Heart failure epidemiology:
Evidence on incidence, management and outcomes

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A thesis submitted for the degree of

Doctor of Philosophy

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To my father, who has instilled in me the love of science, mathematics and problem solving.

To my children, my husband, and all my family. Thank you for your never-failing patience, love and support.

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ABSTRACT

Background: Heart failure is one of the most common, costly, and deadly medical conditions, and its prevention and management present a challenge to health systems worldwide.

Objectives: This thesis aims to investigate the epidemiology of heart failure in a large, representative general population cohort, so as to establish a solid decision basis for public health and service delivery policies in the United Kingdom and other high-income countries.

Methods: Three studies were conducted to investigate temporal trends and patterns of (i) heart failure incidence and prevalence, as well as (ii) the delivery of care and (iii) health outcomes among newly diagnosed heart failure patients. Analyses relied on data from the Clinical Practice Research Datalink (CPRD), which contains anonymised electronic health record information from primary care, secondary care, and death certificates, for a representative sample of the UK population.

Results: Analyses of incidence and prevalence showed that, despite a modest decline in age-sex-standardised incidence from 2002 to 2014, the absolute number of individuals with newly diagnosed heart failure increased by 12%, largely due to an increase in population size and age. The absolute number of prevalent heart failure cases increased even more strongly, by 23%. Socio-economically deprived individuals were 61% more likely to develop heart failure and did so 3.5 years earlier in life than those from the most affluent group. The study of patients' trajectories of care following incident heart failure further revealed important gaps in care that affected screening, continuity of care, and medication titration. Outpatient diagnoses and follow-up after hospital discharge in primary care declined substantially (ranging from 56% in 2002 to 36% in 2014, and 20% to 14%, respectively). Moreover, although primary care referral for diagnostic investigations and appropriate initiation of essential drugs increased significantly, the average daily dose prescribed remained below guideline recommendations and was largely unchanged beyond the first 30 days after diagnosis. Finally, investigations of patients' health status one year after heart failure diagnosis, revealed novel evidence explaining the standstill in mortality rates observed in many high-income countries since the mid 2000s. A decline in cardiovascular mortality (rate ratio comparing 2013 with 2002: 0.73 [0.67, 0.80]) was offset by an increase in non-cardiovascular deaths (rate ratio comparing 2013 with 2002: 1.22 [1.11, 1.33]), that was largely explained by an increase in respiratory conditions and infections. As a result, at the end of the study period (2013), non-cardiovascular causes accounted for the majority of deaths and hospitalisations. Moreover, at same age and sex, patients from deprived socioeconomic backgrounds were 21% more likely to die within one year of diagnosis than those from affluent backgrounds.

Conclusions: These findings have important implications for clinical practice, health policy and future research. Most importantly, results highlight the need to address socioeconomic disparities that affect disease incidence and outcomes; and call for increased efforts to improve the coordination of care among health settings and specialities so as to ensure continuity of care and more effective management of comorbidities associated with heart failure.

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LIST OF ABBREVIATIONS

ACE	Angiotensin converting enzyme
ACE-I	Angiotensin converting enzyme inhibitor
ARB	Angiotensin receptor blocker
CALIBER	ClinicAl disease research using LInked Bespoke studies and Electronic health Records
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
CVD	Cardiovascular diseases
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EHR	Electronic health record
ESC	European Society of Cardiology
GIS	Geographic information systems
GP	General practitioner or General practice
HES	Hospital Episode Statistics
HF	Heart failure
HF-PEF	Heart failure with preserved ejection fraction
HF-REF	Heart failure with reduced ejection fraction
HF-UNS	Heart failure with preserved or unspecified ejection fraction
ICD	International Classification of Diseases and Health-Related Problems
IMD	Index of Multiple Deprivation
IRR	Incidence rate ratio
ISAC	Independent Scientific Advisory Committee of the CPRD
LVEF	Left ventricular ejection fraction
MHRA	Medicines and Healthcare products Regulatory Agency
MRA	Mineralocorticoid receptor antagonist
NHFA	National Heart Failure Audit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NP	Natriuretic peptide
ONS	Office for National Statistics
QOF	Quality and Outcomes Framework
RR	Rate ratio
SBP	Systolic blood pressure
SES	Socioeconomic status
UK	United Kingdom
US	United States of America
WHO	World Health Organization

