the WMD (weighted mean difference) versus the WMD in studies of exercise time.

3.5.5 PVO_2

Baseline

Of the 25 studies retrieved from the database search, 16 were eligible for inclusion in the preliminary analysis. The excluded studies were trials recruiting heterogeneous patient groups, with and without HF, and publications of the HF-action trial, which did not publish the data necessary for the meta-analysis(144, 224-229). Excluded data were, where possible, used for sensitivity analysis.

Ninety per cent of the studies were based on exercise training alone (Table 5.5). A minimum of three times/weekly of exercise training was seen in all the interventions, which had a mean duration of 7.4 months, ranging from one up to 12 months, with an average follow-up time of 11.6 months (range, 6 to 72).

There were on average 103.9 patients per trial and they were aged 57.1 years (range, 52.2 to 65.5) old. Overall, women accounted for 18% of the population. A former diagnosis of IHD was seen in 65% (range, 16 to 100) of the cases, and their mean LVEF was 30.8% (range, 22.0 to 44.2). The PVO_2 measured at the baseline was 18.1 ml/min/kg (range, 13.5 to 27.4).

Table 3.9. Baseline characteristics. Studies including the PVO_2 test.

Variables	**PVO_2, Mean (Range) (No. of studies) N= 16**
Epidemiology	
Age (mean), years	57.1 (52.5- 65.5) (14)
Women, proportion	0.18 (0-0.30) (10)
IHD, proportion	0.65 (0.16-1) (11)
Study characteristics	
Sample size (mean), patients	103.9 (24-185) (16)
Recruitment in-hospital, proportion	0.11 (0-1) (16)
Comprehensive, proportion	0.10 (0-1) (15)
Follow-up time (mean), months	11.6 (6-72) (16)
Exercise duration (mean), months	7.4 (1-12) (16)
≥3 times/week, proportion	1.00 (1) (16)
Combined aerobic and strength training, proportion	0.53 (0-1) (15)
Adherence, proportion	0.79 (0.11-1) (14)
Clinical tests	
Baseline exercise capacity (mean), PVO_2	18.1 (13.5-27.4) (16)
NYHA II-III, proportion	0.94 (0.82-1) (10)
LVEF (mean) %	30.8 (22-44.2) (14)
Medications	
ACE-I, proportion	0.88 (0.74- 1) (12)
Beta-blockers, proportion	0.54 (0.07- 0.75) (10)
Digoxin, proportion	0.50 (0.11- 0.91) (9)
Anti-platelets, proportion	0.58 (0.40- 0.75) (2)
Statins, proportion	0.37 (0.29- 0.48) (3)
Diuretics, proportion	0.73 (0.31- 1.00) (12)

IHD, Ischemic heart disease; LVEF, Left ventricular ejection fraction; NYHA: New York Heart association Functional Classification; () shows the number of studies used in the calculations; NA, Non-applicable; ACE-I, Angiotensin-converting enzyme, but also included were angiotensin-type 2 receptor blockers.

Effect of the intervention

A high degree of heterogeneity was observed from the chi-squared statistics (%) translated into the variation, but they were not explained within the studies (I^2=77.7, P< 0.001); see Figure 5.7. The WMD between the exercise and control disclosed a value of 3.47 ml/min/kg (95% CI, 2.56 to 4.39; P< 0.001), thus favouring exercise intervention in a random effect model. The value changed to 3.48 (95% CI, 3.10 to 3.86; P< 0.001) ml/min/kg when the fixed effect model was applied.

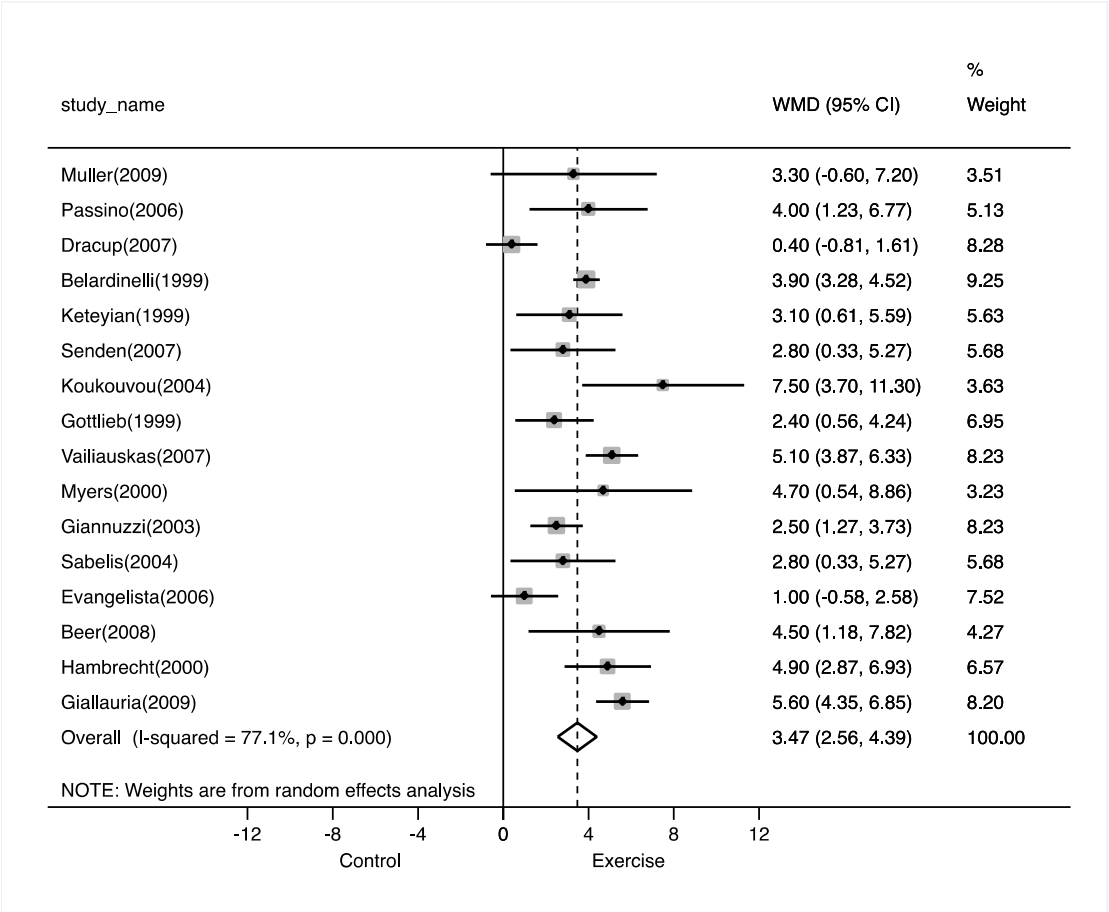


Figure 3.13. Forest plot. Exercise effect on the PVO_2 test. The sizes of the squares (grey) are proportional to the weight of each study's sample size; The diamond shows the overall 95% CI (Confidence interval); WMD: Weighted mean difference; % Weight; Weight calculated from the percentage of the study compared to the population of the pooled study population.

Meta-regression was employed to investigate the high level of heterogeneity (Table 5.6). According to a univariate model, PVO_2 had univariate positive relations with baseline PVO_2, IHD and ACE-Is ($P< 0.001$; $P= 0.03$; and $P= 0.05$), whilst it had negative univariate relations with female sex and statins ($P<0.001$ & $P= 0.001$).

Another attempt to explain heterogeneity was made via the Galbraith plot (Figure 5.8). Outliers were overall the studies by Dracup et al., Vasiliauskas et al., Evangelista et al. *and* Gialluria et al.

Table 3.10. Univariable meta-regressions. Statistical associations between baseline characteristics and the PVO_2 test.

Variables	**PVO_2, coefficient (95% CI)**
Age (mean), years	-0.04 (-0.31- 0.24)
Women (proportion)	-11.89 (-17.84- (-) 5.94)*
IHD (proportion)	4.03 (0.42- 7.65)¶
Sample size (mean)	-0.01 (-0.03- 0.01)
Comprehensive (proportion)	1.72 (-0.76- 4.20)
Follow-up time (mean), months	-0.01 (-0.08- 0.07)
Exercise duration (mean), months	-0.18 (-0.49- 0.13)
≥3 times/week (proportion)	NA
Combined aerobic and strength training (proportion)	-1.31 (-2.93- 0.31)
Adherence (proportion)	-0.22 (-4.99-4.56)
Baseline exercise capacity (mean), PVO_2	0.40 (0.24- 0.56)*
NYHA II-III, proportion	
LVEF (mean) %	0.16 (0.05- 0.26)§
ACE-I (proportion)	12.60 (-0.23- 25.43)¶
Beta-blockers (proportion)	-1.30 (-5.83- 3.24)
Digoxin (proportion)	-2.79 (-7.78- 2.19)
Anti-platelets (proportion)	NA
Statins (proportion)	-23.53 (-38.00- (-) 9.07)*
Diuretics (proportion)	-3.48 (-8.38- 1.43)

¶ P ≤ 0.05; § P ≤ 0.01; * P ≤ 0.001; 95% CI: 95% Confidence interval;
IHD, Ischemic heart disease; LVEF, Left ventricular ejection fraction; NYHA: New York Heart association Functional Classification; () shows the number of studies used in the calculations; NA, Non-applicable; ACE-I, Angiotensin-converting enzyme, but also included were angiotensin-type 2 receptor blockers.

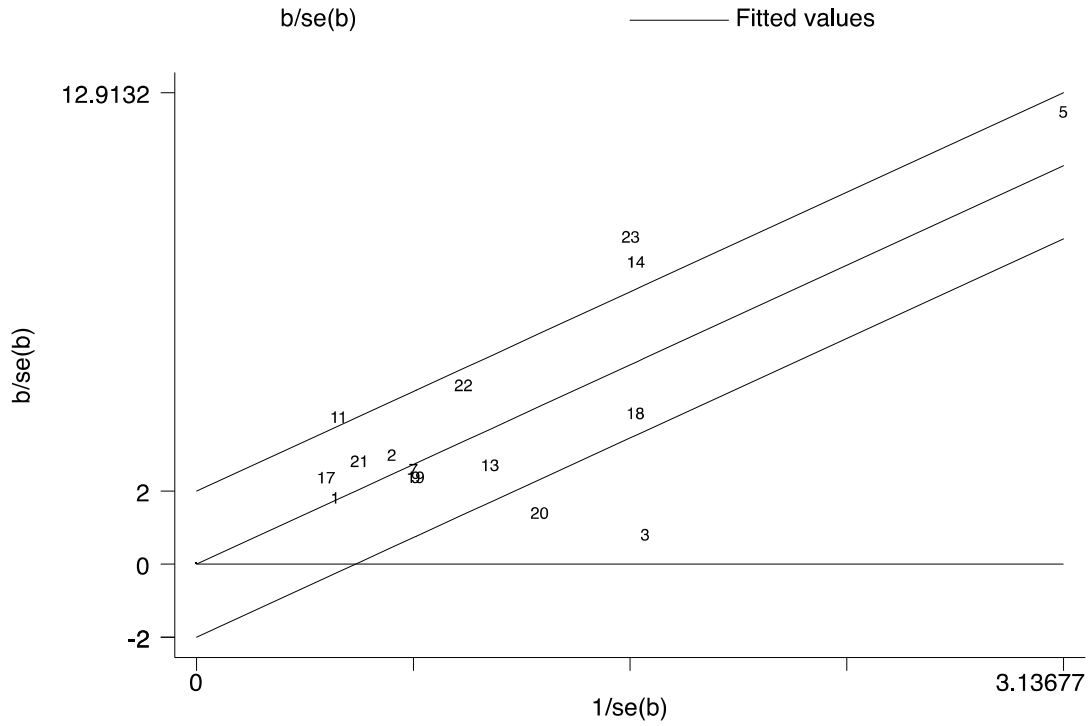


Figure 3.14. Galbraith plot. The WMD (Weighted mean difference) divided by its standard error versus the reciprocal of the standard error in studies of the PVO_2.

Heterogeneity

A funnel plot investigated publication bias (Figure 5.9). There were no immediate reasons to suspect publication bias, as the selected studies were symmetrical around the average WMD of 3.48 ml/min/kg (95% CI, 3.10 to 3.86, P< 0.001) (fixed effect model). Finally, a sensitivity calculation was processed including studies with a mix of HF, non-HF patients encompassing the HF-Action population. The WMD was 3.10 ml/min/kg (95% CI, 2.21 to 3.98, P< 0.001), which was computed from a random effect model due to the unchanged high heterogeneity of 84.6% (I^2).

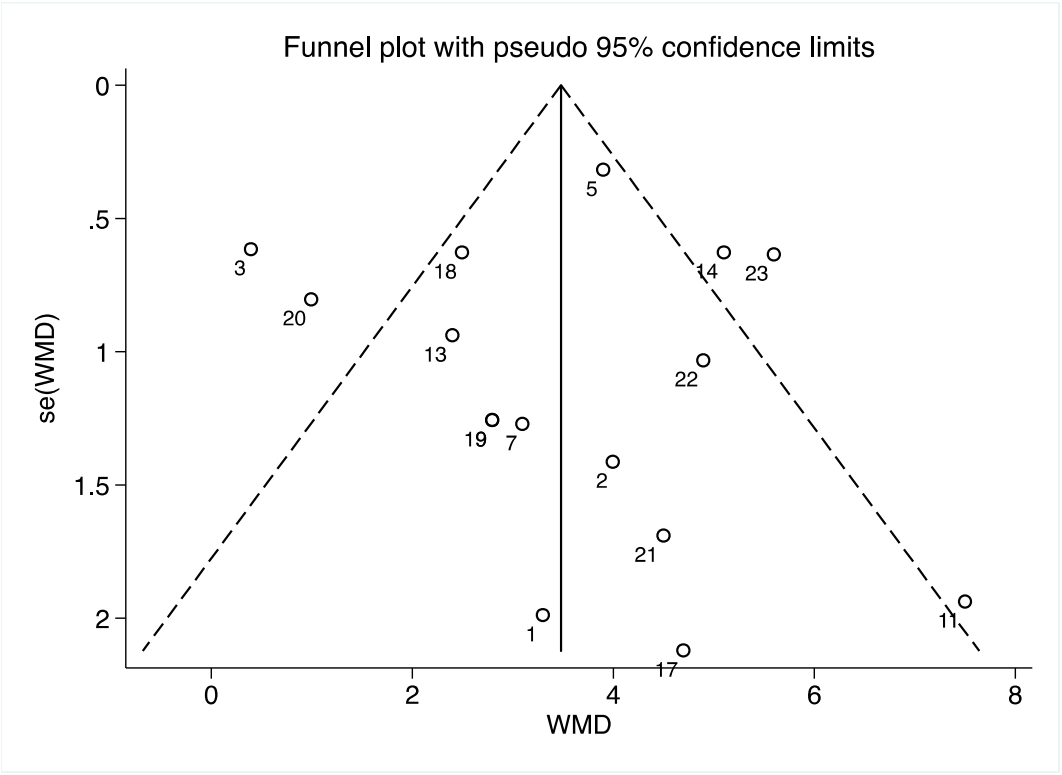


Figure 3.15. Funnel plot. The standard error of the WMD (Weighted mean difference) versus the WMD in studies of the PVO_2.

3.5.6 Watts

Baseline

Five sub-studies were excluded from the initial 16 trials retrieved from the databases(222, 227, 230, 231) due to the studies' enrolment of subjects other than HF patients and a lack of standard deviations. Comprehensive CR programs, which were seen in 29% of the studies investigating exercise training in HF patients (Table 5.7), had a mean duration and follow-up time of 6.3 months (range, 1 to 14) and 10.5 months (range, 6 to 72), respectively. The proportion of exercise interventions at least three times a week was 80%.

The average sample size was 70.3 (range, 16-99) HF patients, who were aged 60.2 years (range, 54.0 to 70.2). Of these, 18.1% were women. The percentage of IHD was 61.0 (range, 37.2 to 100) and the mean LVEF was 30.0% (range, 22.0 to 42.2). At baseline, the average exercise power was 95 watts (range, 74.0 to 145.4).

Table 3.11. Baseline characteristics. Studies including exercise power (watts).

Variables	**Exercise Power,** **Mean** **(Range) (No. of studies)** **N= 11**
Epidemiology	
Age (mean), years	60.2 (54.0-70.2) (10)
Women, proportion	0.18 (0-0.28) (8)
IHD, proportion	0.61 (0.37-1) (6)
Study characteristics	
Sample size (mean), participants	70.3 (16.0-99.0) (11)
Recruitment in-hospital, proportion	0.10 (0-1) (10)
Comprehensive (mean), proportion	0.29 (0-1) (11)
Follow-up time (mean), months	10.5 (6-72) (11)
Exercise duration (mean), months	6.3 (1-14) (11)
≥3 times/week, proportion	0.80 (0-1) (11)

Combined aerobic and strength training, proportion	0.60 (0-1) (11)
Adherence, proportion	0.88 (0.55-1) (9)
Clinical tests	
Baseline exercise capacity (mean), Exercise power	95.0 (74.0-145.4) (11)
NYHA II-III, proportion	0.96 (0.84-1) (5)
LVEF (mean) %	30.0 (22.0-42.2) (11)
Medications	
ACE-I, proportion	0.93 (0.79-1) (10)
Beta-blockers, proportion	0.58 (0.07- 0.93) (9)
Digoxin, proportion	0.56 (0.26- 0.91) (6)
Anti-platelets, proportion	0.95 (0.95) (1)
Statins, proportion	0.51 (0.34- 0.75) (2)
Diuretics, proportion	0.84 (0.52- 0.94) (9)

IHD, Ischemic heart disease; LVEF, Left ventricular ejection fraction; NYHA: New York Heart association Functional Classification; () shows the number of studies used in the calculations; NA, Non-applicable; ACE-I, Angiotensin-converting enzyme, but also included were angiotensin-type 2 receptor blockers.

Effect of the intervention

A random effect model was chosen due to a heterogeneity index (I^2) equal to 52.0% (Figure 5.10). The mean difference between the exercise and control group was 20.51 watts (95% CI, 13.88 to 27.15, P< 0.001).

Heterogeneity

Subgroup analyses by meta-regression could slightly explain the presence of heterogeneity. Exercise power was significantly negatively associated with the combined aerobic and strength exercise mode and the prescription of diuretics (P= 0.03 and P= 0.03) (Table 5.8). A Galbraith plot was designed in an attempt to select studies which might be causing heterogeneity (Figure 5.11). The study by Myers et al. was located outside the 95% CI, thus indicating heterogeneity.