1. INTRODUCTION

1.1 Motivation

Heart failure is one of the most common, costly, disabling, and deadly medical conditions encountered in primary and secondary care, and its prevention and management present a challenge to health systems worldwide.[1–3] Several recent observational studies have reported little or no improvements in mortality rates among heart failure patients since the mid 2000s, despite the introduction of a range of life-saving treatments.[1,4] The reasons underlying these trends are unclear, and could potentially be due to changes in patient characteristics, insufficient adherence to evidence-based care or specific patterns affecting mortality. I set out to review the state-of-the-art evidence on heart failure epidemiology, and have designed my thesis research to address gaps in knowledge that could help explain the observed standstill in patient prognosis.

1.2 Aims of the thesis

This doctoral thesis aims to investigate the epidemiology of heart failure in a large and representative general population cohort and to establish a solid decision basis for public health and service delivery policies in the United Kingdom (UK) and other high-income countries.

To this end, my research addresses the following three objectives:

(i) to describe the incidence and prevalence of heart failure, and investigate its variation over time and by important patient features such as age, sex, socioeconomic status, and region;

(ii) to examine the clinical care received by heart failure patients, in particular provider-adherence to guideline-recommended diagnostic tests and medicines;

(iii) to investigate health outcomes that affect patients newly diagnosed with heart failure, specifically all-cause and cause-specific hospitalisations and deaths.

1.3 Structure of the thesis

To achieve these goals, significant preparatory work was necessary. First, I performed an in-depth review of the scientific literature describing the epidemiology of heart failure. This step has allowed me to synthesise state-of-the-art evidence, delineate gaps in knowledge and refine my research objectives. I present the key components of this review in Chapter 2. Second, I researched potential sources of data to address my research objectives, and selected the Clinical Practice Research Datalink (CPRD), which contains anonymised electronic health record information from primary care, secondary care, and death certificates, for a representative sample of the UK population.[5] The reasons that have led to this decision are described in Chapter 3. Third, I researched published literature and consulted with experts to define disease phenotypes (i.e. a set of diagnostic codes that can be used to identify patients with a given condition in the studied datasets) for heart failure and a range of comorbid conditions, and then extracted, cleaned and converted the data into a format appropriate for analysis. I present the details of these methodological considerations in Chapter 4.

Building up on this solid foundation, I completed three analytical studies. Temporal trends and patterns of heart failure incidence and prevalence are described in Chapter 5. Trajectories of care in patients with heart failure and the analysis of diagnostic tests, drug prescriptions and follow-up patterns are presented in Chapter 6. Finally, the Chapter 7 reports findings relating to cause-specific mortality and morbidity following a new diagnosis of heart failure. A synthesis of results and overall implications for policy and research are discussed in Chapter 8.

2. BACKGROUND

2.1 Heart failure

2.1.1 Clinical definition of heart failure

Clinically, heart failure (HF) is defined as a syndrome characterised by symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures.[6] HF can have a number of causes, including amongst others damaged heart tissue due to myocardial infarction, valve disease, or high blood pressure.[7] In younger age groups, viruses causing an inflammation of the heart muscle or dilated cardiomyopathy (an enlarged and weakened left ventricle) are amongst the prevalent causes of HF.[8]

HF is divided into sub-types based on measurement of Left ventricular ejection fraction (LVEF), a measure of the amount of blood that is pumped out of the left ventricle as a percentage of the amount of blood entering the ventricle. LVEF is usually assessed using echocardiography, a radionuclide technique or cardiac magnetic resonance, and typically ranges from 50% to 70% in healthy adults. Two sub-types of heart failure are most commonly used: (i) HF with reduced ejection fraction (HF-REF), generally considered as LVEF < 40%, and also known as left ventricular HF or systolic HF, and (ii) HF with preserved EF, typically defined as LVEF >=50%, sometimes also referred to as diastolic HF. Patients with an LVEF in the range of 40–49% represent a 'grey area', which the latest guidelines from the European Society of Cardiology define as HF with mid-range ejection fraction.[6] Depending on the exact sub-type of HF, patients present with different underlying aetiologies, demographics, comorbidities and also respond differently to treatments.[9]

Heart failure is further described as chronic when patients have relatively stable symptoms of breathlessness, fatigue and ankle swelling, or acute, when the symptoms become severe and the

patient usually requires admission to hospital. However, in many cases deterioration occurs gradually over several weeks before hospital admission and the typical course of chronic heart failure is punctuated by periods of acute or sub-acute decompensation.[7]

2.1.2 Diagnosis

Clinical examination: An initial HF assessment is based on a detailed evaluation of a patient's signs, symptoms and their history of cardiovascular disease. Symptoms and signs are often unspecific and difficult to identify, particularly in obese individuals, elderly and patients with chronic lung disease, but HF is unusual in individuals with no relevant medical history (e.g. a potential cause of cardiac damage).[6] An electrocardiogram (ECG) can sometimes be used to complete the clinical assessment. An abnormal ECG increases the likelihood of the diagnosis of HF, but has low specificity, so that the routine use of an ECG is mainly recommended to rule out HF.[6]

Natriuretic peptides: If at least one element of the patient's clinical examination is abnormal, plasma concentration of natriuretic peptides (NPs) can be used as an initial diagnostic test, especially in non-acute settings or when echocardiography is not immediately available. Natriuretic peptides are produced as a result of pressure changes in the heart and their concentration is raised in patients with HF.[6,10] Elevated NPs help establish an initial working diagnosis and identify those who require further cardiac investigation. In patients with normal plasma NP concentrations a diagnosis is generally ruled out.[6]

Cardiac imaging: Echocardiography is the most useful and widely available test in patients with suspected HF to establish the diagnosis. It provides immediate information on chamber volumes, ventricular systolic and diastolic function, wall thickness, valve function and pulmonary hypertension. This information is crucial in establishing the diagnosis and in determining appropriate treatment.[6]

The information provided by careful clinical evaluation and the above-mentioned tests will permit an initial working diagnosis and treatment plan in most patients. Other tests are generally

required only if the diagnosis remains uncertain (e.g. if echocardiographic images are suboptimal or an unusual cause of HF is suspected).[6]

2.1.3 Management

For HF and reduced left-ventricular systolic function, several treatments exist, largely relying on drug therapy, and their effectiveness has been demonstrated by a large number of randomised controlled trials.[6,11] Clinical guidelines recommend the prescription of angiotensin converting enzyme (ACE) inhibitors, or angiotensin receptor blockers (ARBs) in patients intolerant to ACE-inhibitors, as well as beta blockers. Mineralocorticoid receptor antagonists (MRAs) are also recommended in patients who remain symptomatic despite treatment with an ACE-inhibitors and beta-blocker.[6,12,13] Medicines are to be initiated at low dose and regularly uptitrated up to a target dose under consideration of the maximal dose tolerated by the patient. Further medicines recommended for the management of heart failure and reduced ejection fraction include Ivabradine in patients with an elevated heart rate, or Digoxin in symptomatic patients in sinus rhythm. Diuretics can also be used to improve symptoms and exercise capacity in patients with signs or symptoms of congestion.[6] A recently developed drug combination, Sacubitril/valsartan, has been shown to be superior to ACE-inhibitors in reducing the risk of death and of hospitalisation. Since 2016, guidelines from the European Society of Cardiology recommend that physicians replace ACE-inhibitors with Sacubitril/valsartan in ambulatory patients who remain symptomatic despite optimal therapy.[6] Under specific indications, implantable cardioverter-defibrillator and cardiac resynchronisation therapy have the potential to further reduce morbidity and mortality.[6]

By contrast, for heart failure with preserved systolic function, no treatment has yet been shown, convincingly, to reduce morbidity or mortality. In these patients, therapy essentially aims to alleviate symptoms, improve well-being, and target the underlying causes of heart failure or comorbidities (e.g. hypertension or atrial fibrillation).[6,11]