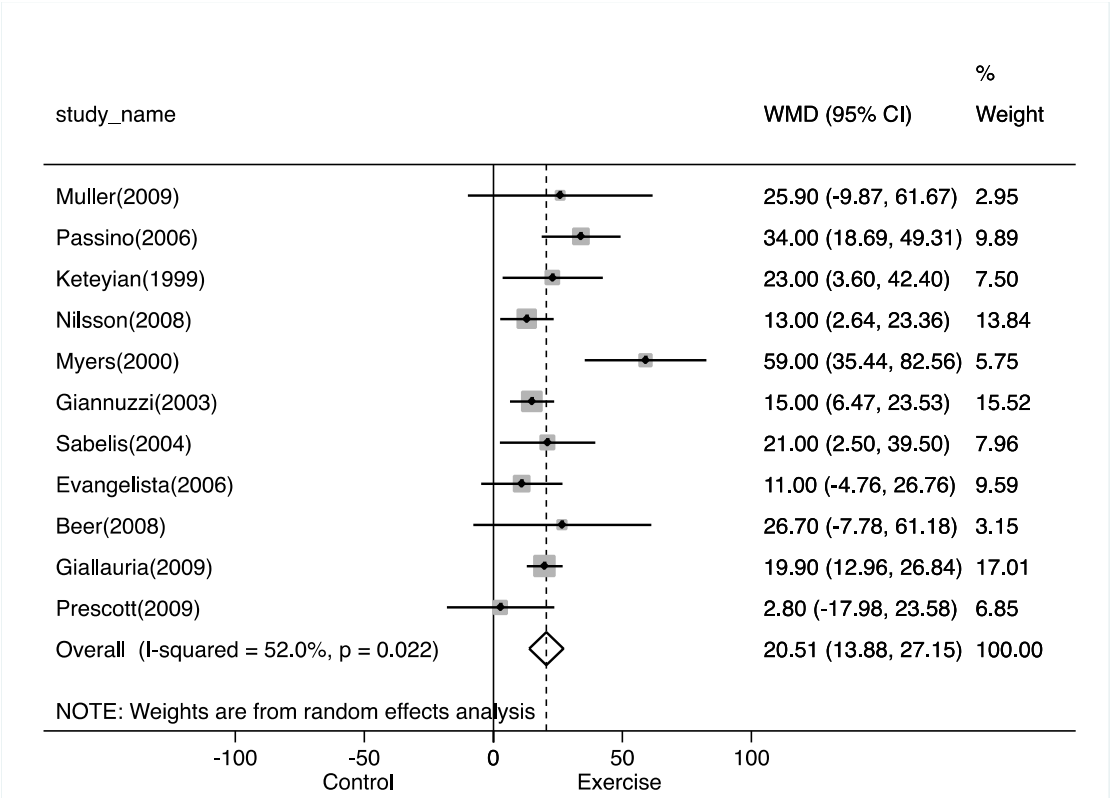


Figure 3.16. Forest plot. Exercise effect on exercise power (watts). The sizes of the squares (grey) are proportional to the weight of each study's sample size; The diamond shows the overall 95% CI (Confidence interval); WMD: Weighted mean difference; % Weight; Weight calculated from the percentage of the study compared to the population of the pooled study population.

Table 3.12. Univariable meta-regressions. Statistical associations between baseline characteristics and the exercise power test.

Variables	Exercise power, coefficient (95% CI)
Age (mean), years	-1.1 (-2.9- 0.82)
Women, proportion	-88.0 (-178.5- 2.4)
IHD, proportion	8.0 (-20.9- 36.8)
Sample size (mean), participants	-0.22 (-0.57- 0.13)
Recruitment in hospital, proportion	0.10 (0-1)(10)
Comprehensive, proportion	6.6 (-12.8- 26.0)
Follow-up time (mean), months	0.05 (-0.72- 0.82)
Exercise duration (mean), months	-1.8 (-4.8- 1.1)
≥3 times/week, proportion	14.0 (-6.4- 34.4)
Combined aerobic and strength training, proportion	-14.7 (-27.9- (-)1.5)¶
Adherence, proportion	33.16 (-18.1-84.5)
Baseline exercise capacity (mean), exercise power	0.34 (-0.12- 0.80)
NYHA II-III, proportion	0.96 (0.84-1) (5)
LVEF (mean) %	0.25 (-1.3- 1.7)
ACE-I, proportion	0.01 (-152.8- 152.8)
Beta-blockers, proportion	-0.45 (-22.6- 21.7)
Digoxin, proportion	13.7 (-91.7- 119.1)
Anti-platelets, proportion	NA
Statins, proportion	NA
Diuretics, proportion	-63.2 (-119.9- (-)6.6)¶

¶ P ≤ 0.05; § P ≤ 0.01; * P ≤ 0.001; 95% CI: 95% Confidence interval;

IHD, Ischemic heart disease; LVEF, Left ventricular ejection fraction; NYHA: New York Heart association Functional Classification; () shows the number of studies used in the calculations; NA, Non-applicable; ACE-I, Angiotensin-converting enzyme, but also included were angiotensin-type 2 receptor blockers.

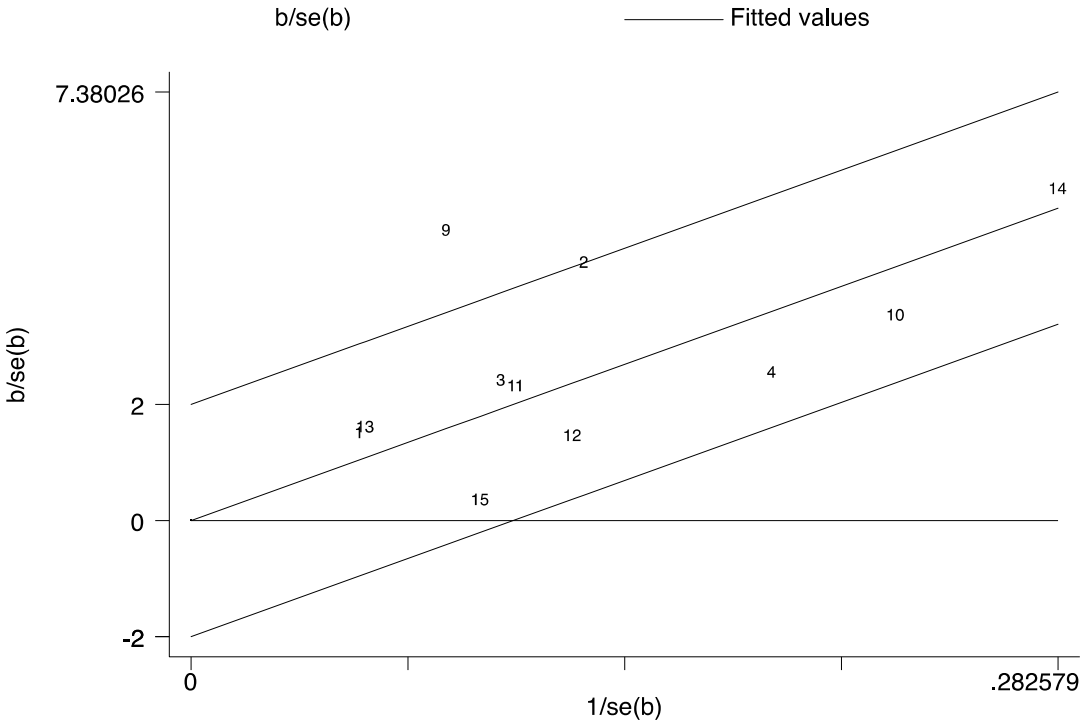


Figure 3.17. Galbraith plot. The WMD (Weighted mean difference) divided by its standard error versus the reciprocal of the standard error in studies of exercise power.

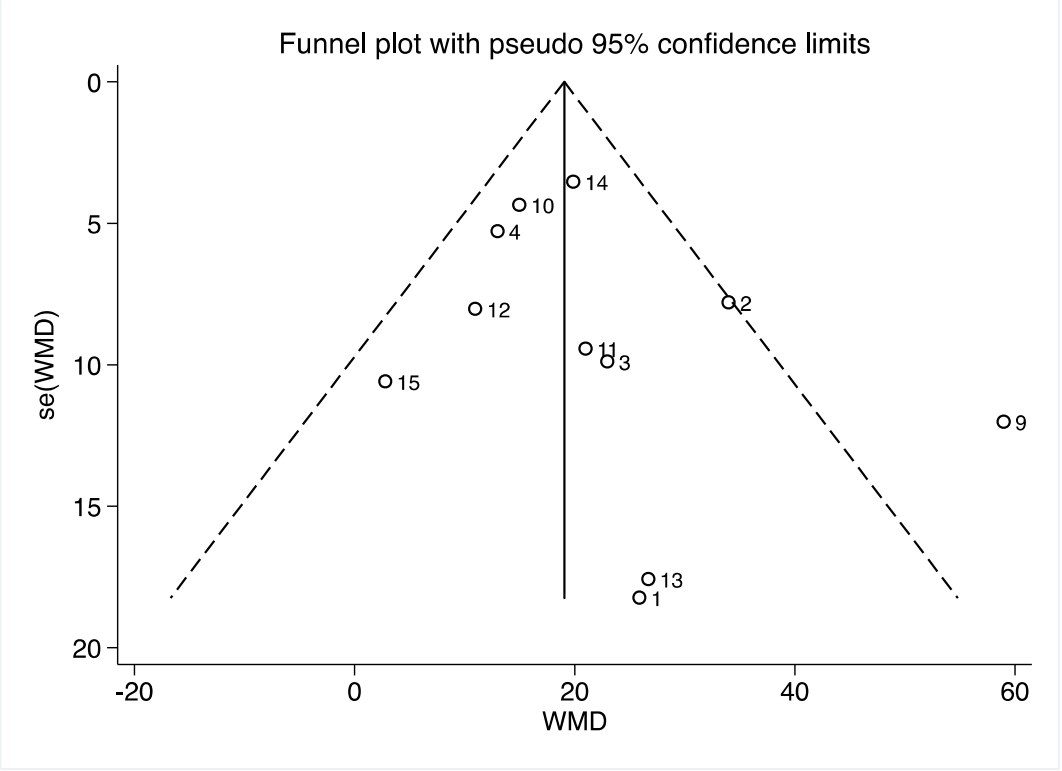


Figure 3.18 Funnel plot. The standard error of the WMD (Weighted mean difference) versus the WMD in studies of exercise power.

A funnel plot did not indicate publication bias, due to asymmetry in the plot. The only study which was an outlier compared to the rest of the study population was the trial by Myers et al. (Figure 5.12). Its status as an outlier was due primarily to the much larger exercise effect the authors found in their study.

3.5.7 Sensitivity analyses

When the pooled populations were enlarged – potentially increasing the effect of exercise interventions due to a larger proportion of patients without HF recruited in the trials – it was shown that the benefits of all four exercise capacities actually decreased numerically, although presumably not significantly (Appendix 4.3).

Taking only the predominant subtype of HF-REF patients into account, the benefits of exercise interventions did not change remarkably (Appendix 4.5). However, this should not be interpreted as the exercise having identical effects on HF-REF and HF-PEF, because the HF-PEF populations were too few in number to affect the final exercise outcomes.

The time-dependency benefits of exercise in HF patients were examined by comparing studies with a maximum of 12 months' follow-up and those without constraints in their follow-up. The former group was found to be marginally larger than the former.

3.6 Discussion

3.6.1 Summary

In contrast to their past counterparts, meta-analyses adjusted for contemporary medical advancements showed hospital admissions to be reduced, but not mortality when exercise interventions for HF patients were evaluated. Of the initial 14,875 studies found through data searches, a total of 11 and 18 studies were eligible to be incorporated in the final meta-analysis for hospital admissions and mortality, respectively.

Between-study effects of the exercise intervention were identified through the random effect measure, which was calculated as the heterogeneity between the studies. Heterogeneity was established as low for the mortality (0%) and moderate (49%) for the hospital admission outcomes. Therefore, a random effect method was deployed for the hospital admission meta-analysis. Specifically, to examine variation in the outcome of hospital admissions more closely, univariate meta-regressions were undertaken with pre-specified baseline variables (Table 4.5). Among these, positive statistical linear relations to hospital admission were found with the combined aerobic and strength exercise mode and the follow-up time. Conversely, negative statistical linear relations to hospital admission were found with increasing LVEF and a proportion of IHD.

Baseline variables may have influenced the outcomes, as overt differences were observed between patients incorporated in the meta-analyses of mortality and hospital admissions, respectively. Variables such as women, IHD and comprehensive CR were all considerably higher in the hospital admission population compared to the mortality parallel (Table 4.1 and 4.3). Conversely, exercise duration and the exercise regime of aerobic and strength components were all notably higher in the mortality population. An essential part of the studies did not report on the pharmacological therapies prescribed to the participants. However, variations between endpoint groups did not appear to be large when their minimum-maximum intervals were observed.

Among the four outcomes of exercise capacities, all of them improved significantly through exercise-based CR, while the average treatment effects in each included study were not the same. Therefore, between-study variations in intervention effect were calculated as

heterogeneity (%), which was highest in the 6-MWT – estimated at 94.4% – and lowest in the exercise power test, equating to 52.0%. In an attempt to unravel underlying reasons for these heterogeneities, univariate meta-regressions showed significant positive associations between sample size, follow-up time and the outcomes of the 6-MWT; the baseline exercise time test and the follow-up exercise time; the baseline PVO_2 test, IHD, ACE-Is and the follow-up of PVO_2. Significant negative associations were found between female sex, statins and the follow-up PVO_2 as well as diuretics, combined aerobic and strength exercise mode and the follow-up exercise effect.

In general, the included studies were agreed with studies incorporated in other meta-analyses showing under-enrolment of the elderly and women. Furthermore, HF was predominantly based on a background of IHD and the exercise programmes were restricted to exercise, whereby patients were mainly classified to NYHA class II to III and recruited as outpatients. The average LVEF was around 30%, and the most frequent medications prescribed were ACE-Is and diuretics.

Sensitivity analyses examining the effect of exercise on mixed populations of patients with and without HF, but all having being diagnosed with IHD, were similar to each other in all the outcomes. Reducing studies to include only HF-REF patients did not change the outcomes either. Furthermore, reducing the follow-up to 12 months showed the exercise intervention effect to grow marginally in the hospital admission analysis and all the exercise capacities.

3.6.2 Strengths of the study

Contemporary insights

The search period, constrained to 11 years and 8 months (Jan 1999 to Aug 2010), aligned the data automatically with contemporary medicine. This seems to be a virtue to the analysis, as patients attending an exercise intervention two decades ago may have benefitted more from an exercise intervention as the same patients would today, due to improvements in background medical treatments. According to this hypothesis, exercise is less central in secondary prevention in HF, corresponding to the mechanistic advantages of invasive and pharmacological cardiovascular therapy(232, 233). Despite the fact that exercise appears to be less imperative if complications post-MI are less than in generations before due to medical improvements, other points of view also exist. It could also be posited that a better physical stage associated with the HF disease is the underlying reason for a larger HF population feeling capable of exercising. The reasons for exercise not being an opportunity in the era of less effective HF treatment could be tiredness, anaemia, cachexia and breathlessness(68, 202, 234) Although adjusting the time period should have been sufficient to ensure that patients recruited in the selected studies received guideline-recommended treatments, it was not known whether or not therapies additional to the reported drugs had been given. Potentially overlooked therapies would mainly have been ICD, CRT, revascularisations and reperfusions.

The broad spectrum of recorded baseline variables is another virtue of the data. These included factors such as adherence, exercise mode, comprehensiveness, HF-PEF and long-term insights, which only rarely have been investigated in exercise-based CR. Taking these factors into account made sensitivity analysis feasible, varying from inter-study comparisons to intra-study associations.

Search strategies

A strong advantage of the meta-analyses was their broad data search capability, in that they counted five separate databases. This strategy enhanced the chances of finding papers dealing with exercise-based CR, and it also increased the likelihood of finding abstracts from conferences not registered in traditional internal medicine databases. The substantial amount of studies found in non-English languages highlighted the broad search strategy. Furthermore, plural searching resulted in 2,238 duplicates, thus underscoring their relevance. The total of 12,637 different abstracts reviewed for the pre-specified objectives was another quality related to the search.

The fact that the search syntaxes were only modified editions of those used in the most previous Cochrane Review warranted positively for their reproducibility. Moreover, it also reduced the likelihood that key studies would be ignored.

The concomitant embedding of six separate outcomes in the search syntaxes also increased the chances of discovering recorded outcomes which were not properly reported in abstracts summarising only one of the pre-specified outcomes. Although it may occur opportunistic for the reader to include outcomes found by chance, doing so would impact on reproducibility.

Diversity

A general strength in the analysis of exercise capacity was the choice of four separate measurement entities, as it provided the opportunity to underscore clearly exercise benefits for HF patients. Another cornerstone was setting a minimum six-month follow-up, which has not been undertaken in previous meta-analyses investigating exercise capacities. The broad range of statistical methods applied in this study also shed light on possible biases in the data, which in general were poorly reported at the individual study level. This was provided both through summarising and stratifying tools.

3.6.3 Limitations of the study

RCTs

Even before retrieving the data it could have been predicted that the a priori decision to only include RCT studies in the meta-analysis increased the likelihood of repeated pitfalls observed in previous meta-analyses, e.g. under-enrolment of the elderly, women and minorities. Patient selection in RCTs is well-recognised, and the main way to circumvent the problem is to take it into consideration in the protocol design (RCT), before the trial is undertaken(235). In the current set-up of post-hoc meta-analyses this course of action is understandably not possible. Another reason underlying comprehensive hesitation amongst investigators to include these fragile groups could be their higher risk for generating missing values(236). For instance, are older patients more likely to attrition compared to younger patients, due to commodities such as osteoarthritis or their higher mortality risk? The latter is explained by higher age. Language skills and misconception of the importance in the

contributing to medical science by participating in RCTs are other issues impairing the recruitment of minorities.

Foreign data

After the relevant abstracts were read, it was observed that a non-ignorable number were related to foreign publications. The linguistic barrier was predominantly related to authors from China, Russia, Italy and Poland. Although contact via email was attempted, the approach was unsuccessful regarding access to full-sized papers for further translation. The effect of not being able to include studies published in non-Anglo-Saxon languages is hard to assess, as the quality of these studies is not possible to quantify.

Bias and data reporting format

A general limitation in the studies was the poor reports of biases. By and large, it was only the HF-ACTION study and the study by Witham et al. which reported thoroughly on matters of bias(144, 237) and did explain clearly how they dealt with potential pitfalls associated with adequate sequence generation, allocation concealment, blinding of subjective outcomes, blinding of mortality, how incomplete outcome data were addressed, freedom of selective reporting and freedom of other biases.

Although it is unfair to criticise individual studies for their choice of statistical reporting on outcome data, it became a shortcoming in the analysis of this thesis if, for instance, continuous numbers were calculated as medians instead of means. For such cases a normal approximation was used, which meant a normal distribution was assumed to underlie the variable. From this assumption, the mean and the median displayed identical values. The mean of continuous variables was used in meta-regression analysis and was therefore a risk factor for bias.

Heterogeneity

The large amount of heterogeneity found in the meta-analyses for exercise capacity was a weakness in evaluating exercise interventions in HF patients. Although the high amount of heterogeneity was hard to predict before the meta-analysis had been processed, such results make it hard to generalise their conclusions into clinical practice. One way to avert heterogeneity, however, could be to restrain studies included for the analysis into austere and

narrow criteria regarding exercise interventions. In this way, the number of studies attained through the database searches would have been expected to be much lower than the number retrieved through the current loose restraints. Despite heterogeneity, a great deal of effort was deployed in order to highlight underlying confounders between studies. Meta-regressions, however, only revealed a few confounders for each exercise capacity. Hence, the majority of the heterogeneity must be ascribed to unmeasured confounders and a lack of available data.

Variations in the outcomes of mortality and hospital admissions were only significant for the latter. The I^2 was measured at 49% (p=0.03), which is a factor for the random effect within studies. A value of 49% indicates a moderate degree of heterogeneity. I attempted to adjust for this variation by using the random effect method in the meta-analysis. This model assumes that each exercise effect is different for each study and is therefore random. Furthermore, it assumes that the within-study random effect is normally distributed and centred on the mean of the random effect. The confidence intervals for random effect models are usually wider than for a fixed effect model, which was also the case for the hospital admission data.

Lack of information

Retrospectively, several unrecorded variables in the individual studies could have contributed importantly to further elaborations in the analyses. In addition, and in order to pinpoint the diagnosis of HF, regular measurements of NT-proBNP would also have been a useful predictor of measuring adhesion to exercise programmes and achieving exercise benefits. CRT is an intervention offered to HF patients with NYHA class II to IV, and it could similarly provide important insights into how patients with pacemakers benefit from exercise(238). Added to the fact that only a few pharmacological therapies were reported in the included studies, their dosages were in general unavailable. The importance of the optimal up-titration of leading HF therapies before CR referral could equally become crucial in achieving exercise benefits.

Statistically, the lack of reporting correlations between baseline and follow-up measurements in the exercise measurements made it unfeasible to adjust for the baseline values of exercise tests. Instead, unstandardised mean differences were calculated between the follow-up results among controls and patients allocated to the intervention.

Taking the variation of covariates in the included studies into account may generate the idea that a higher-level organisation of future CR studies could be beneficial, in order to acquire complete data. Although leading peer-reviewed journals require the documentation of a priori

trial registrations before publication, most attempts to summarise data are mainly done on a post-hoc basis. With the attempt to avoid different measurements in different studies leading to overall heterogeneity, central trial regulations could be managed by heart associations such as ESC and AHA. This approach should only demand the collection of some pre-specified data, but it should still allow freedom for individual investigators to examine key areas of interest. Implicitly, several trials with common data collection methodologies would collectively be acceptable counterparts to multicentre RCTs, eventually deducing valuable conclusions for clinical practice.

3.6.4 Previous literature

Compared with the latest Cochrane systematic review by Davies et al., hospital admission was significantly reduced in the meta-analysis of this thesis(8). Nevertheless, mortality was still not significantly improved by exercise-based CR, which was a finding similar to the Cochrane review.

The EXTRA-MATCH meta-analysis, which elegantly included complete trial data in its analysis, demonstrated that exercise interventions reduced all-cause deaths and the combined outcome of all-cause death and hospital admission(203). However, this methodology was constrained exclusively to database searching in MEDLINE, in contrast to the Cochrane counterpart, which included five different database searches.

The distinction between short- and long-term insights into exercise capacities is another question which has not been answered by investigators. Including a minimum follow-up of six months, all four pre-specified exercise capacities were significantly improved in the current thesis in patients with HF allocated to exercise-based CR. Rees et al. published a recent Cochrane systematic review in 2004, dealing with the subject without timeframes. They found that four measures of exercise capacities, including PVO_2, exercise time, 6-MWT and exercise power, favoured HF patients attending exercise-based CR significantly(10). Other attempts to evaluate the association between exercise capacities and exercise-based CR have also failed to distinguish between short- and long-term follow-up(206, 239).

The largest RCT completed until now, the HF-ACTION multicentre study by O'Connor et al., could only show improved survival after adjusting key baseline covariates(144). These results were therefore similar to the outcome of the meta-analysis of mortality in this thesis.

Investigating the subset of HF-PEF patients in the meta-analyses was not possible, as only two studies included patients with diastolic dysfunction. An overt weakness of most large datasets investigating the effect of exercise-based CR in HF patients is also that they are restricted to the HF subtype of HF-REF. By excluding HF patients with HF-PEF, about one half of the total HF population is censored from contributing to the evidence on CR. This may cause a clinician to hesitate in the CR referral process for HF-PEF patients, although they should have a prevalence similar to HF-REF patients. The negative selection of HF-PEF in meta-analyses is implicitly related to the low participation of HF-PEF patients in clinical trials of CR. A recent meta-analysis, pre-specified to include HF-PEF, found only three RCTs in their investigation of the effect of exercise training(240).

3.7 Conclusion

Two separate contemporary meta-analyses established that exercise interventions significantly reduce hospital admissions during at least six months of follow-up, but not mortality. Intra-study variations measured in heterogeneity were shown to be moderate for the hospital admission outcome but absent for mortality. Variables found to cause inequalities in the exercise effect on hospital admissions were higher LVEF and IHD proportions with a reducing effect. In contrast, combined aerobic and strength exercises and follow-up times increased hospitalisation events.

A priori specified factors of HF-PEF, adherence and CR format did not seem to affect the two distinct outcomes.

Finally, the meta-analyses appeared to be sufficiently powered, as the hospital admission population was much smaller than the mortality counterpart. Although a significant outcome was generated only in the former analysis, the obvious difference in the quality of the outcomes of hospitalisation and mortality should be taken into account.

Four exercise capacities were significantly improved in HF patients attending exercise interventions with a minimum follow-up of six months. Variations in the intervention effect between the included studies varied between moderate to high and were calculated as I-squared heterogeneity. Overall, these heteroskedastic exercise effects indicate a lack of consensus among health care professionals for the most efficient form of exercise-based CR, or simply the enormous diversity of suggestions on how to design exercise programmes. Despite a few significant univariate linear associations between the outcomes and pre-

specified baseline variables, the measured heterogeneity remained unexplained. Therefore, the results encourage further research into which CR format may be the most efficient, including integrated versatility for the various subtypes of HF patients.

Chapter 4 – The influence of aspirin and statins in heart failure

4.1 Introduction

Anti-platelet drugs, predominantly prescribed as aspirin, are widely administered to HF patients as a remedy in the secondary prevention of coronary thrombosis. Their main aim is to counteract the aggregations of platelets in cases of intravascular bleeding which potentially have fatal outcomes in the development of acute MI(241).

Statins are another anti-inflammatory pharmacological compound administered to HF patients with a history of IHD. Similarly, their aim is also to prevent events of acute MI. The inhibition of the enzyme HMG-CoA reductase, which produces cholesterol in the liver, is the main target in its reaction pathway(242). The rationale behind lowering cholesterol is linked to the impairment of atherosclerotic plaque in the coronary arteries and thus finally reducing the likelihood of contracting an acute MI(243).

Described in several reports on statins use are side-effects such as diabetes, liver disease, polyneuropathy and myalgia(244). Furthermore, in addition to increasing the risk of prolonged bleeding, aspirin has been linked to the destruction of prostaglandins in the vessels' intima, which may have a deteriorating circulatory response in HF patients by, for example, hampering the effect of ACE-Is(245). Several pros and cons therefore coexist for the use of aspirin and statins.

The aim of this chapter is to investigate long-term survival in discharged HF patients who are prescribed statins and/or aspirin after admission for acute MI. All HF patients enrolled in the EMMACE-I and II studies were followed up for a minimum of 90 months. The primary objective is to assess the impact on mortality of aspirin and statins separately in HF patients enrolled in the EMMACE studies. Secondary objectives are the combined impact of aspirin and statins and the unadjusted impacts of aspirin and statins on long-term mortality in HF patients. The research question of the chapter is therefore extrapolated from the lack of evidence relating to whether long-term treatments with aspirin and statins in HF patients might have an adverse effect on HF pathogenesis(5, 12).

4.2. Methods

4.2.1 Pooling of EMMACE data

The characteristics of the EMMACE data were described in Chapter 2. The HF populations of each EMMACE cohort were pooled to a single HF study cohort. The HF diagnosis was identified through the clinical recognition of HF symptoms such as breathlessness, fatigue, periphery oedema and echocardiographic measurements of LVEF counting systolic and diastolic abnormalities. Finally, a past history of HF recorded in the notes of the patients was considered as a valid marker of HF, too.

4.2.2 Objectives

The primary objective was an evaluation of all-cause mortality at 1, 6, 12, 24 and 90 months, as assessed by the average treatment effects (ATEs) of aspirin and statins, separately, or the combined impact of aspirin and statins prescribed together in the pooled HF cohort hospitalised with acute MI. The secondary objective was to determine long-term survival in patients discharged after acute MI, stratified by the EMMACE study year and HF diagnosis.

4.2.3 Statistics

Calculated numbers (%) or medians (IQR) were reported for baseline characteristics. The strength of associations between continuous variables was assessed via the Kruskal Wallis test, whereas the Pearson's Chi-square was used for discrete values. P-values less than 0.05 indicated significance. All patients with a HF diagnosis were pooled to a single population independent of the EMMACE study year. The single HF population proceeded to the final analysis.

The average treatment effect (ATE) on mortality was performed through a propensity score-matching model constructed on an underlying probit model. This model was chosen, as models including propensity scores are more robust than regression parallels when parametric assumptions are violated (see 4.4.3 Limitations below). In the following chapter this was the case possibly because the HF population was pooled from both EMMACE years. This created an interaction between statins, and year, and aspirin and year in the Cox regression model. In Chapter 2, which dealt with CR referral, the analysis of CR referral strictly separated the

EMMACE cohorts in contrast to Chapter 4. The pooling of HF patients was mainly made in order to increase the power. Three separate treatment outcomes were constructed. ATE I demonstrated the difference between aspirin and statins versus none; ATE II was aspirin versus none; and ATE III was statins versus none. In brief, the model calculated the risk of death for each treatment group subtracted by the risk of death in the control group. The control group was allocated to none of the drugs. Positive ATEs indicated a lower mortality associated with either aspirin or statin benefits, or both of them, whereas a negative value suggested higher mortality in patients prescribed aspirin and statins(246). Time-dependency was assessed with right-censoring at 1, 6, 12, 24 and 90 months. The 95% CI for the ATEs was computed by bootstrapping with 100 repetitions.

Multivariate adjustment in each ATE was performed in the propensity score through the pre-identified covariates of EMMACE study year, gender, age, diabetes, COPD, hyperlipidaemia, admitting Cardiologist, revascularisation, reperfusion and the prescription of beta-blockers and ACE-Is. A balance between the covariates was mandatory before the final outcome assessment was completed. All the analyses were based on the intention to treat, as it remained unknown if the medication was changed after discharge.

Furthermore, an individual risk factor assessment was performed in a mini-model of the GRACE score, estimating six-month mortality constrained to the covariates HR, age, SBP, electrocardiographic ST-segment deviation and cardiac arrest on hospitalisation(163). In this case a logistic regression model was chosen to construct the propensity score.

Kaplan Meier curves were constructed for each treatment category: none, one of and both aspirin and statins. These categories were stratified by EMMACE study year. The follow-up time was 90 months as a result of the common observation time in the two EMMACE studies.

The propensity score matching method was compared to a sensitivity model based on propensity score stratifications incorporating covariates identical to the primary model. To undertake stratification a block ID number was generated in order to attain balance between the covariates. The influence of clopidogrel together with aspirin was also investigated, although the former only was on the market at the time of the EMMACE-II study recordings. Another analysis of sensitivity was the proportional hazard Cox regression model adjusted for the same covariates as the two propensity-matching models. Interactions between study year, aspirin and statin were equally investigated in the Cox regression model.

Finally, the impact of missing data was imputed through the multiple imputation ICE method, based on the final outcome in the propensity matching model(174).

4.3 Results

4.3.1 Baseline

In total, 2,196 and 2,055 patients were hospitalised following the diagnosis of acute MI in the EMMACE-I and II studies, respectively. Among the patients with acute MI, 1,142 (52.0) and 672 (32.7) had HF in the EMMACE-I and II studies, respectively. In the HF population the median age was 74 years (IQR, 66 to 81) and 41% were women. The baseline characteristics of patients in the EMMACE-I and II studies, including nested HF patients, can be seen in Table 6.1. Baseline characteristics were not similar in patients with and without HF. HF patients were more frequently older, female, smokers, diabetic, prone to less frequent hyperlipidaemia, more often IHD, CVA, lower SBP, higher HR, more frequently STEMI, Killip-Class 2 to 4, cardiac arrests, higher modified GRACE risk score, prone to fewer revascularisations, more reperfusions, fewer Cardiologist inputs, less aspirin, statins and BB therapy and more often prescribed warfarin and ACE-Is on discharge.

Aspirin (78%) was prescribed to almost twice as many HF patients compared to statins (42%). Regarding the combination of statins and aspirin, 191 (14%) were not administered any of them, while 708 (52%) were discharged with just one of the drugs. Finally, 475 (35%) were prescribed aspirin and statin at the same time. Warfarin was prescribed to 148 (9%) HF patients, taking the two EMMACE studies into account. Clopidogrel only appeared on the market in 2003 and was recorded in 286 out of 670 (43%) HF patients.

Table 4.1 Baseline characteristics in the EMMACE studies and nested HF population

Characteristics	EMMACE-I, 1995 (N= 2196)	EMMACE-II, 2003 (N= 2055)	HF patients[§] (N=1706)
Referred for cardiac rehabilitation, n (%)	986 (74)*	1256 (64)	833 (70)
Median (IQR) age, years	72 (62-79)	71 (62-79)	74 (66-81)*
Female sex, n (%)	865 (39)	737 (36)	697 (41)*
Current smokers, n (%)	542 (28)	589 (31)	451 (30)*
Hypertension, n (%)	633 (29)*	867 (43)	590 (35)
Diabetes mellitus, n (%)	283 (13)	348 (17)	296 (17)*
Chronic obstructive pulmonary disease, n (%)	320 (15)	328 (16)	277 (16)
Chronic heart failure, n (%)	1142 (52)*	672 (33)	NA
Hyperlipidaemia, n (%)	156 (7)*	678 (35)	269 (16)*
Ischaemic heart disease, n (%)	1019 (46)	985 (48)	856 (50)*
Cerebrovascular disease, n (%)	213 (10)	232 (11)	203 (12)*
Median (IQR) systolic BP, mmHG	140 (120 -160)*	141 (120 -160)	140 (119-160)*
Median (IQR) heart rate, bpm	80 (68-100)*	80 (66 -96)	85 (70-101)*
Atrial fibrillation, n (%)	587 (29)	NA	NA
ST-elevation myocardial infarction, n (%)	957 (47)*	670 (33)	712 (43)*
Killip-Class 1, n (%) Class 2 to 4, n (%)	1045 (49)* 1096 (51)	1469 (71) 568 (28)	468 (28)* 1332 (72)

Cardiac arrest, n (%)	450 (21)*	199 (10)	334 (20)*
Median (IQR) modified-GRACE risk score[π], per unit	14.2 (6.2-33.6)*	12.2 (5.0-25.4)	18.9 (8.9-37.3)*
Median (IQR) propensity for CR[π]	73.8 (58.4-85.5)*	67.7 (55.6-78.1)	71.7 (61.5-78.1)
Reperfusion, n (%)	920 (42)*	511 (25)	621 (36)*
Revascularisation, n (%)	43 (2)*	291 (14)	111 (7)*
Specialist cardiology input, n (%)	786 (37)*	959 (47)	657 (39)*
Aspirin on discharge, n (%)	1361 (87)*	1602 (80)	1074 (78)*
Clopidogrel on discharge, n (%)	NA	861 (42)	286 (43)
Warfarin on discharge, n (%)	128 (6)	131 (6)	148 (9)*
Statins on discharge, n (%)	138 (8)*	1640 (82)	575 (42)*
ACE-I on discharge, n (%)	629 (38)*	1298 (65)	893 (65)*
Beta-blocker on discharge, n (%)	696 (42)*	1345 (67)	563 (41)*
One-year mortality rate (95% CI)[ψ]	0.32 (0.30-0.34)*	0.21 (0.20-0.23)	0.37 (0.34-0.39)*

[§] Total HF patients from both decades * Indicates significant differences between the EMMACE studies or the HF population and the EMMACE studies; IQR: BP: blood pressure; interquartile range between the 25 and 75 percentile; [π] Built on heart rate, systolic blood pressure, cardiac arrest and ST-deviations; ACE-I: angiotensin-converting-enzyme inhibitor; 95% CI: 95% confidence interval; [ψ] Based on a cumulative hazard assumption given in percentage values, e.g. 0.12 equals 12%.

4.3.2 Outcomes

Comparing one-year cumulative mortalities showed that 37% of HF patients (95% confidence interval CI, 0.34 to 0.39) were dead within one year compared to 32% (95% CI, 0.30 to 0.34) and 21% (95% CI, 0.20 to 0.23) of all patients with MI in the EMMACE-I and II studies, respectively.

HF patients had a median survival rate of 39 months compared to 63 months and 83 months for the acute MI populations in 1995 and 2003. The median survival rates in HF patients, stratified by no aspirin and statins, either statins or aspirin and both aspirin and statins, were 25 months, 50 months and 85 months, respectively.

Survival

The median propensity scores for the three combinations (ATE I to III) of aspirin and statins prescriptions were 11.4 (IQR, 3.5 to 23.9), 0.81 (IQR, 0.71 to 0.88) and 0.22 (IQR, 0.03 to 0.85). At the six-month follow-up ATE I significantly favoured the group of HF patients who had been prescribed aspirin and statins on discharge (ATE I-6 month, 0.21; 95% CI, 0.11 to 0.32) (Figure 4.1). The benefits in survival observed in ATE I at six months was now supported by a significant ATE II and ATE III (ATE II–6 month, 0.10; 95% CI, 0.03 to 0.18; & ATE III–6 months, 0.15; 95% CI, 0.07 to 0.23). Conversely, compared to these corresponding treatment effects, ATE II was non-significant (ATE II–6 months, 0.14; 95% CI, -0.05 to 0.23). Except for the increase in absolute values, the same picture was present for the follow-ups at 12 and 24 months (ATE I– 12 month, 0.23; 95% CI, 0.10 to 0.36; ATE II–12 month, 0.10; 95% CI, 0.03 to 0.18 & ATE III–12 months, 0.12; 95% CI, 0.01 to 0.22). At 90 months, which was the end of the follow-up period, all ATEs were significantly improved, measuring the difference in risk of death between HF patients prescribed aspirin and/or statins on discharge compared to HF patients not prescribed any of them (ATE I– 90 month, 0.20; 95% CI, 0.05 to 0.36).