2.1.4 Comorbidities

Heart failure does not occur in isolation. It is caused by an underlying cardiac defect, generally in elderly individuals, many of whom are being treated for other medical problems.[11] Consequently, many patients with heart failure have comorbidity related to the underlying cardiac problem or its cause (e.g. angina, hypertension, diabetes, smoking-related lung disease) and age (e.g. osteoarthritis), as well as a consequence of heart failure (e.g. arrhythmias) and its treatment (e.g. gout from diuretics).[11] Multimorbidity creates further challenges for the management of heart failure, such as possible drug intolerances (e.g. ACE-inhibitors and renal dysfunction) or drug interactions (e.g. non- steroidal anti-inflammatory drugs and ACE inhibitors).[11,14–18] Alongside heart failure pathophysiological processes and age, multimorbidity is a major determinant of patient prognosis.[11]

2.2 Prior evidence on incidence and prevalence

In the past 20 years, heart failure has been regularly singled out as an epidemic and a major public health problem in high-income countries.[1,19–21] Despite the very large number of studies investigating and discussing the epidemiology of heart failure, underlying determinants of this epidemic remain poorly understood. It is unclear for example what share of the increasing number of patients with heart failure is due to changes in the incidence of the disease, ageing populations, or increased survival; or how different sub-groups of patients contribute to the overall burden. Yet delineating the respective responsibility of each of these factors is essential to understand disease epidemiology and to define adequate public health and service delivery planning.

I sought to establish a synopsis of prior evidence on the incidence and prevalence of heart failure. Starting with incidence, I searched Pubmed for reports published from 1 January 2000 to 30 April 2017 that included “heart failure” and “incidence” in their title, reviewed references of clinical practice guidelines and consulted with experts for relevant studies. I found that estimates of heart failure incidence rates, trends over time, and association with patient features were scarce and inconsistent. Studies frequently referred to restricted populations or to

limited data sources, either from general practice consultations or hospitalisations. Hospitalisation statistics are event based, as opposed to person based, and hence unable to distinguish between first and subsequent admissions, so that incidence cannot be derived from such data.[21] In an attempt to compare reports of heart failure incidence, I selected a subset of studies that (i) referred to a community-based cohort, (ii) included outpatient diagnoses in their case identification, (iii) presented incident rates in the general population (all ages and sexes), and (iv) considered all sub-types of heart failure. I found that reports differed greatly in their approach to age-standardisation - some studies presented crude rates within the population of interest,[20,22] others standardised rates to the census populations within the country and year of interest,[1,23,24] or simply adjusted trends over time for differences in the denominator population.[25,26] Very few studies referred to an independent and internationally available population structure, such as the European Standard Population.[27] As a result, comparisons amongst studies was challenging and reported incidence rates varied tenfold across studies – from 60 to 650 per 100,000 person-years at risk (**table 2.1**). In addition, I found that long-term trends on incident heart failure in the general population by important features such as age or socioeconomic status to be rarely reported; and found no study that investigated how individual factors, such as changes in the population's age distribution, contributed to a change in the overall burden of heart failure.

I found data on prevalence to be more commonly reported, albeit almost exclusively for high-income countries. Studies generally report between 1% and 2% of the adult population to have heart failure.[21,26,28–30] The burden of heart failure is disproportionately distributed among the elderly. Over half of patients hospitalised with heart failure are aged >75 years.[31] The prevalence of heart failure generally doubles for each decade of life, and the prevalence is <1% for those aged <40 years, and >10% for those aged >80 years.[26,30] The lifetime risk of developing heart failure is approximately 20% between the ages of 40 and 80 years for both men and women.[32,33] The prevalence of heart failure in high income countries is projected to increase steeply over time. The ageing of the population, together with improved survival among patients with heart failure due to the advancement in treatments and diagnostic technology are likely to be major

drivers for the projected increased.[34] One study has notably projected that, due to the demographic changes alone (i.e. assuming stable prevalence by age and sex), the prevalence of heart failure in the USA will increase by 46% to >8 million people (2.97%) in 2030.[35] Although decreasing incidence rates have recently been reported in some countries, it is unclear whether prevention measures will be sufficient to contain the increasing burden on health services. In addition to this, the risk factors are multifactorial and complex and prevention essentially relies on treatment of the risk factors, such as hypertension, diabetes and obesity.[34]

Table 2.1: Selected studies reporting heart failure incidence in the general population