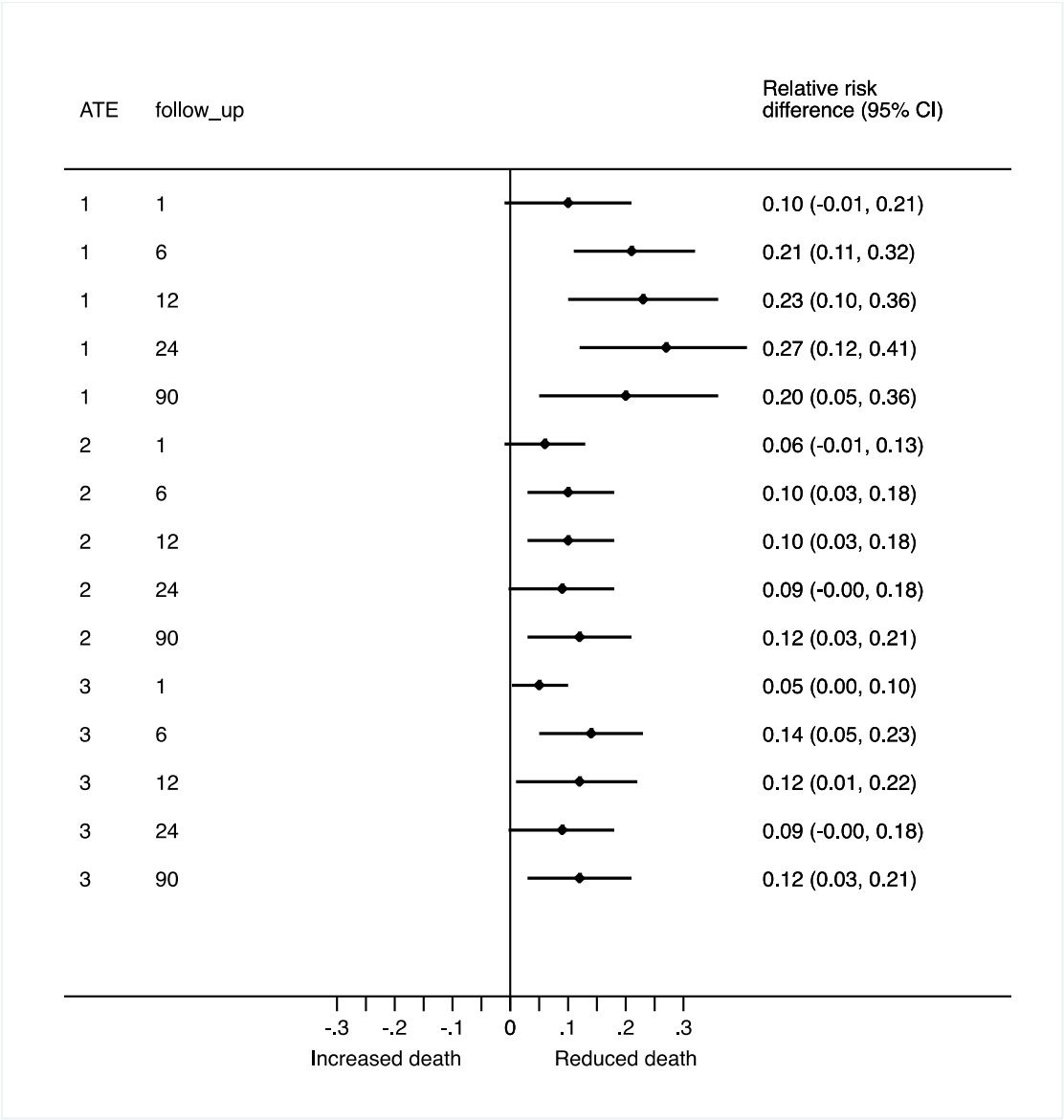


Figure 4.1. Average treatment effect (ATE I to III) on mortality deduced from propensity matching. ATE I, aspirin and statins; ATE II aspirin; ATE III, statins. ATE (the average treatment effect) was measured as risk difference; The ATE was measured in relative risk differences; Follow-up was measured in months.

The Kaplan Meier survival plots compared long-term mortality for patients with and without HF during the two decades of observations. It was demonstrated that the diagnosis of acute MI complicated by HF in both EMMACE studies was associated with a significantly worse prognosis than for those without confirmed HF (log-rank, P< 0.001) (Figure 2.4, page 75). Each independent treatment of statins and aspirin was depicted as being superior for the control group (P<0.001) (Figure 4.2).

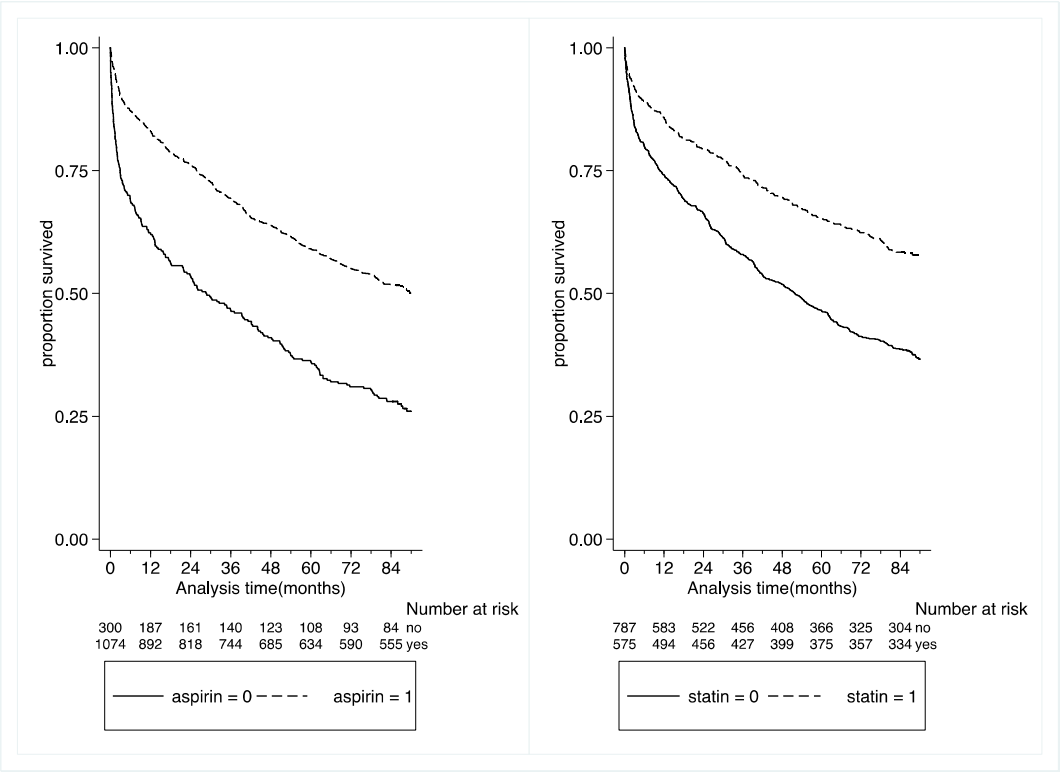


Figure 4.2. Survival curves stratified by aspirin and statins.

4.3.3 Sensitivity

Applying the stratification method provided outcomes similar to those found for the propensity matching method (Figure 4.3). In this method ATE I was shown to be significantly beneficial for the group prescribed both aspirin and statins in the follow-ups of 1, 6, 12 and 24 months. In comparison to the propensity models, ATE II significantly favoured aspirin during all the follow-ups in the stratification model.

In contrast to the model based on propensity matching, the result at one months in ATE III was the single significantly reduced mortality rate found through stratification, although the other follow-ups suggested improved outcomes in the statins group.

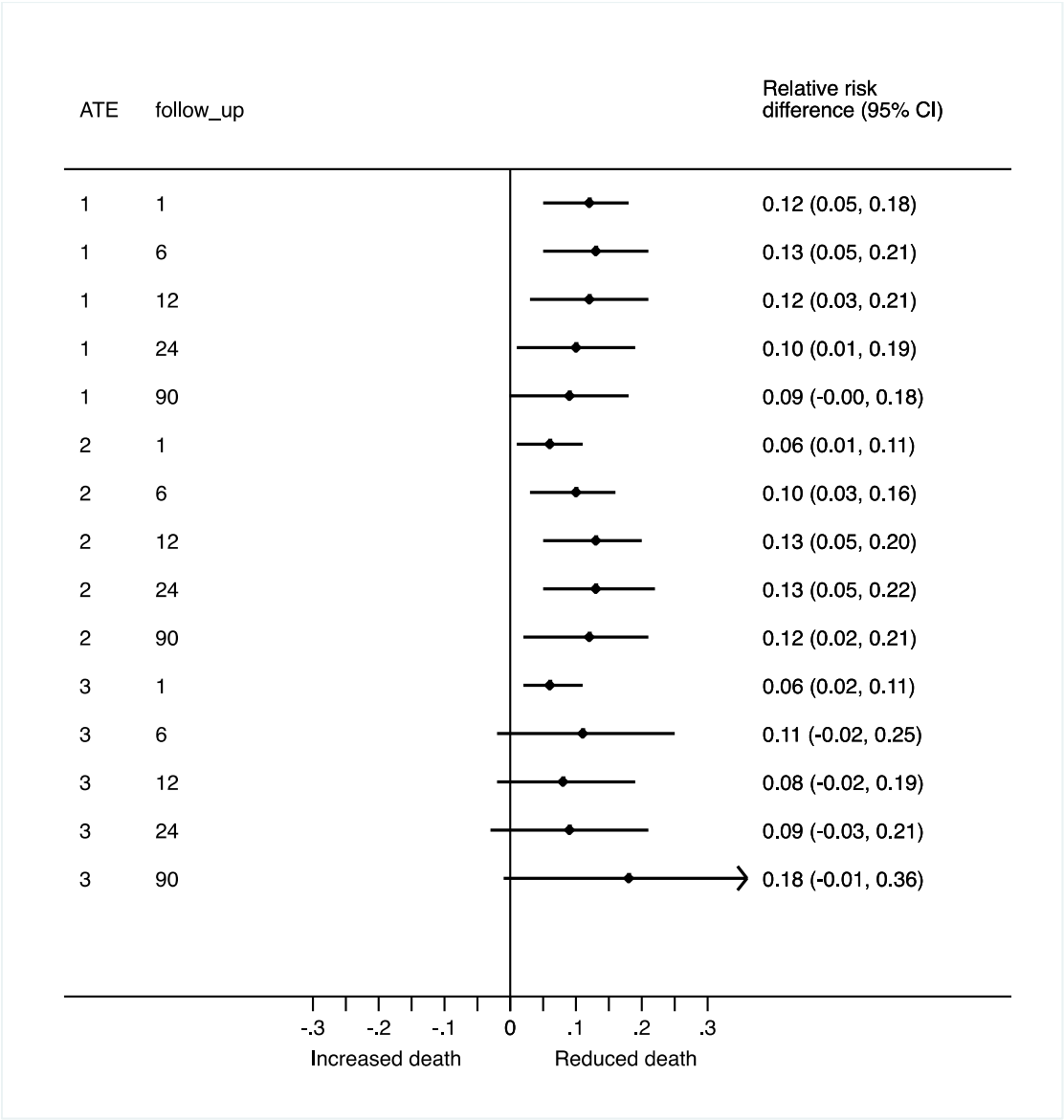


Figure 4.3. Stratification of propensity scores. ATE I, aspirin and statins; ATE II aspirin; ATE III, statins. ATE (the average treatment effect) was measured as risk difference; The ATE was measured in relative risk differences; Follow-up was measured in months.

The HR for all-cause death did not significantly favour treatments with statins and aspirin during a follow-up of 90 months when prescribed statins and aspirin therapy on discharge were compared to patients without these prescriptions (HR for aspirin, 1.06; 95% CI, 0.76 to 1.50; P= 0.72; and HR for a statin, 1.49; 95% CI, 0.77 to 2.91; P= 0.24). An interesting observation was the significant interactions between statin and aspirin prescriptions and the year of the EMMACE study (P<0.001 & P<0.001). The impact of the interaction of EMMACE year on the HRs of statin and aspirin treatment was shown to have a reducing effect in both medications (Appendix 4.1), i.e. each drug had a reducing effect on mortality, together with the incremental of eight years corresponding to the time interval between the two EMMACE studies.

Additionally, it was established that the addition of clopidogrel to aspirin, generating a composite variable of anti-platelet therapy, did not change the ATEs in the analysis of statins and aspirin (Figure 6.4). Overall, it should be added that patients with either anti-platelets or statins, or both anti-platelets and statins, prescribed had a significantly better mortality outcome during the whole follow-up period, except at 12 months (ATE 1) and 24 months (ATE 3).

Multiple imputations did not endorse the results from the primary analyses, by demonstrating the almost overall non-significance of most of the ATEs (Appendix 4.2).

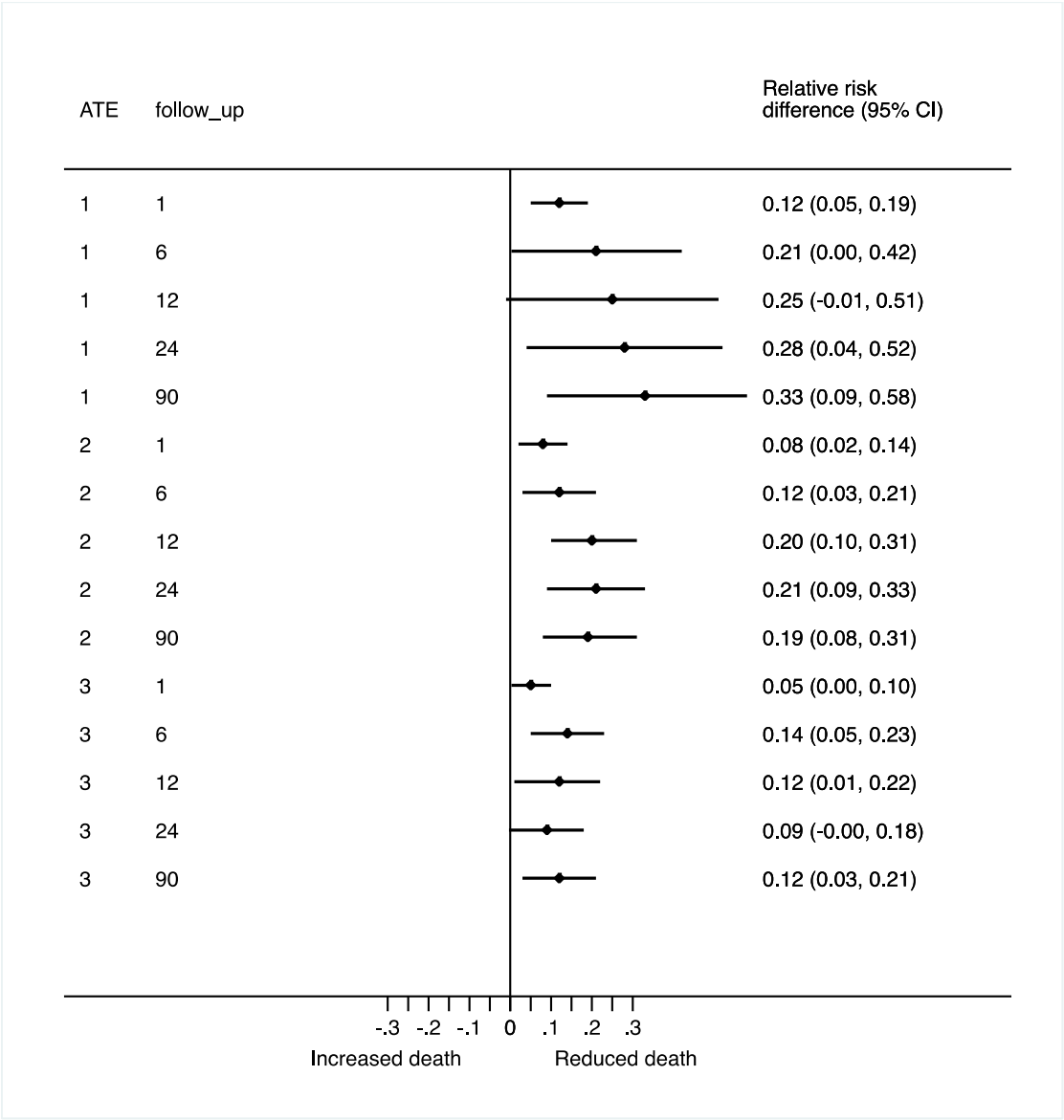


Figure 4.4. Average treatment effect (mortality) deduced from propensity matching distinguished by anti-platelets and statins. Anti-platelets were aspirin and clopidogrel; ATE I, anti-platelets and statins; ATE II anti-platelets; ATE III, statins. ATE (the average treatment effect) was measured as risk difference; The ATE was measured in relative risk differences; Follow-up was measured in months.

4.4. Discussion

4.4.1 Summary

According to recently published guidelines for HF treatments, authorised by the ESC, neither anti-platelet therapy nor statins are recommended(3). By and large this can be explained by the lack of proven evidence behind their use in HF patients. Therefore, gaps remain in clinical pharmacology to justify the prescription of aspirin and/or statins in HF patients. Controversially, the administration of these drugs could even harm patients as a result of their side-effects and hence aggravate the HF pathology. Through retrospective longitudinal analyses an attempt was made in the current thesis to investigate these widely used drugs in HF patients. Overall, we followed 1,814 HF patients for up to 90 months. They were all admitted to hospital with acute MI and discharged with HF in the EMMACE-I & II studies in 1995 and 2003, respectively. Unadjusted survival analyses indicated that both aspirin and statins were significantly beneficial if used in the long term (Figure 4.2). In agreement with the unadjusted analyses, multivariable models applying propensity scores adjusted by demographics, comorbidities, invasive cardiac interventions and evidence-proven medications revealed that the use of statins and aspirin could improve mortality by 10 to 27% in risk difference during follow-ups varying from one to 90 months. Noteworthy of mention were baseline imbalances between patients with and without HF suggesting lower quality of standard care in the HF group (Table 6.1).

4.4.2 Strengths

The virtues and caveats of these results are partly intertwined with their parallels in the CR referral outcomes illustrated in Chapter 3. Hence, the focus in this chapter has been on influences specifically related to aspirin and statins in HF patients. Some repetition occurs in line with the strengths described in Chapter 3, but the context is different.

Lack of evidence

The strength of the analyses of aspirin and statins in HF patients recorded in the EMMACE studies can be attributed to the lack of existing evidence on the subject.

Investigations into areas with unknown or conflicting evidence should be commended and treated as a key strength of any study. Conflicting consensuses amid existing clinical trials and meta-analyses of antithrombotic agents and statins act as a great incentive to re-examine the area(5, 11, 43, 247), which is in stark contrast to evidence on the benefits in CAD patients without HF recommending both drugs(13). To refresh our memory, existing ESC guidelines do not recommend the use of either aspirin or statins in HF patients, which seems unlikely to be followed in the practical setting(3); first, because an undisclosed number of HF patients go undiagnosed, and second due to the large overlap between HF and CAD, which literally presents doctors with a paradox when deciding whether or not statins and aspirin should be prescribed. For instance, it is unknown whether aspirin and a statin should be prescribed to a patient with HF indefinitely after an MI event(13).

Real-world data

The reproducible data collection in the two separate decades was part of a study design that is seen rarely. In addition to the unique framework of the EMMACE designs, their large patient populations, examined for variables in coexisting medical conditions, performance status and cardiovascular risk factors, deserve to be commended. The observational character of the data gives a real-world sincerity which reveals outcomes otherwise hidden by patient selection in the artificial set-up of RCTs.

Supporting that real-world data in the EMMACE studies play an important role is that the distributions of aspirin and statins prescriptions were not uniform or bimodal, showing 78% of patients receiving aspirin and 42% statins. The former meant that 22% of the patients did not receive aspirin, which would not be a plausible set-up in an RCT. As a rule, RCTs randomise to about two equal halves if the intervention is a single treatment, although 2 to 1 randomisation is possible. At the moment there is no consensus on randomising aspirin versus a placebo in HF patients despite the lack of evidence on the effectiveness of aspirin in HF. Therefore, observational data represent a valid and convenient shortcut to assessing the survival effect in HF patients not prescribed aspirin. It cannot be precluded that patients without aspirin could have had warfarin or clopidogrel prescribed; however, the latter was included in the analyses without affecting the results remarkably.

Another quality marker of the data in this thesis is that they were all collected in the same geographical area of West Yorkshire. Although social variables were unavailable for further adjustments, the environmental exposures would presumably be similar for most of the

patients. A priori hospital treatments are also surmised to be of equal quality, even though a post-hoc study taken from the EMMACE-I study demonstrated differences in treatment performance between a smaller district hospital and a larger university hospital running a referral function for all other hospitals in the area(248). This study calculated expected numbers of deaths of admitted patients through the patient characteristics of age, heart rate and systolic blood pressure. The comparison of performance between the two hospitals showed that the district hospital had an excess of five deaths more than predicted over a three-month period, whereas the larger central hospital had four fewer deaths than expected.

Long-term follow-up

A virtue of the EMMACE studies is their long-term follow-up approach. Their minimum follow-up of 90 months provides for a great variety of possible analyses to be performed. This was exemplified by the short-, medium- and long-term follow-ups of the primary endpoint measuring death. Therefore, insights into time-dependent changes of mortality associated with the prescription of aspirin and statins on discharge were possible. The longitudinal prospective cohort follow-up also made it feasible to compare mortalities between HF patients stratified by EMMACE study year.

MI set-up

The set-up observing HF patients prospectively after an MI event is rather unusual compared with the conventional HF studies either recruiting patients through HF hospital admission or in HF outpatient clinics. The advantage of the EMMACE design is the potentially automatic left-sided censoring of previous HF history. Patients experiencing an MI are likely to develop HF, especially in the two eras where reperfusion was not as frequently used in the acute phase compared with today(249). Furthermore, HF patients do have a smaller risk of acquiring an acute MI than a patient without HF(250). Adding these factors together augurs for a low inclusion rate of patients with coexisting HF in the EMMACE studies. From this perspective the great confounder of HF history in a survival analysis measuring years is likely to be reduced.

Patient recruitment at the time of hospital admission may also be superior to outpatient recruitment, another methodology frequently employed in observational as well as experimental studies in HF patients. Primarily, the prolonged observational period of each patient during hospital admission could have provided supplementary time for the investigators to gather necessary information on research details. Furthermore, the scenario of

being admitted to hospital could also motivate patients to give informed consent to participate in research compared to patients seen briefly in an outpatient clinic(251).

4.4.3 Limitations

Observational data

Regarding the estimation of causality, the observational study design was truly a shortcoming. Concomitant randomisation of a statin and aspirin would have made it feasible to demonstrate causal associations between aspirin, statins and the long-term endpoint of death. So far, randomised designs of aspirin and statin studies through a factorial set-up are missing in HF patient research. Nevertheless, the factorial RCT design has been tried in patients with pulmonary hypertension and did not show that either drug affected the 6-MWT(252). Propensity score-matching methods generated statistically similar treatment groups receiving none, one or both aspirin and a statin. It has been claimed that propensity-score based analysis approximate causal association estimates in observational studies(253); however, in the these of examples of Chapter 4 it cannot be excluded that HF patients receiving statins and aspirin were less ill than those in the non-treated group, which consequently causes a treatment paradox.

Furthermore, the pooling of HF patients between two consecutive decades is another potential weakness of the study, although statistical adjustment was deployed for several clinical variables and the year of the study. The major reason for being sceptical in this instance is the difficulty in equalising patients in the two consecutive decades, as treatments and diagnostics underwent time-dependent changes.

Additionally, it could not be assured whether a GP or another physician changed the aspirin and statin prescription during the follow-up period. A longitudinal design with pre-specified time intervals for collecting data on drug prescriptions would likely improve the survival analysis of aspirin and statins.

Missing data

Another caveat of the EMMACE data was the substantial degree of missing values. Compared to the analysis in Chapter 3, investigating the impact of CR referral on HF patients, the data on aspirin and statin use were more complete and had fewer missing values. Peak missing data were 20.2% for statins and 19.5% for aspirin. Other missing data applied to, for

instance, atrial fibrillation, which was only recorded in 1995. Missing data on clopidogrel in 1995 is harder to claim as detrimental, because the drug simply was not licenced at that time. Sensitivity analyses built on multiple imputations incorporated into the propensity-matching models did not yield similar ATEs for aspirin and statins. Therefore, the generalisability of the drug benefits supporting the primary data outcomes could not be concluded. Whether missing data was believed to influence the chosen statistical models in a way that biased the interpretation of the dividends of aspirin and statins in HF patients is hard to say. More likely is that the ICE model and the propensity score model were incompatible, which means that replacing missing variables in the propensity score model was unfeasible through automatic integration, similar to the regression models. For that reason, the replacement was based only on a single calculation and not on multiplications of ten, which definitely was a caveat.

Unmeasured confounders

Further potential pitfalls in the analyses were unrecognisable and non-available covariates. BNPs were only starting to be identified as a strong clinical marker for HF at the beginning of the new millennium(254); therefore, noticeable numbers of undiagnosed HF patients on discharge were likely to occur in the EMMACE studies. Knowledge of a previously mentioned period living with HF or another comorbidity before the EMMACE studies would have contributed importantly to the survival analysis. However, this unknown time span is a general weakness in observational studies. The study design enrolling only patients with an MI event could reduce this issue, suggesting that patients had their first incident of HF. Physical function during admission could have been another variable worthy of analysis. Moreover, information on daily physical activity and independence after discharge would have been useful, too. Closer and repeated follow-ups of the variables instead of only observing the single endpoint of death would have strengthened the analysis further.

In the acknowledgement of unmeasured confounders, sensitivity analyses agreed with other alternative outcome assessments. The single outcome of death for the pre-specified intervals was robust and independent of the type of propensity score. The Cox proportional regression model did not show a significant effect of aspirin and statins on survival when interactions between the drugs and study years were adjusted in the model independently of the study year. In contrast, both drugs were independently strong predictors for survival in the model as soon the interactions were removed. Reasons for the interactions between the study year and drug type could be speculated as the more frequent prescription of aspirin and statins in 2003, which possibly increased the likelihood of achieving statistical power shown through

significant outcomes. Regarding the two significant interactions between year, statin and aspirin, respectively, it was not advisable to use the Cox regression model due to the violation of the model through lack of proportionality. However, if the model is used despite this interaction, an adjustment of the interaction in the model is mandatory. Another solution to the problem could be to split the variables into separate models. In the case of the present study this would have meant a model for 1995 and 2003, which equally was the strategy in the CR referral analysis.

Composite endpoints

In addition to the already mentioned weaknesses associated with an observational design, additional outcomes and characteristics could have made the analyses more distinct. First, side-effect events related to aspirin and statins would have complemented the primary endpoint. The proverb stating that 'the surgery was a success but the patient died' confirms that the price to achieve a beneficial effect can be too high. In particular, the gathering of bleeding episodes associated with aspirin and myalgia and diabetes linked to statins would have enhanced the results further(244).

Despite the fact that previous histories of stroke, myocardial infarction and HF were obtained through patient notes, prospective registration of these events would have favoured the effect measures of aspirin and statins.

For these reasons almost every large clinical study planned and conducted today will pre-specify multiple endpoints and construct combined hierarchical outcomes from these, in addition to single classic outcomes such as death.

4.4.4 Previous literature

Aspirin (ATE II) was shown to improve survival significantly in the propensity-matching model with controls. Tenuous documentation on anti-platelet benefits through aspirin and clopidogrel administration in HF patients currently prevails. Despite secondary prevention through aspirin and statins so far has been found inadequate in survival outcomes of HF patients, they have been proven effective on survival in patients with CAD(255, 256).

Furthermore, the comparison between aspirin, clopidogrel and warfarin is inconclusive with regard to the efficacy of the drugs in recent studies(43, 247). The sombre message concerning aspirin, cited in the Warfarin and Anti-platelet Therapy in Chronic Heart Failure trial

(WATCH)(12), suggests that it may increase HF hospitalisations compared to warfarin. Other existing RCTs have so far not demonstrated the beneficial long-term effect of aspirin or other anti-platelets when compared to controls in HF patients(4, 247, 257).

Similar to aspirin, statins were found to improve survival significantly compared with controls in a propensity score model ranging between 5 and 14% for risk differences. Previous investigations of statins in the controlled rosuvastatin multinational trial in heart failure (CORONA), the GISSI-HF trial (Gruppo Italiano per lo studio della Sopravivenza nell'Insufficienza Cardiaca Heart Failure) and the pravastatin in elderly individuals at risk of vascular disease (PROSPER) trial all concurred to show non-significant differences between treatment and control groups in all-cause mortality among HF patients(5, 258, 259). The meta-analysis undertaken by Lipinski et al. validated these results indirectly by showing the absent effect of statins on all-cause mortality or cardiovascular mortality in HF patients(260).

A factorial trial of aspirin and statins has so far not been completed. However, Kawut et al. did not demonstrate a significantly improved 6-MWT in 92 patients with pulmonary arterial hypertension and who were randomised to aspirin and/or statins(252).

4.5 Conclusion

The ATE outcomes from the propensity score methods provided a different message than the ESC HF guidelines(3). The endpoint of death adjusted by the propensity scores for aspirin and statins suggested that both aspirin and statins can be and are used safely on a concomitant basis. Nonetheless, as aspirin was prescribed to 78% of HF patients compared to 42% statins, aspirin added greater weight to the results. Taking into account that previous RCTs lacked evidence for aspirin use, and 29% of the patients had atrial fibrillation in the EMMACE-I study, the continuous evaluation of long-term aspirin prescription for HF patients is required. Concerning new trials providing new evidence, the clopidogrel versus aspirin in chronic HF (CACHE) RCT being conducted at the moment will hopefully unravel some of the current uncertainties regarding anti-platelet therapy in HF patients(261).

Chapter 5– Overall discussion

5.1. Introduction

This chapter will discuss the findings compared to the aims, objectives and questions pre-specified in the thesis which, in short, investigated the benefits of exercise-based CR and associated referrals and aspirin and statin prescriptions in an acute MI population of HF patients. MI is the most frequent cause of HF in the Western world. The reason for examining this area is that current interventions have been well-demonstrated to benefit patients with CAD and without HF, but their impact on outcomes in HF patients is still less convincing. In addition to evaluating the results, an attempt will also be made to confine the influence of the pre-specified interventions on patients, health policy, clinicians and researchers.

5.2. Secondary preventions

5.2.1 Index events

The two cohorts in the EMMACE studies included patients recruited after an incident of acute MI. The studies collected details on CR referral, aspirin and statin prescriptions and followed up patients until the event of all-cause death or censoring at the end of follow-up on 23rd September 2010. Regarding the RCTs incorporated into the meta-analyses, the majority recruited patients from outpatient clinics, although a minority enrolled patients during hospital admission.

5.3 CR referral in the EMMACE studies

5.3.1 Between the EMMACE studies

Key epidemiological factors, such as age and sex, were not significantly different between the two EMMACE studies. Because the EMMACE studies took place in identical geographical areas there were no apparent reasons to suspect that these patterns would alter unless certain treatments or exposures were harmful in the area during the period.

Fewer patients were referred for CR in 2003 (64%) than in 1995 (74%), which one can assume can be attributed to the almost 10 times greater missing variables in 1995, suggesting that the missing data can be associated with the lack of CR referral.

In order to highlight confounders affecting the proportion of patients referred for CR in the EMMACE studies, comorbidities, risk factors and treatments were reviewed. Concerning risk factors and comorbidities, significant differences showed higher proportions of HF, Killip-classes and modified GRACE risk scores in the EMMACE-I study compared with the EMMACE-II study. Conversely, hypertension and hyperlipidaemia were significantly more frequent in the EMMACE-II study. These comparisons indicate that patients were in clinically worse conditions in the EMMACE-I population compared to the EMMACE-II population, due to higher proportions of comorbidities and risk factors.

Fundamentally, treatment quality increased between the two EMMACE studies. One exception was that reperfusion was used less in 2003 than in 1995. Anti-platelets were prescribed to 86% of the patients in both EMMACE cohorts. Presumably, this is down to the evidence underlying the use of anti-platelets in patients with MI, which had already been established prior to the first of the EMMACE studies.(262) In contrast to anti-platelets, statins, ACE-Is and beta-blockers were all significantly more prescribed in the EMMACE-II population compared to the EMMACE-I cohort (Table 1).

5.3.2 CR referral

Contemplating CR referral, referred patients tended to be young smoking men with less comorbidity compared to the non-referred patients. Surprisingly, HF shifted from a comorbidity represented more from among the non-referred in 1995, to being more frequent amid the CR-referred in 2003 in the EMMACE studies.

Furthermore, the level and variety of treatments were in general larger in the CR-referred population compared with the non-referred ones, during both EMMACE studies. Despite the fact that treatment inequalities remained, there were some changes, suggesting that the care given to patients who were not CR-referred actually improved. First, CR-referred patients were older and were more often smokers in 2003 compared to 1995. Second, in 2003, the comorbidities of hyperlipidaemia, diabetes and cerebrovascular disease were more frequently represented in the CR-referred population.

During the decade between the EMMACE studies a noticeably larger number of variables became significant predictors for CR referral. The majority were statistically positive predictors and predominantly guideline-recommended treatments. A total of 64% referred for CR in 2003 corroborated the existence of a treatment watershed among patients admitted with acute MI, depending on their risk factors. Considering that the number, duration and staff for CR all increased over the EMMACE studies, a stronger interest in and support for CR in West Yorkshire was underscored. Major unknown confounders were still the unknown degree of comprehensive CR and the geographical distribution of community CR in the county.

5.3.3 CR referral outcomes

In contrast to the improvement in the one-year mortality rate, favouring the EMMACE-II population compared to the EMMACE-I parallel, was the comparison between one-year mortalities in CR-referred patients in 1995 and 2003, as they were not significantly different. However, during both decades CR-referred patients had significantly lower one-year risk ratios than non-referred MI patients.

Conversely to the one-year mortalities, the adjusted HRs were only significantly reduced for the CR-referred patients in 2003 by 43%. This suggested an increasing importance of CR referral during the decade between the EMMACE studies. Hypothetically, the growing survival benefits of CR referral during the interim years between the EMMACE studies could be explained by a larger patient selection, i.e. patients with the largest amount of risk factors and comorbidities were overlooked for CR referral. This seems unlikely, because the baseline characteristics showed that CR-referred patients had more risk factors and comorbidities in 2003 compared to 1995 (Table 2).

Excluding patients dying during the first three months made the risk reduction of CR referral fall to 21% in the EMMAGE-II study. This strongly supports that patients with a high level of risk factors and comorbidities were not CR-referred, independently of unmeasured confounders.(167) Left-censoring at three months in EMMACE-I study did not affect the HR importantly, implying that this cohort had fewer unmeasured confounders, or rather that patients with unmeasured confounders (high risk factors) were excluded from the primary analysis of CR referral.

Patients without CR referral data stood at almost 40% in 1995 compared to about 4% in 2003. After multiple imputations of both EMMACE studies, data without left-censoring (0 to 90 months) generated a similar HR for referral in the EMMACE-II study. In contrast, the HR in the EMMACE-I study significantly improved for CR referral in 1995. When both MIs and left-censoring were taken into account in the survival analysis, it was only the CR referral HR for the EMMACE-II study which remained statistically significant by showing a risk reduction of 20%. It is suggested from these results that patients with missing data had a high level of comorbidities and risk factors. Especially in the EMMACE-I study a large proportion of patients with missing CR referral data died during the first three months following an acute MI.

In the subgroup analyses of HF patients, CR referral remained a significantly independent factor for survival in the EMMACE-II study, but not in the EMMACE-I study.

5.3.4 Aims, objectives and questions

The aim of examining CR referral on the long-term prognosis of patients included in the EMMACE studies was successful, although a large proportion of patients in 1995 had missing CR referral recordings. Following the aim, the primary objective of long-term mortality was successfully demonstrated as being reduced in the EMMACE-II study, but not in the EMMACE-I counterpart. Similarly, our secondary objective of determining long-term mortality rates in HF patients was shown to have reduced only in the EMMACE-II study. The secondary objective of estimating predictors for CR referral revealed that characteristics trends varied between the two cohorts. In the EMMACE-I study, age was a negative factor and beta-blockers and reperfusion were positive factors. In 2003, reperfusion was equally a positive factor, similar to HF, anti-platelets, statins and ACEIs. Conversely, diabetes and the modified GRACE score were negative factors in 2003. Overall, the response to the initial

research question did not find any difference in the benefits of CR referral in patients with or without HF.

5.3.5 Implications

In the following discussion, which evaluates CR referral in the EMMACE studies, it is essential to keep in mind that the CR referral data did not include information about CR attendance, which should be understood both as enrolment and completion. Furthermore, it was a caveat that the EMMACE studies were undertaken in a delimited area in the UK, which makes it difficult to generalise the outcomes. The take-home message in the EMMACE-II study of the improved survival of patients being CR-referred suggests the importance of completing CR. Intuitively, CR referral cannot be a significant factor in improved survival unless the patient complies with the programme.

Although patients with better health conditions were more likely to be CR-referred, a trend was also observed which indicated that patients with more comorbidities and risk factors were CR-referred in the EMMACE-II study compared with the EMMACE-I study. Despite that fact that the results do not prove that it is feasible to exercise and attend CR with multiple comorbidities, it could be extrapolated that since patients were referred for CR with more diseases than in the past, they became gradually more ill when enrolled into a CR programme. Consequently, it seems fair to suggest that patients should be confident in their physical capacity and trust their ability to improve it, even though they may be living with a chronic illness such as HF which makes them dependent on several medications(263).