Study	Country	Time Period	Population	Size	Design	Case Identification	Case Definition	Reported Incidence Rate/100,000 Person-years			Comments
								All (Trend)	Men (Trend)	Women (Trend)	
Levy 2002 (Framingham)[25]	US	1950–1969	General Population	10,311 subjects	Prospective cohort	Population based screening, including physical examination, electrocardiography, and review of hospital records, physicians' records, and pathology reports.	Framingham heart failure diagnosis criteria	-	627	420	The study uses a prospectively collected population cohort and validated diagnoses. The number of cases is comparatively small.
		1970–1979							563 (↔)	311 (↓)	
		1980–1989							536 (↔)	298 (↓)	
		1990–1999							564 (↔)	327 (↓)	
Roger 2004 (Olmsted County)[23]	US	1979-1984	General Population	4,537 HF cases	Prospective cohort	Outpatient and hospital discharge records	Clinical diagnosis codes, validated by Framingham criteria on a subset	-	360	284	The study uses a county-wide cohort and partly validated diagnoses. The number of cases is comparatively small.
		1985-1990							390 (↔)	292 (↔)	
		1991-1995							375 (↔)	260 (↔)	
		1996-2000							383 (↔)	315 (↔)	
Gerber 2015 (Olmsted County)[1]	US	2000	General Population	2,762 HF cases	Prospective cohort	Outpatient and hospital discharge records	Clinical diagnosis codes, validated by Framingham criteria on a subset	316	Graphical (↓)	Graphical (↓)	The study uses a county-wide cohort, partly validated diagnoses, and distinguishes between preserved and reduced ejection fraction. The number of cases is comparatively small.
		2010						219 (↓)			
Ezekowitz 2011 (Canada)[24]	Canada	2000	General Population	82,323 HF cases	Retrospective longitudinal cohort	GP, specialist, and hospital discharge records	Clinical diagnosis codes	538	-	-	The study focuses on incidence trends by place of diagnosis (e.g. emergency department vs. outpatient). Incidence rates are not stratified by sex or age-group.
		2006						403 (↓)			

Study	Country	Time Period	Population	Size	Design	Case Identification	Case Definition	Reported Incidence Rate/100,000 Person-years			Comments
								All (Trend)	Men (Trend)	Women (Trend)	
Zarrinkoub 2013 (Sweden)[26]	Sweden	2006 2010	General Population	2,056,173 subjects	Retrospective longitudinal cohort	GP, specialist, and hospital discharge records	Clinical diagnosis codes	-	390 290 (🡻)	360 290 (🡻)	The study presents incidence rates and trends by sex and age group in a large general population cohort. Considerations for changes in the denominator size over time and their impact on incidence rates are not presented.
Hawkins 2012 (CPRD 2007)[36]	UK	1999 2007	General Population	12,412 HF cases 13,330 HF cases	Retrospective longitudinal cohort	GP records	Clinical diagnosis codes	200 60 (🡻)	-	-	The study presents stratification by socioeconomic quintiles and incidence rates are standardised to the European Standard Population. Cases are identified based on primary, but not secondary, care records.
Cowie 1999 (Hillingdon)[22]	UK	1996	General Population > 25y	101,885 subjects	Prospective cohort	GP and hospital referrals	Clinical assessment, electrocardiography, chest radiography and transthoracic echocardiography	130 (O)	140 (O)	120 (O)	One of the first community-based heart failure incidence studies. The number of cases is comparatively small. This study does not report temporal trends within the cohort.
Murphy 2004 (Scotland)[30]	UK (Scotland)	1999-2000	General Population	307,741 subjects	Cross-sectional cohort	GP records	Clinical diagnosis codes associated with a ''first'' modifier	200 (O)	180 (O)	220 (O)	Cases are identified based on primary, but not secondary, care records. Age-standardised rates or temporal trends are not reported.
Gomez-Soto 2011 (Spain)[37]	Spain	2000 2007	General Population >=14	267,231 subjects	Prospective cohort	Diagnosis by GP or hospital admission	Framingham criteria	296 390 (🡹)	306 400 (🡹)	286 380 (🡹)	The study reports crude rates. Age-standardised rates are not reported.