The implications of CR referral on health policy can be translated into various plans. First, it can be stated that automatic CR referral for all patients with IHD or HF is supported by the improved survival rate of CR-referred patients in the EMMACE-II study. In fact, GRACE et al. have already posited the suggestion of automatic CR referral for patients with MI(264) by demonstrating that it resulted in superior enrolment compared with usual referrals among 661 Canadian patients treated for heart disease in two acute care centres ($P<0.001$). Another method which could be employed to improve CR referral would be to apply pay performance incentives in hospitals treating patients with MIs and HF. A recent large study was conducted at 24 hospitals in the Northwest region of England(265). The 30-day mortality rates of 134,435 patients admitted for acute MI, HF and pneumonia in these hospitals were compared to 722,139 patients admitted for the same three diseases in 132 other hospitals in England. The comparison showed that an introduced pay-for-performance programme had significantly

decreased mortality by a relatively high risk reduction factor of 6% – equivalent to 890 deaths. It could therefore be posited that funding to hospitals could be withheld until they are able to document satisfactory secondary prevention for patients on discharge, including CR referral. Imagining a CR referral success rate of 100% in HF patients is not feasible, though. A recent study in the UK, investigating CR feasibilities for HF patients through a nationwide survey, showed that only 40% of the centres offered CR for HF patients. Among these, less than half (39%) offered specific CR HF programmes.

The implications for researchers, translated from the benefits of CR referral in the EMMACE studies, can also be seen on a level above the CR referral process, as both automatic referral and health care liaison have already been shown to be beneficial for key outcomes. One step further could therefore involve evaluating how to make patients adhere to exercise and a healthy lifestyle after completing the CR programme. Higher exercise adherence was remarkably greater in the RCT conducted by Belardinelli et al. (88%) compared with the HF ACTION and the EXERT studies (both about 60%)(144, 266, 267). The main difference between these designs was that the former example offered supervised exercise during the whole trial. Therefore, interactions between supervising Cardiologists, exercise Physiologists and patients can be interpreted to enforce adherence and benefit key outcomes.

Regarding clinicians, CR referral seems mandatory when discharging patients with heart disease from a hospital. It could therefore be juxtaposed with the prescription of guideline-recommended medications on discharge. Compliance with CR and medications is a crucial aspect of the patient care, but it was not investigated in the EMMACE studies.

As described above, treatment inequalities were persistent during both EMMACE studies. Therefore, clinicians are obligated to pay extra attention in order to ensure that patients with multiple comorbidities and risk factors receive the best available treatments. Data from ‘Get with the Guidelines – Coronary Artery Care’, suggest that the treatment paradox could be alleviated during a follow-up period of six years(268). Although the risk-treatment paradox remained, patients in the high risk tercile received 91% of all guideline-recommended interventions. Taking into account this percentage, the risk-treatment paradox was definitely alleviated in this case.

In addition to making a referral, recent research also demonstrates some benefit if clinicians spend time explaining to patients before discharge the importance of regular exercise and sticking to a healthy lifestyle in general(186).

5.4. Exercise-based CR in HF patients

5.4.1 Baseline

Regarding epidemiological characteristics, women and older patients were as a rule represented as a minority. This raised doubt about the practical impact of the outcomes, because HF patients in real life are older and are mainly women. Older patients may often be excluded from trials, as they are less likely to complete them successfully(269). However, the majority of patients suffering from IHD are men, which may excuse the fact that very few women in the RCTs were included in the meta-analyses(270).

NYHA classes II to III were at a minimum observed in 94% of HF patients in the meta-analyses. One rationale underlying this NYHA distribution may be that patients with NYHA class I do not need CR, as they already are in good shape in contrast to those with NYHA class IV, who are too frail for regular physical activity. An average LVEF, varying between 25.9% and 32.0%, underscored that patients with HF recruited in RCTs examining CR were mainly of the HF-REF subset. From this point of view the current meta-analyses were not much different from the previous ones undertaken. Therefore, the inclusion of patients with HF-PEF should be encouraged in both RCTs and meta-analyses.

There was inconsistency in the reporting of baseline medications in the studies included for the meta-analyses. Among those who published the data, ACE-Is and diuretics were the favourable choice. In general, statins were prescribed to less than 50% of the patients reported, in contrast to anti-platelets, which varied between 46% and 95%. This large variation was hard to explain, but it may be associated with proportions of patients with atrial fibrillation and previous IHD. With the exception to studies measuring hospital admission, beta-blockers were prescribed to between 50 and 60% of HF patients. In the former subgroup, 85% of the patients were prescribed beta-blockers. Overall, beta-blocker prescription was disappointing, as they would be expected to be offered to more than 90% of the patients(3).

The CR format highlighted some interesting features. First, programmes based exclusively on exercise were the preferred intervention in the included RCTs. It can be speculated that the higher price of comprehensive CR programmes may explain their lower prevalence among the RCT data. Moreover, studies focusing solely on exercise-based programmes measured more often the outcomes of exercise capacities pre-specified in the analyses compared to studies examining comprehensive CR programmes. The majority of studies combined aerobic and strength training as the exercise mode, despite the fact that there is no evidence

suggesting that a combined exercise mode is more effective than aerobic exercise alone. Nevertheless, the leading trend in recent RCTs is to employ the combined aerobic and strength exercise mode(144).

5.4.2 Outcomes of the meta-analyses

In an attempt to assess the effect of exercise training in HF patients with access to contemporary medical treatments, slightly adjusted search terms from the Cochrane review by Davies et al. were applied.(8) The major tweak was the restriction of studies to the period between 1999 and August 2010. Despite these alterations, the minimum six-month follow-up period for all-cause mortality in HF patients, randomised to exercise-based CR interventions versus a placebo, was not shown to favour the experimental group.

The first event of hospital admission (any cause) in the follow-up of HF patients was significantly reduced in the exercise intervention group compared to the control group in the meta-analysis. The quantitative risk reduction was found to be 28%. Davies et al. found no significant differences in all-cause hospital admissions, before or after a 12-month follow-up, but they did uncover a significant difference in HF-related admissions (RR, 0.72; 95% CI, 0.52 to 0.99; P = 0.04)(8).

Independent of quality, all four exercise capacities – PVO_2, exercise time, exercise power (watts) and 6-MWT – were demonstrated in the meta-analysis to be significantly improved in the exercise group compared to the control group. Specifically, the differences between the meta-analyses of this thesis and the Cochrane version by Rees et al. are time adjustment, the updating of included studies and the minimum follow-up of six months used in the version of this thesis(10). Heterogeneity, which was substantial in all four measurements of exercise capacity and hospital admission, spanned from moderate in the outcomes of hospital admission and exercise power (48.8% and 52.0%) to high in the outcomes of PVO_2, exercise time and the 6-MWT (77.1%; 82.4%; and 94.4%). A similar pattern has been recognised in previous meta-analyses (206, 207).

5.4.3 Aims, objectives and questions

Undertaking an updated systematic review to investigate the effect of exercise-based CR on key clinical outcomes in HF patients, adjusted for contemporary treatments, was successful. The primary objectives of determining mortality, hospital admission and four separate exercise capacities were, except for the former, shown to be significantly improved for the group assigned to exercise-based CR. Among the secondary objectives, IHD was statistically

positively associated with PVO_2 and negatively associated with hospital admissions, suggesting an overall beneficial impact as a marker compared with non-ischemic cardiomyopathy. As surmised intuitively, baseline measures of PVO_2 and exercise time were independently positively associated with their follow-up measurements. Surprisingly, the combination of aerobic and strength exercise was negatively associated with exercise power and positively related to hospital admissions, suggesting aerobic exercise to be better in the comparison between combined aerobic and strength exercise versus aerobic exercise alone, respectively. Finally, the answer to the research question – whether a pre-specified timeframe indirectly adjusting for contemporary treatments can influence the outcomes of mortality, hospital readmission and four separate exercise capacities – was first that hospital readmission was significantly reduced in the CR-allocated group with HF. This finding was different to the most recent Cochrane review, indicating that coronary-invasive treatments, short admissions and extensive anti- and coagulative medications may have helped to optimise the secondary prevention of exercise-based CR. Second, similar to previous systematic reviews, exercise capacities were significantly improved in the exercise group, and mortality was still not significantly reduced compared with the usual care group. The largest weakness possibly affecting the research question was the lower attendance of the elderly and women in the included RCTs.

5.4.4 Implications

The implications of the results in the meta-analyses on patients with HF highlight the importance of exercise-based CR, first because hospital admissions were significantly reduced in the exercise group. Such an improvement tends to ameliorate crucially the quality of life. Secondly, four separate exercise capacities were significantly improved in the exercise group. These improvements also suggest great benefits in the quality of life of patients with HF, as they will increase their freedom to complete physical activities such as walking and buying groceries through to being an active climber in the Alps.

The meta-analyses are a strong incitement to health policies to provide exercise-based CR for as many patients with HF as possible. Despite the fact that health costs have been reduced as much as possible in the current financial climate, secondary prevention through exercise-based CR may be the cleverest way to save costs, as it keeps patients with HF out of hospital. Furthermore, health care expenditure has been compared to a ‘cost disease’ in a recent book by William Baumol(271), according to whom health care cannot be as frugal as the car industry, for instance. He also compares medical science with a classical music concert, both of which depend on human skills and forecasts their working time not to change significantly

over the next 100 years. Cost reductions may be achievable, but should they be sought from the wages of health care staff and unnecessary interventions? He concludes from these factors that the cost disease is almost incurable.

Concerning clinicians, it is important to state that the outcomes of hospital admissions and exercise capacities were mainly achieved in trials recruiting younger men with few comorbidities additional to HF. In general interventions show benefits in most subgroups, if they have already been proven to work in one of them. Frequently, they will be even more effective in subgroups with the most sickly patients.(167) Therefore, clinicians should refer and enrol as many patient subsets with HF as possible, although these meta-analyses did not demonstrate the benefits of exercise-based CR as a generalisable trait.

The implications of the meta-analyses should impact on researchers in several ways, too. Regarding terminology, the differentiation between comprehensive CR and HF management programmes is not always distinct, as both interventions have in common many of the same components(272, 273). Consequently, it would be helpful for future meta-analyses and discussions on evidence if a sharp line were drawn between the two practices. The studies chosen in the present research did not answer what type of exercise training is associated with the best outcome. This may suggest that aerobic exercise or a combination of aerobic and resistance training provide similar outcomes. However, future research should attempt to answer this question. Another answered question which needs to be illuminated is what benefits HF-PEFs patients gain from exercise-based CR. As the minority of the included studies recruited patients with HF-PEF, future RCTs of HF patients and exercise should focus on the HF-PEF subgroup.

The large amount of heterogeneity found in five out of the six studies is also a call for stronger organisation among conducted RCTs. It is therefore tempting to suggest that trial investigators examining similar fields should meet before they design outcomes and covariates in RCTs. The idea of cooperative networks among trials may lead to common recordings of variables and some outcomes in studies in the same area. Moreover, it is also a hope that such networks might reduce missing numbers, as investigators get an extra chance to reflect on the weaknesses and strengths of their future measurements. Eventually, meta-analysis will have a greater opportunity to generate robust evidence, if RCTs have more congruent designs.

5.5. Aspirin and statins

Aspirin and statins are widely used in the secondary prevention of CAD. Nevertheless, unmet evidence remains in the subset of CAD patients with HF. Reasons for this may be that the underlying pathology of HF is different from isolated CAD. Moreover, it is unknown whether aspirin and statins interact on the outcome of all-cause mortality in patients with HF.

5.5.1 Average treatment effects

The average treatment effect assessment of aspirin adjusted by comorbidities, invasive and pharmacological therapy on discharge, epidemiological variables and year of the EMMACE study was convincing. Significant risk of death differences were observed at 6, 12 and 90 months' follow-up, spanning from 10 to 12%. Congruent to aspirin, statins showed a significant risk difference in death, varying from 5% to 14% at follow-ups between one and 24 months.

A stronger effect on mortality was shown through the combination of both statin and aspirin prescription on discharge compared to neither drug. During one- to 90-month follow-up, the treatment effects varied between 10 and 27 percentage points on mortality. Taking into account missing values in the EMMACE studies, the databases showed neutral effects of aspirin and statins on mortality. However, the results were largely flawed by the incompatibility in Stata between the propensity model and multiple imputations, which meant that the latter were impossible to effect. Paradoxically, multiple imputations reduced the number of patients who could be compared as the propensity score changed. The overall caveat by using multiple imputations was that the propensity score method and the imputation programme had to be carried out manually, compared to the Cox proportional hazard regression method in which all imputed numbers are integrated automatically, which makes it feasible to repeat a larger set of imputations.

5.5.2 Aims, objectives and questions

The aim of Chapter 4, which tried to establish the impact of aspirin and statins on the HF subset of the EMMACE-I and II, was successful. In contrast to experimental designs, this observational design found both aspirin and statins to improve the survival. The secondary

objective, to assess the combined impact of aspirin and statins, also suggested that both drugs used together improved mortality significantly, at least with an additive effect. The other secondary objective assessing the unadjusted impacts of aspirin and statins also highlighted that both drugs are independent statistical markers of mortality. The answer to the pre-specified research question – asking whether aspirin and/or statins were useful in HF patients with known CAD – was that they should both be recommended during hospital admission or in general, as soon they are experienced.

5.5.3 Implications

Full compliance with aspirin and statins are the main implications of these results taken from the EMMACE studies. Their significant associations with the improved outcome of all-cause mortality support this recommendation. Nevertheless, for improved survival, the EMMACE studies did not examine whether the side-effects of aspirin and statins play an important role in the long-term follow-up of patients with HF. How the drugs are tolerated in HF patients therefore remains unknown.

The impact on health policy is more neutral, as aspirin and statins are already recommended according to the leading guidelines for patients with CAD(274). However, results from the EMMACE studies may enlighten health authorities and encourage them to provide research grants in order to investigate the effect of aspirin and statins more thoroughly. It would be relevant, for instance, to increase knowledge about the LVEF, NT-proBNP, echocardiographic measurements such as longitudinal strain and the HF subgroup of HF-PEF in patients prescribed aspirin and statins compared with those who do not receive the drugs.

The combination of aspirin and statins in the same research design, through a factorial RCT similar to the study by Kawut et al., which enrolled patients with pulmonary hypertension, should also be undertaken in patients with HF(252). Although, the first study was neutral in its measurement of 6-MWT outcomes, this factorial design has not been investigated in HF patients. Such stratification demands more courage among researchers, as the majority of the HF population are diagnosed with underlying CAD compared with patients with pulmonary hypertension, which is idiopathic(275). Standing against conduction of a factorial design in HF patients with CAD is particularly the patient group allocated to none of aspirin and statins.

Clinicians should prescribe aspirin and statins to patients with HF and CAD unless they are known to have obvious contraindications. Despite these results from the EMMACE studies,

supporting the use of aspirin and statins in patients with HF, it still remains unclear as to whether patients with HF but no CAD benefit from both drugs as a form of secondary prevention.

II. Conclusion

Interventions supported by incomplete evidence in the secondary prevention of HF were investigated in this thesis, beginning with a cardiac event leading to HF. The primary objectives of long-term mortality, hospital admission and functional capacity were associated with CR referral, exercise-based CR and aspirin and statin treatment. The majority of patients included in the analyses had CAD, so they could therefore be categorised predominantly to the HF-REF phenotype, which limits the generalisability of the thesis's findings to other HF phenotypes.

The first step on a HF patient's journey was CR referral. The observational EMMACE-I and II studies suggested only in 2003 that CR referral improved survival significantly. The results were not only robust for the entire cohort suffering from MI, but also in the HF subgroups. Patient selection for CR referral was shown in both EMMACE decades. In general, patients were overlooked for CR referral if they exhibited high risk factors or comorbidities. However, a vast amount of missing values associated with CR referral in the EMMACE-I study made it difficult to outline statistical predictors for CR referral. In contrast to 1995, CR referral data were almost complete in 2003, indicating a growing interest in the area. Furthermore, HF became an independent positive predictor of CR referral in the EMMACE-II study. Despite the fact that the EMMACE results were at least a decade old, they suggested a great challenge to health professionals in order to secure CR referral and the adherence of HF patients and other fragile patients with cardiovascular disease.

The second step on the HF journey after CR referral is ideally attendance on an exercise-based CR programme. Similar to the HF-ACTION study and most meta-analyses in HF patients, exercise training (ET) did not improve survival chances, although the meta-analysis of this thesis was indirectly adjusted to the modern era of medicine. Conversely, the outcomes of hospital admission and four separate exercise capacities were all significantly improved in HF patients after ET. These results were breaking news in similar meta-analysis, as they have not established exercise-based CR reducing hospital admissions or improving exercise capacities over a minimum of a six-month follow-up(8, 10). Based on the positive results, and

according to the existing literature, adherence to ET in the studies included in the meta-analyses is satisfactory(276). Following closer examination, the minimum exercise adherence (mean) was estimated at 66%. Exercise adherence could be the key to interpreting the outcomes of exercise programmes for HF patients. The standardisation of exercise adherence through leading cardiovascular societies and regular publications would ease the assessment of exercise studies. However, an attempt has already been initiated in this respect(277).

An apparent caveat associated with the meta-analyses was heterogeneity in the significant outcomes. Furthermore, the selection of younger men in the respective analyses' studies was highlighted. In an attempt to delineate any variations in effect sizes, meta-regressions were examined between baseline characteristics and separate outcomes. Intriguingly, IHD was significantly associated with improved outcomes in PVO_2 and hospital admission. Regarding the latter, the significant association between the increasing LVEF and reduced hospital admission enforced this link. IHD was therefore associated with a better exercise outcome, which has also been reported conversely in the past. Finally, consecutive sensitivity tests encompassing one-year mortality and subgroup analyses of HF-REF and mixed patient populations of HF and CAD patients did not change the significance of the outcomes. Therefore, the results of these meta-analyses strongly underscore the importance of implementing exercise-based CR as an integrated component in HF treatment. Furthermore, it is doubtful whether the mortality endpoint is relevant for the HF population when we take into account the significance of other outcomes associated with exercise. Ultimately, an attempt to reduce heterogeneity should be undertaken through cooperative networks organising outcomes and covariates in similar fields of cardiovascular disease.

Aspirin and statin prescriptions were the last step in the HF journey, with indistinct evidence in this thesis. The EMMACE studies were similar to CR referral examined for aspirin and statin prescriptions on discharge for MI. Only HF patients were followed up for the common endpoint of 90 months. In contrast to the already conducted RCTs investigating aspirin and statins separately, the observational design of the EMMACE studies revealed aspirin and statins to be beneficial for long-term survival. These benefits were even stronger when the composite effects of the drugs were compared to the outcome for just one of them. These observational upshots advocate for an experimental factorial design of aspirin and statin treatment in HF patients. Until now this strategy has only been ventured in patients with pulmonary hypertension, suggesting that statins impair the primary outcome of the 6-MWT (252). Obstacles to conducting an RCT randomising HF patients to statins, aspirin and a placebo appear to be ethical. It is more than likely that hesitancy regarding withholding aspirin and statins in HF patients with concomitant CAD will come to the fore. This final

challenge, to establish the use of aspirin and statins in HF patients, may succeed if interim analyses are calculated closely after randomisation. The alternative is to continue prescribing aspirin and statins to HF patients, which may be harmful for a much larger proportion of the population.