***Abbreviations**: HF = Heart Failure HF, GP = General Practice, UK= United Kingdom, US = United States of America, ESC = European Society of Cardiology.*

*Trends: 🡸🡺 indicates stable trend, 🡻 indicates declining trend, and **O** indicates trends are not reported*

2.3 Prior evidence on clinical practice gaps

Effective heart failure management involves a complex process of investigations, step-wise initiation of medicines, and dose-titration, that often takes place in different care settings over several months, and can be difficult to implement consistently. Diagnostic and therapeutic guidelines have been progressively introduced seeking to improve evidence-based heart failure management,[6,12,38–42] and provide a valuable tool to support physicians. Nevertheless, ensuring optimal use of evidence-based therapies in routine clinical practice remains a major concern and challenge to health services worldwide.[2,3]

In the UK, the majority of heart failure care is carried out or coordinated by primary care services, with regular input from specialist cardiology professionals - either from outpatient consultations or during hospitalisations. Two major programs have been introduced to improve physicians' adherence to evidence-based practices: the 'quality and outcomes framework' (QOF),[43] a healthcare reporting and incentives scheme that applies to primary care physicians and was initiated in 2004; and the 'national heart failure audit' (NHFA),[7] a large-scale reporting scheme for secondary care launched in 2007. Each scheme individually produces yearly reports on selected heart failure care indicators and present very high rates of adherence to clinical guidelines.[44,45] Yet, these programs only consider the clinical setting for which they were designed and have not assessed their broader impact on patient care across the continuum of primary and secondary services, which chronic conditions, such as heart failure, rely on.

To synthesise contemporary evidence on the evaluation of clinical care in patients with heart failure more generally, I searched Pubmed for reports published from 1 January 2005 to 30 October 2017 that included "heart failure", "guideline" and "adherence" in their title, reviewed references of clinical practice guidelines and consulted with experts for relevant studies.

I found numerous registry and observational cohort studies that investigated care delivery in patients with heart failure. Most studies presented single-point-in-time measures, such as treatment plan at the time of registry enrolment, or were restricted to secondary care settings, which do not allow longitudinal assessment of chronic disease management across the

continuum of care. To compare reports of physicians' adherence to guidelines for the diagnosis and management of chronic heart failure, I selected observational studies that (i) referred to European or north American cohorts, (ii) considered outpatient settings, and (iii) included at least 1,000 patients. I found that reports frequently focused on a single aspect of guidelines (mostly pharmacological treatment initiation). Only a few studies reviewed other aspects such as diagnostic tests or treatment titration, although these are essential components of clinical care guidelines. Moreover, studies generally assessed care indicators in prevalent heart failure cases, and had no ability to describe and compare patient trajectories following a new diagnosis of heart failure (**table 2.2**). Finally, little is known of variations in care practices by important patient characteristics, such as age, sex or socioeconomic status.

Understanding how health services adhere to evidence-based guidelines is important to guide public health policy and research, and effective service delivery policies need to consider the full spectrum of care, rather than selected indicators or individual care settings. Patient-centred assessments of care, covering a broad range of indicators and spanning across both in- and outpatient settings over several months following diagnosis, would support such efforts but are not available.

Table 2.2: Selected studies reporting on the delivery of care among patients with heart failure