Appendices

Chapter 2

Appendix 2.1. Syntaxes used in Stata for CR referral

Baseline

```
tabulate reh_miss year if mi == 1, chi2

tabulate Rehab year if mi == 1, chi2

kwallis age if mi == 1, by(year)

tabulate SEX year if mi == 1, chi2

tabulate Smoking year if mi == 1, chi2

tabulate Hypertension year if mi == 1, chi2

tabulate diabetes year if mi == 1, chi2

tabulate COPD year if mi == 1, chi2

tabulate hf year if mi == 1, chi2

tabulate hyp_lipid year if mi == 1, chi2

tabulate IHD year if mi == 1, chi2

tabulate CVA year if mi == 1, chi2

kwallis SystolicBP if mi == 1, by(year)

kwallis HeartRate if mi == 1, by(year)

kwallis p_6_1 if mi == 1, by(year)

kwallis prop_1 if mi == 1, by(year)
```

tabulate stemi year if mi == 1, chi2

tabulate killip_class year if mi == 1, chi2

tabulate card_arrest year if mi == 1, chi2

tabulate reperfusion year if mi == 1, chi2

tabulate revascularisation year if mi == 1, chi2

tabulate admis_cardio year if mi == 1, chi2

tabulate anti_platelet year if mi == 1, chi2

tabulate statin year if mi == 1, chi2

tabulate ace_i year if mi == 1, chi2

tabulate beta_blocker year if mi == 1, chi2

ltable time status if mi == 1, by(year) failure

csi 634 441 1371 1611, or

Logistic regression

1995

logistic Rehab COPD SEX revascularisation reperfusion diabetes anti_platelet beta_blocker ace_i statin hf p_6 admis_cardio age if year == 1995 & mi == 1

estat gof, group(10)

2003

logistic Rehab COPD SEX revascularisation reperfusion diabetes anti_platelet beta_blocker ace_i statin hf p_6 admis_cardio age if year == 2003 & mi == 1

estat gof, group(10)

Survival

1995

stcox Rehab prop SEX revascularisation reperfusion diabetes anti_platelet beta_blocker ace_i statin COPD hf admis_cardio age if mi == 1 & year == 1995

2003

stcox Rehab prop SEX revascularisation reperfusion diabetes anti_platelet beta_blocker ace_i statin COPD hf admis_cardio age if mi == 1 & year == 2003

stset time, failure(status) enter(time 3) exit(time 90)

stcox Rehab prop SEX revascularisation reperfusion diabetes anti_platelet beta_blocker ace_i statin COPD hf admis_cardio age if mi == 1 & year == 2003

Post-estimations

Martingales residuals (linearity) used for age

stcox if mi == 1 & year == 1995, efron estimate

predict mg if mi == 1 & year == 1995, mgale

lowess mg age if mi == 1 & year == 1995

Goodness-of-fit tests (proportionality)

linktest

stphplot, by(Rehab)

stphplot, by(SEX)

stphplot, by(revascularisation)

stphplot, by(reperfusion)

stphplot, by(diabetes)

stphplot, by(anti_platelet)

stphplot, by(beta_blocker)

stphplot, by(ace_i)

stphplot, by(statin)

stphplot, by(COPD)

stphplot, by(hf)

stphplot, by(admis_cardio)

Variance of inflation factors(VIF)

Rehab did not show convincing fit above.

regress Rehab prop SEX revascularisation reperfusion diabetes anti_platelet beta_blocker ace_i statin COPD hf admis_cardio age if mi == 1 & year == 1995

estat vif (but not multicollinarity)

Multiple imputations

1995

stset time, failure(status) exit(time 90)

mi set mlong

mi misstable sum

sts generate cumhaz=na

mi register imputed prop Rehab revascularisation diabetes anti_platelet beta_blocker

ace_i statin COPD hf admis_cardio age

mi register regular cumhaz status SEX reperfusion

mi impute chained (regress) age prop (logit) revascularisation diabetes anti_platelet beta_blocker ace_i statin COPD hf admis_cardio = cumhaz status SEX reperfusion, add(10) augment

mi estimate, dots: stcox Rehab SEX revascularisation reperfusion diabetes anti_platelet beta_blocker ace_i statin COPD hf admis_cardio agemi estimate, dots: stcox Rehab prop SEX revascularisation reperfusion diabetes anti_platelet beta_blocker ace_i statin COPD hf admis_cardio age

Chapter 3

Appendix 3.1. Search terms in Medline

1. exp HEART DISEASE/
2. (MYOCARD$5 adj (ISCHAEMI$ or ISCHEMI$2)).ab,ti.
3. ((ISCHAEMI$2 or ISCHEMI$2) adj HEART).ab,ti.
4. CORONARY.ab,ti.
5. exp MYOCARDIAL REVASCULARISATION/
6. (MYOCARD$5 adj INFARCT$5).ab,ti.
7. (HEART adj INFARCT$5).ab,ti.
8. ANGINA.ab,ti.
9. exp HEART FAILURE CONGESTIVE/
10. (HEART adj FAILURE).ab,ti.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. (HEART adj DISEASE$2).ab,ti.
13. MYOCARD$5.ab,ti.
14. CARDIAC$2.ab,ti.
15. CABG.ab,ti.
16. PTCA.ab,ti.
17. (STENT$4 and (HEART or CARDIAC$4)).ab,ti.
18. Heart Bypass, Left/
19. exp HEART BYPASS RIGHT/
20. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. exp REHABILITATION CENTERS/
22. exp REHABILITATION/
23. exp SPORTS/
24. Physical Exertion/
25. exp EXERCISE/
26. REHABILITAT$5.ab,ti.
27. (PHYSICAL$4 adj (FIT or FITNESS or TRAIN$5 or THERAP$5 or ACTIVIT$5)).ab,ti.
28. (TRAIN$5 adj (STRENGTH$3 or AEROBIC or EXERCISE$4)).ab,ti.
29. ((EXERCISE$4 or FITNESS) adj (TREATMENT or INTERVENT$4 or PROGRAM$2 or THERAPY)).ab,ti.
30. Patient Education as Topic/
31. (PATIENT$2 adj EDUCAT$4).ab,ti.

32. ((LIFESTYLE or LIFESTYLE) adj (INTERVENT$5 or PROGRAM$2 or TREATMENT$2)).ab,ti.
33. Self Care/
34. (SELF adj (MANAGE$5 or CARE or MOTIVAT$5)).ab,ti.
35. exp AMBULATORY CARE/
36. or/21-35
37. 11 or 20
38. 36 and 37
39. Randomised Controlled Trials as Topic/
40. RANDOMISED CONTROLLED TRIAL.ab,ti.
41. CONTROLLED CLINICAL TRIAL.ab,ti.
42. Controlled Clinical Trial/
43. Random Allocation/
44. Double-Blind Method/
45. Single-Blind Method/
46. (RANDOM$ or PLACEBO$).ab,ti.
47. ((SINGL$3 or DOUBL$3 or TRIPL$3 or TREBL$3) adj (BLIND$3 or MASK$3)).ab,ti.
48. exp RESEARCH DESIGN/
49. CLINICAL TRIAL.pt.
50. exp CLINICAL TRIAL/
51. (CLINIC$3 adj TRIAL$2).ab,ti.
52. 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
53. 38 and 52
54. exp ANIMALS/ not HUMANS/
55. 53 not 54
56. limit 55 to yr="1999 -Current

Appendix 3.2. Risk of bias

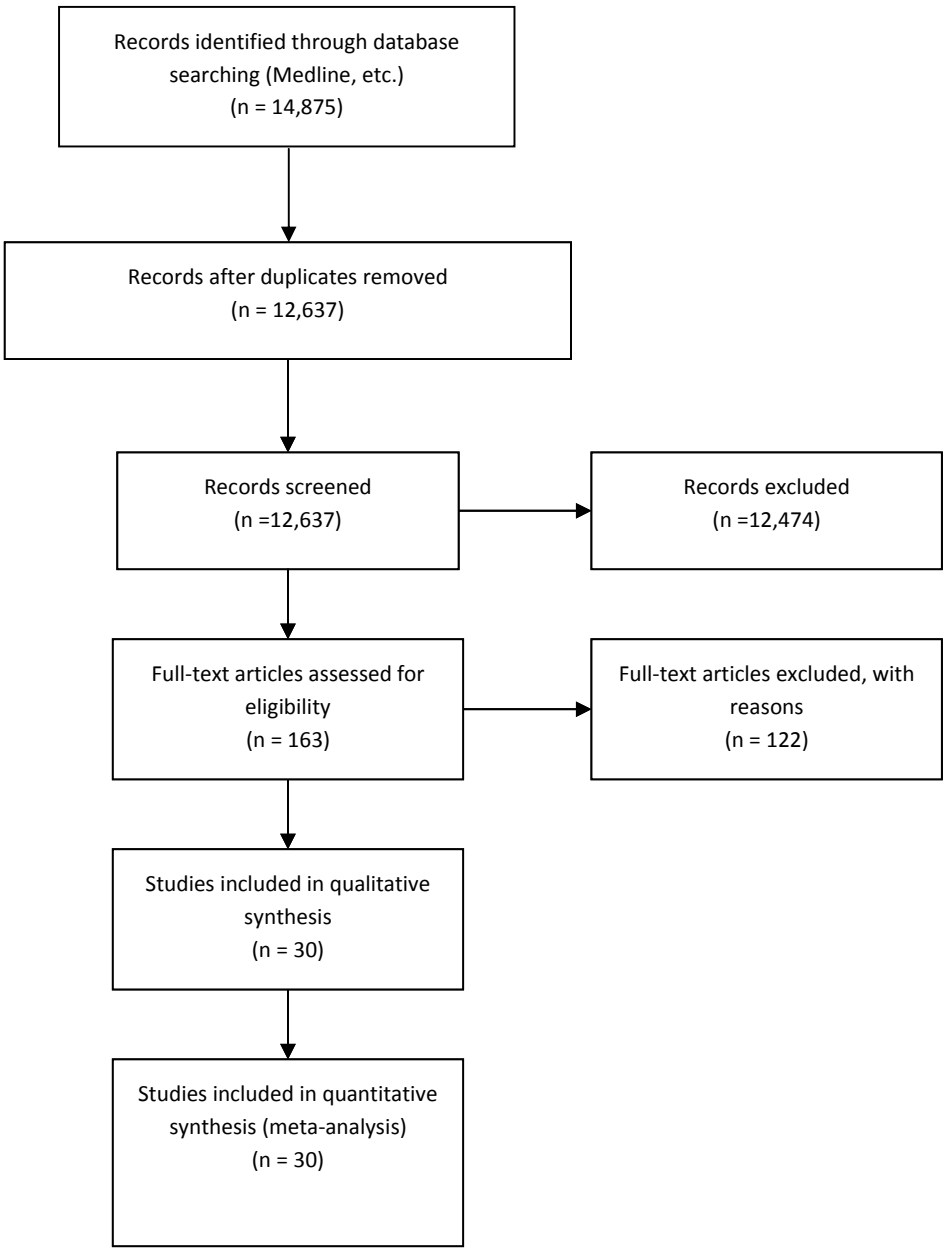
Study name (year)	Adequate sequence generation	Allocation concealment	Blinding (exercise capacity)	Blinding (mortality and readmission)	Incomplete outcome data addressed (exercise capacity)	Incomplete outcome addressed (mortality and readmission)	Free of selective reporting	Free of other bias
1. Muller (2009)	+	?	+	+	+	+	-	?
2. Passino (2006)	?	?	?	n.a.	+	n.a.	+	-
3. Dracup (2007)	?	?	?	?	+	+	+	-
4. Belardinelli (1999)	?	?	?	+	+	+	+	+
5. Kateyian (1999)	?	?	?	?	+	+	?	-
6. Senden (2005)	?	?	?	n.a.	+	n.a.	?	?
7. Koukouvou (2004)	?	?	+	n.a.	+	n.a.	+	-
8. Gottlieb (1999)	?	?	?	?	+	+	+	?
9. Vasiliauskas (2007)	?	?	+	+	+	+	?	?

10. Myers (2000)	?	?	?	?	+	+	+	+
11. Giannuzzi (2003)	+	?	?	?	+	+	+	?
12. Sabelis (2004)	?	?	?	n.a.	+	n.a.	?	?
13. Evangelista (2006)	-	?	?	?	+	+	-	+
14. Beer (2008)	?	?	+	n.a.	+	n.a.	+	?
15. Hambrecht (2000)	+	?	?	?	+	+	-	?
16. Giallauria (2009)	?	?	?	n.a.	+	n.a.	+	?
17. Nilsson (2008)	+	?	?	?	+	+	+	+
18. Prescott (2009)	+	+	?	?	+	+	+	+
19. Austin (2005)	+	+	+	?	?	?	+	+
20. Jolly (2009)	+	?	-	-	+	+	+	-
21. McKelvie (2002)	+	?	?	?	+	+	?	?
22. Witham (2005)	+	+	+	+	+	+	+	?
23. Austin (2008)	+	+	+	?	?	?	+	+
24. Davidsons (2010)	+	+	+	+	+	+	+	-
25. Mueller (2007)	+	?	?	?	?	?	+	?
26. Jonsdottir (2005)	?	?	n.a.	?	n.a.	+	+	+

27. O'Connor (2009)	+	+	+	+	+	+	+	+
28. Willenheimer (2001)	?	?	+	+	+	+	+	-
29. Pozehl (2008)	?	?	?	?	?	?	+	-
30. Giallauria(2008)	?	?	?	?	?	?	+	+

+, low risk of bias; ?, unclear ; -, high risk of bias ; n.a., not applicable

Appendix 3.3. PRISMA 2009 Flow Diagram of the data search



Appendix 3.4. Inclusion of studies with partially documented HF populations

Primary objectives of exercise capacities	
Endpoint	WMD, complete follow- up (95% [CI])
PVO_2	3.10 (2.21- 3.98)*
Exercise time	2.72 (1.74-3.70)*
6-MWT	37.39 (-0.49- 75.28)¶
Exercise power- watt	17.86 (12.90- 22.83)*
Secondary objectives of mortality and hospital admission*	
Mortality- RR ratio	0.88 (0.77- 1.01)
Hospital admission- RR ratio	0.67 (0.58- 0.78)*

¶ $P \leq 0.05$; § $P \leq 0.01$;* $P < 0.001$; PVO_2: peak oxygen uptake; 6-MWT: six-minute walk test; RR: risk ratio; WMD: weighted mean difference; 95% CI: 95% Confidence interval.

Appendix 3.5. Outcomes adjusted by length of follow-up period and HF subtype

Primary objectives of exercise capacities			
Endpoint	WMD, ≤ 1 year (95% [CI])	WMD, complete follow- up (95% [CI])	HF-REF only
PVO_2-MWD (ml/kg/min)	3.53 (2.34- 4.72)*	3.47 (2.56- 4.39)*	3.27 (2.35-4.19)*
Exercise time-WMD (minutes)	3.65 (2.24- 5.06)*	2.96 (1.83- 4.09)*	3.20 (1.94-4.47)*
6- MWT-WMD (metres)	59.73 (21.93- 97.52)§	41.58 (5.00- 78.17)¶	42.54 (5.22-79.86)¶
Exercise power-WMD (watts)	23.47 (15.50- 31.43)*	20.51 (13.88- 27.15)*	21.85 (14.39-29.32)*
Secondary objectives of mortality and hospital admission*			
Mortality- RR ratio	0.95 (0.63- 1.42)	0.89 (0.78- 1.03)	0.91 (0.79-1.05)
Hospital admission- RR ratio	0.69 (0.53- 0.91)§	0.73 (0.58- 0.91)§	0.72 (0.54-0.95)¶

WMD, Weighted mean difference; RR: relative risk; 95% CI: 95% Confidence interval; HF-REF: Heart failure with reduced ejection fraction; ¶ $P \leq 0.05$; § $P \leq 0.01$;* $P < 0.001$; PVO_2: peak oxygen uptake; 6-MWT: six-minute walk test.

Appendix 3.6. Syntaxes used in Stata for the meta-analysis

Mortality

Baseline characteristics

sum age_met [weight = _SS] if n != 3 & n != 7 & n != 11 & n != 18 & n != 20 & n != 22

(analytic weights assumed)

sum women_ratio [weight = _SS] if n != 3 & n != 7 & n != 11 & n != 18 & n != 20 & n != 22

(analytic weights assumed)

sum ihd_11_ratio [weight = _SS] if n != 3 & n != 7 & n != 11 & n != 18 & n != 20 & n != 22

(analytic weights assumed)

sum _ss1 [weight = _SS] if n != 3 & n != 7 & n != 11 & n != 18 & n != 20 & n != 22

(analytic weights assumed)

sum in_hosp_recruit [weight = _SS] if sensitivity == 0

(analytic weights assumed)

sum comprehensive [weight = _SS] if n != 3 & n != 7 & n != 11 & n != 18 & n != 20 & n != 22

(analytic weights assumed)

sum follow_up_time [weight = _SS] if n != 3 & n != 7 & n != 11 & n != 18 & n != 20 & n != 22

(analytic weights assumed)

sum exe_dur [weight = _SS] if n != 3 & n != 7 & n != 11 & n != 18 & n != 20 & n != 22

(analytic weights assumed)

sum exercise_duration_months [weight = _SS] if n != 3 & n != 7 & n != 11 & n != 18 & n != 20 & n != 22

(analytic weights assumed)

```
sum freq [weight = _SS] if n != 3 & n != 7 & n != 11 & n != 18 & n != 20 & n != 22
(analytic weights assumed)
sum comb_aer_res [weight = _SS] if n != 3 & n != 7 & n != 11 & n != 18 & n != 20 & n != 22
(analytic weights assumed)
sum adherence [weight = sample_size] if n != 3 & n != 7 & n != 11 & n != 18 & n != 20 & n != 22
(analytic weights assumed)
sum NYHA_2_3 [weight = _SS] if sensitivity == 0
(analytic weights assumed)
sum lvef_met [weight = _SS] if n != 3 & n != 7 & n != 11 & n != 18 & n != 20 & n != 22
(analytic weights assumed)
sum acei_ratio [weight = _SS] if n != 3 & n != 7 & n != 11 & n != 17 & n != 18 & n != 20 & n
>  != 22
(analytic weights assumed)
sum bb_ratio [weight = _SS] if n != 3 & n != 7 & n != 11 & n != 18 & n != 20 & n != 22
(analytic weights assumed)
sum digoxin_ratio [weight = _SS] if n != 3 & n != 7 & n != 11 & n != 18 & n != 20 & n != 22
(analytic weights assumed)
sum antip_ratio [weight = _SS] if n != 3 & n != 7 & n != 11 & n != 18 & n != 20 & n != 22
(analytic weights assumed)
sum statin_ratio [weight = _SS] if n != 3 & n != 7 & n != 11 & n != 18 & n != 20 & n != 22
(analytic weights assumed)
sum diur_ratio [weight = _SS] if n != 3 & n != 7 & n != 11 & n != 18 & n != 20 & n != 22
(analytic weights assumed)
```

Forest plot

metan event_exp_1 non_event_exp event_con_1 non_event_cont if n != 3 & n != 7 & n != 11 & n != 18 & n != 20 & n != 22, lcols(study_name) counts texts(135) xlabel(0.005, 0.01, 0.02, 0.04, 0.08, 0.16, 0.32, 0.64, 1, 2, 4, 8, 16, 32, 64, 128)

Galbraith plot

galbr b _selogES if n != 3 & n != 7 & n != 11 & n != 18 & n != 20 & n != 22, id(ID) yline(0) xlabel(0 (2) 12)

Funnel plot

metafunnel b _selogES if n != 3 & n != 7 & n != 11 & n != 18 & n != 20 & n != 22, mlabel(ID) xtitle("RR ratio") xlabel(-3 (1) 3) xtick(-3 (1) 3)

note: default data input format (theta, se_theta) assumed

PVO_2

Baseline

sum age [weight = sample_size] if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & & n != 24 & n != 25 & n != 26

(analytic weights assumed)

sum wom_ratio [weight = sample_size] if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25 & n != 26

(analytic weights assumed)

sum IHD_RATIO [weight = _SS] if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25 & n != 26

(analytic weights assumed)

sum _SS [weight = _SS] if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25 & n != 26

(analytic weights assumed)

sum recruit_inhosp [weight = _SS] if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25

(analytic weights assumed)

sum comprehensive [weight = _SS] if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25

(analytic weights assumed)

sum follow_up_time [weight = _SS] if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25

(analytic weights assumed)

sum exercise_duration_months [weight = _SS] if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25

(analytic weights assumed)

sum more_than_two_ex [weight = _SS] if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n ! = 25

(analytic weights assumed)

sum aerobstrength [weight = _SS] if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25

(analytic weights assumed)

sum adherence [weight = _SS] if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25

(analytic weights assumed)

sum PVO2_base [weight = _SS] if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25

(analytic weights assumed)

sum NYHA_II_III [weight = _SS] if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25

(analytic weights assumed)

sum LVEF [weight = _SS] if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25

(analytic weights assumed)

sum acei_ratio [weight = _SS] if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25

(analytic weights assumed)

sum bb_ratio [weight = _SS] if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25

(analytic weights assumed)

sum antip_ratio [weight = _SS] if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25

(analytic weights assumed)

sum statin_ratio [weight = _SS] if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25

(analytic weights assumed)

sum diuretics_ratio [weight = _SS] if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25

(analytic weights assumed)

Forest plot

metan sample_size_exp mean_vo2_exp s_2 sample_size_cont mean_vo2_cont s_4 if n != 4 & n != 6 & n != 8 & n != 10 & n!= 12 & n != 24 & n != 25, favours(Control # Exercise) lcols(study_name) random nostandard xlabel(-15, -10, -5, 0, 5, 10, 15)

Meta-regression

metareg _ES age if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25, wsse(_seES)

metareg _ES wom_ratio if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25, wsse(_seES)

metareg _ES IHD_RATIO if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25, wsse(_seES)

metareg _ES _SS if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25, wsse(seES)

metareg _ES comprehensive if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25, wsse(_seES)

metareg _ES follow_up_time if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25, wsse(_seES)

metareg _ES exercise_duration_months if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25, wsse(_seES)

metareg _ES more_than_two_ex if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25, wsse(_seES)

metareg _ES aerobstrength if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25, wsse(_seES)

metareg _ES adherence if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25, wsse(_se ES)

metareg _ES PVO2_base if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25, wsse(_se> ES)

metareg _ES NYHA_II_III if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25, wsse(seES)

metareg _ES LVEF if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25, wsse(_seES)

metareg _ES acei_ratio if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25, wsse(_seES)

metareg _ES bb_ratio if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25, wsse(_seES)

metareg _ES statin_ratio if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25, wsse(seES)

metareg _ES diuretics_ratio if n != 4 & n != 6 & n != 8 & n != 10 & n != 12 & n != 24 & n != 25, wsse(_seES)

Galbraith

galbr _ES _seES if n != 4 & n != 6 & n != 8 & n != 9 & n != 12 & n != 24 & n != 25, id(n)

Funnel plot

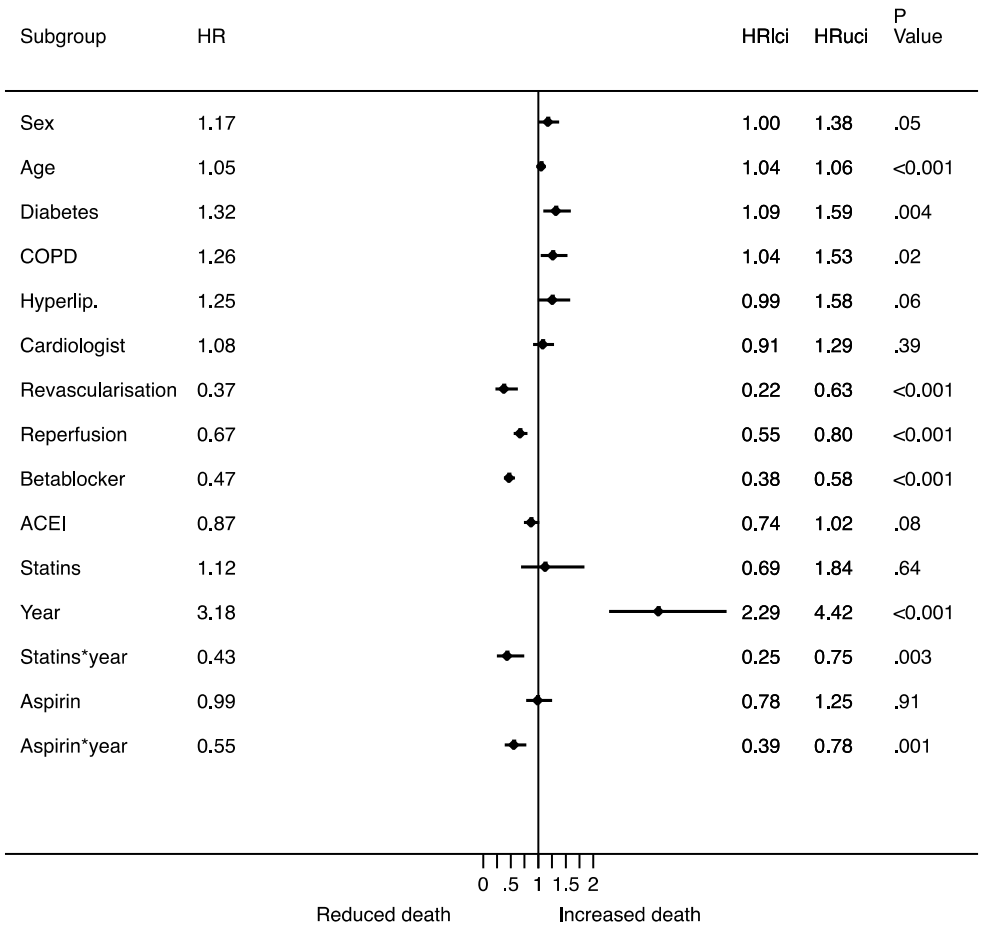
metafunnel _ES _seES if n != 4 & n != 6 & n != 8 & n != 9 & n != 12 & n != 24 & n != 25, mlabel(n)

xtitle("RR ratio") xlabel(0 (2) 8) xtick(0 (2) 8)

note: default data input format (theta, se_theta) assumed

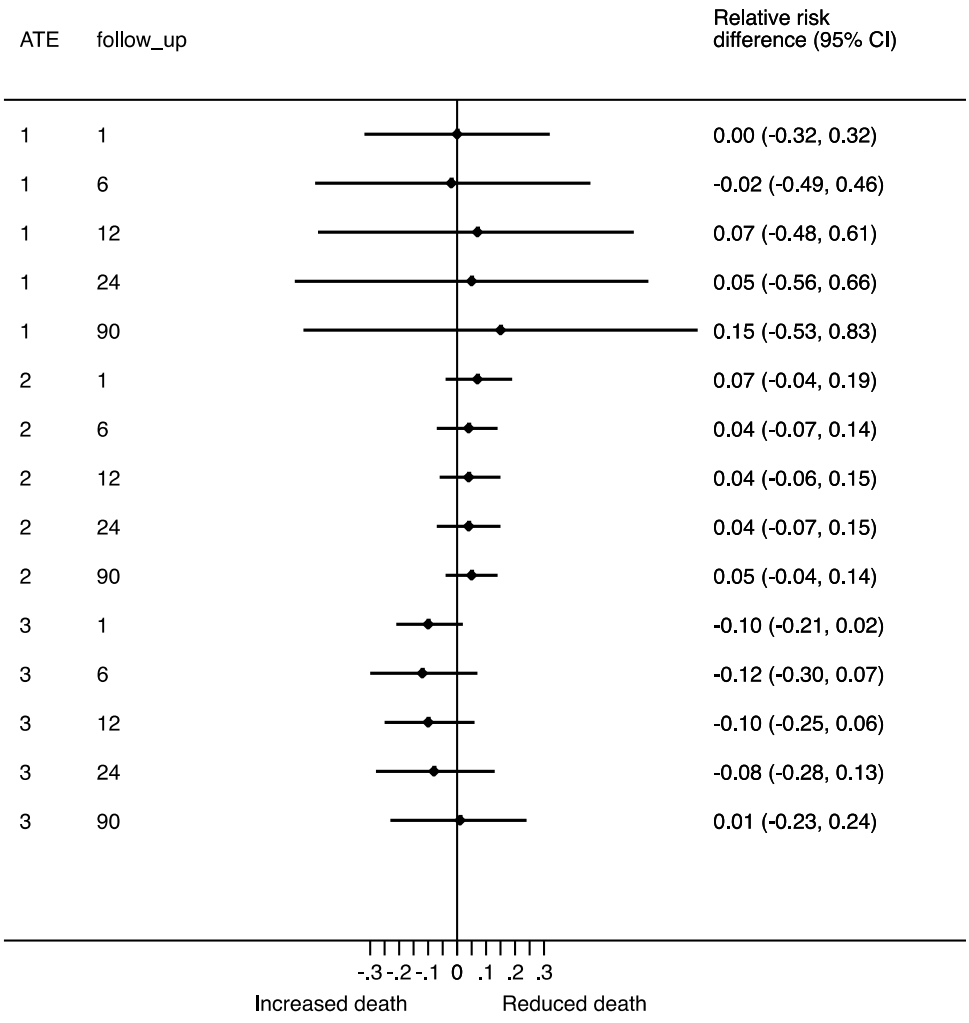
Chapter 4

Appendix 4.1. Cox's regression investigation the interaction between aspirin, statins and the year of the EMMACE studies.



HR: hazard ratio; HRlci: lower limit of the 95% confidence interval; HRUci: Upper limit of the 95% confidence interval; COPD: Chronic obstructive pulmonary disease; ACE-I: Angiotensin-converting enzyme;

Appendix 4.2. ATE (mortality) deduced from propensity matching and adjusted for missing values by multiple imputations.



ATE I, aspirin and statins; ATE II aspirin; ATE III, statins. ATE (the average treatment effect) was measured as risk difference; The ATE was measured in relative risk differences; Follow-up was measured in months.

Appendix 4.3. Syntaxes used in Stata for the propensity-score analysis assessing the average treatment effects of aspirin and statins

Aspirin

```
stset time, failure(status) exit(time 1)

attnd _d aspirin, pscore(pscore_asp) boot reps(100) dots

stset time, failure(status) exit(time 6)

attnd _d aspirin, pscore(pscore_asp) boot reps(100) dots

stset time, failure(status) exit(time 12)

attnd _d aspirin, pscore(pscore_asp) boot reps(100) dots

stset time, failure(status) exit(time 24)

attnd _d aspirin, pscore(pscore_asp) boot reps(100) dots

stset time, failure(status) exit(time 90)

attnd _d aspirin, pscore(pscore_asp) boot reps(100) dots
```

Statins

```
stset time, failure(status) exit(time 1)

attnd _d statin, pscore(pscore_stat) boot reps(100) dots

stset time, failure(status) exit(time 6)

attnd _d statin, pscore(pscore_stat) boot reps(100) dots

stset time, failure(status) exit(time 12)

attnd _d statin, pscore(pscore_asp) boot reps(100) dots

stset time, failure(status) exit(time 24)
```

attnd _d statin, pscore(pscore_asp) boot reps(100) dots

stset time, failure(status) exit(time 90)

attnd _d statin, pscore(pscore_asp) boot reps(100) dots

Both

stset time, failure(status) exit(time 1)

attnd _d group_11 if group_22 != 1, pscore(pscore_stat) boot reps(100) dots

stset time, failure(status) exit(time 6)

attnd _d group_11 if group_22 != 1, pscore(pscore_stat) boot reps(100) dots

stset time, failure(status) exit(time 12)

attnd _d group_11 if group_22 != 1, pscore(pscore_asp) boot reps(100) dots

stset time, failure(status) exit(time 24)

attnd _d group_11 if group_22 != 1, pscore(pscore_asp) boot reps(100) dots

stset time, failure(status) exit(time 90)

attnd _d group_11 if group_22 != 1, pscore(pscore_asp) boot reps(100) dots

Multiple imputations

mi stset time, failure(status) exit(time 1)

attnd _d statin if _mi_m == 5, pscore(pscore_sta_mi) boot reps(100) dots

mi stset time, failure(status) exit(time 6)

attnd _d statin if _mi_m == 5, pscore(pscore_sta_mi) boot reps(100) dots

mi stset time, failure(status) exit(time 12)

attnd _d statin if _mi_m == 5, pscore(pscore_sta_mi) boot reps(100) dots

mi stset time, failure(status) exit(time 24)

attnd _d statin if _mi_m == 5, pscore(pscore_sta_mi) boot reps(100) dots

mi stset time, failure(status) exit(time 90)

attnd _d statin if _mi_m == 5, pscore(pscore_sta_mi) boot reps(100) dots

Example of forest plot

metan RRR_prop_match RRR_L_CI RRR_U_CI, lcols(ATE follow_up) sortby(follow_up) double nohet nowt favours(Treatment reduced death # Treatment increased death) xlabel(-0.35, -0.25, -0.15, -0.05, 0, 0.05, 0.15, 0.25, 0.35) xtick(-0.30, -0.20, -0.10, 0.10, 0.20, 0.30) effect(Relative risk reduction)

Abbreviations

6-MWT	**6-minute walk test**
ACE-I	**Angiotensin converting enzyme inhibitors**
ACS	**Acute coronary syndrome**
AF	**Atrial Fibrillation**
AHA	**American heart association**
AIDS	**Acquired Immunodeficiency Disease Syndrome**
ARB	**Angiotensin Receptor Blockers**
ARD	**Absolute Risk Difference**
ARVC	**Arrythmogenic Right Ventricular Cardiomyopathy**
ATE	**The average treatment effect of the treated**
BBB	**Bundle Branch Block**
BMI	**Body Mass Index**
BMJ	**British Medical Journal**
BNP	**B-type brain natriuretic peptide**
BP	**Blood pressure**
CABG	**Coronary Artery Bypass Graft**
CACHE	**Clopidogrel Versus Aspirin in Chronic Heart Failure**
CAD	**Coronary artery disease**
CK-MB	**Creatinine Kinase-Myocardial Band**
CI	**Confidence interval**
CNS	**Central Nervous System**
COPD	**Chronic Obstructive Pulmonary Disease**
CE	**Cost Effectiveness**
CEA	**Cost Effectiveness Analysis**
CR	**Cardiac Rehabilitation**
CRT	**Cardiac Resynchronization Therapy**
CVA	**Cerebral Vascular Accidents**
CVD	**Cardiovascular disease**
CVD	**Cerebrovascular disease**
CUA	**Cost Utility Analyses**
DCM	**Dilated Cardiomyopathy**
DF	**Degrees of Freedom**
ECG	**Electrocardiography**
EMMACE	**Evaluation of Method and Management of Acute Coronary Events**

EPO	**Erythropoietin**
ESC	**European Society of Cardiology**
ET	**Exercise training**
GDF	**Growth differentiating factor**
GDP	**General Domestic Product**
GFR	**Glomerular Filtration Rate**
GRACE	**Global Registry of Acute Coronary Events**
GP	**General Practitioner**
HADS	**Hospital And Depression Scale**
HbA1	**Glycated Haemoglobin**
HCM	**Hypertrophic Cardiomyopathy**
HF	**Heart failure**
H-ISDN	**Hydralazide and Isosorbide Dinitrate**
HF-PEF	**Heart failure with preserved ejection fraction**
HF-REF	**Heart failure with reduced ejection fraction**
HDL	**High density lipoprotein**
H-FABP	**Heat fatty acid-binding proteins**
HR	**Heart rate**
HR	**Hazard ratio**
HRQoL	**Health Related Quality of Life**
HTX	**Heart Transplanted**
I^2	**Heterogeneity index**
ICD	**Implantable Cardioverter-Defibrillator**
ICE	**Imputation by Chained Equations**
ICM	**Ischemic Cardiomyopathy**
IHD	**Ischemic Heart Disease**
IQR	**Inter Quartile Range**
KM	**Kilometres**
LDL	**Low Density Lipoprotein**
LVEF	**Left Ventricular Ejection Fraction**
LVH	**Left Ventricular Hypertrophy**
LVSD	**Left Ventricular Systolic Dysfunction**
NSTEMI	**Non ST (segment)-elevation myocardial infarction**
MAR	**Missing AT Random**
MCAR	**Missing Completely at Random**
MI	**Myocardial infarction**
MI	**Multiple Imputations**

MINAP	**Myocardial Ischemia National Audit Project**
MK	**Multiple Knot**
MLWHF	**Minnesota Living With HF**
MNAR	**Missing Not at Random**
MRI	**Magnetic resonance images**
MYBP3	**Myosin Binding Protein C3**
MYH7	**Myosin Heavy Chain 7**
MVN	**Multivariate Normalisation**
NACR	**National Audit of Cardiac Rehabilitation**
NHS	**National Health Service**
NO	**Nitrogen Oxide**
OR	**Odds ratio**
PCI	**Percutaneous Coronary Intervention**
PhD	**Doctor of Philosophy**
RAAS	**Renin Angiotensin Aldosterone System**
RD	**Risk difference**
RCM	**Restrictive Cardiomyopathy**
RCT	**Randomised controlled trials**
ROS	**Reactive oxygen species**
RR	**Relative Risk**
PSA	**Prostate serum antigen**
PPCM	**Peripartum Cardiomyopathy**
PTCA	**Percutaneous Transluminal Coronary Angiography**
PVO_2	**Peak Oxygen Consumption**
QoL	**Quality of Life**
QULY	**Quality Adjusted Life Years**
SD	**Standard Deviation**
SE	**Standard Error**
SBP	**Systolic Blood Pressure**
SR	**Sinus Rhythm**
STEMI	**ST elevation myocardial infarction**
TAVI	**Transcatheter aortic valve implantation**
TDZ	**Thiazolidinedione**
TRACE	**Trandolapril Cardiac Evaluation**
UK	**United Kingdom**
US	**United States**
VEGF	**Vascular endothelial growth factor**

VIF	**Variance of Inflation**
VT	**Ventricular Tachycardia**
VT	**Ventilatory threshold**
WMD	**Weighted Mean Difference**

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