Study name	Publication year	Country	Data collection period	Size	Design	Case identification	Assessment time points	Prevalent vs. incident cases	Type of heart failure	Main measures and results
BIOSTAT-CHF[46]	2017	11 European countries	2010-2012	2,100	Prospective registry	Inpatients or outpatient clinics	Three months following registry enrolment	Prevalent	HF-REF or HF with abnormal BNP levels	**Up-titration to target dose** (at 3 months) ACE-I or ARB (22%) Beta-blocker (12%)
QUALIFY[2]	2016	36 countries	2013-2014	7,092	Prospective registry	Inpatients or outpatient clinics	On registry enrolment	Prevalent	HF-REF	**Treatment prescription** (on enrolment) ACE-I (66%) | ARB (22%) Beta-blocker (87%) MRA (69%) Ivabradine (33%) **Up-titration to target dose** (on enrolment) ACE-I (28%) | ARB (7%) Beta-blocker (15%) MRA (71%) Ivabradine (27%)
ESC-HF-LT[47]	2016	21 European and/or Mediterranean countries	2011 - 2013	12 440	Prospective registry	Inpatients or outpatient clinics	On registry enrolment and at 1-year post enrolment	Prevalent	Any heart failure	**Treatment prescription** (on enrolment | at 1 year) ACE-I or ARB (89% | 87%) Beta-blocker (89% | 89%) MRA (59% | 59%) Diuretics (83% | 81%)
Austrian Heart Failure Registry[48]	2014	Austria	2006–2010	1,014	Prospective registry	Outpatient heart failure clinics	On registry enrolment and at 1-year post enrolment	Prevalent	HF-REF	**Treatment prescription** (on enrolment | at 1 year) ACE-I or ARB (91% | 92%) Beta-blocker at baseline (88% | 92%) MRA at baseline (43% | 39%) **Treatment up-titration** Patients achieving a dose of ≥50% of target dose for ACE-I/ARB and BB at one-year follow-up (64%)
QOF[44]	2014	England	2013-2014	405,202 (HF)	Retrospective population-based cohort	Primary care centres	Within -3 and +12 months of incident diagnosis	Incident	Any heart failure	**Diagnostic investigations** (within -3 and +12 months of diagnosis) Echocardiography or specialist assessment (95%)
				119,944 (HF-REF)			By financial year	Prevalent		**Treatment prescription** (yearly assessment) ACE-I or ARB (99%) Beta-blocker (93%)

Study name	Publication year	Country	Data collection period	Size	Design	Case identification	Assessment time points	Prevalent vs. incident cases	Type of heart failure	Main measures and results
Hawkins et al.[36]	2012	UK	1999-2007	13,330	Retrospective population-based cohort	Primary care centres	By calendar year	Prevalent	Any heart failure	**Treatment prescription** (in 2007) ACE-I or ARB (64%) Beta-blocker (41%) Spironolactone (20%)
HELUMA[49]	2010	Germany	2001-2007	3,292	Prospective registry	Outpatient cardiology clinics or hospital admissions	On registry enrolment	Prevalent	Chronic heart failure due to systolic dysfunction	**Treatment prescription** (on enrolment) ACE-I or ARB (87%) Beta-blocker (87%) MRA (49%) **Treatment dose** (% of target on enrolment) ACE-I or ARB (55%) Beta-blocker (56%)
Swedish Heart Failure Registry[50]	2009	Sweden	2004-2006	2,093	Retrospective registry	Primary care centres	On registry enrolment	Prevalent	Any heart failure, with pharmacological treatment for heart failure	**Diagnostic investigations** (on enrolment) Echocardiography (31%) **Treatment prescription** (on enrolment) ACE-I or ARB (74%) Beta-blocker (67%) **Up-titration >=50% of target dose** (on enrolment) ACE-I or ARB (37%) Beta-blocker (31%)
IMPROVE HF[15]	2008	US	2005-2007	15,381	Prospective registry	Outpatient clinics	On registry enrolment	Prevalent	HF-REF	**Treatment prescription** (on enrolment) ACE-I or ARB (80%) Beta-blocker (86%) MRA (36%) Anticoagulant (69%)
MAHLER[53]	2005	6 European countries	2001-2002	1,410	Prospective registry	Outpatient clinics	On registry enrolment and at 6-month post-enrolment	Prevalent	Any heart failure	**Treatment prescription** (at 6 months) ACE-I or ARB (85%) Diuretics (83%) Beta-blocker (58%) Spironolactone (36%) Glycosides (52%)

***Abbreviations**: HF = Heart failure; HF-REF = Heart failure and reduced ejection fraction; ACE-I = angiotensin-converting-enzyme inhibitor; ARB = angiotensin receptor blocker; MRA = Mineralocorticoid receptor antagonists, UK = United Kingdom, US = United States of America.*

2.4 Prior evidence on prognosis

Reliable and contemporary survival estimates are important for public health bodies to monitor trends in prognosis and to commission appropriate services. Insights into underlying patterns of morbidity and mortality may further support the development of more targeted public health strategies and generate hypotheses for additional interventions. At a patient level, these estimates allow informed discussions and shared decision making about treatment options and advanced care planning.[54] In the case of heart failure, the past 25 years have brought considerable improvements in patient care - new medicines and device therapies, as well as changes in the organisation of care such as specialist nurses have been introduced.[55–61] Although clinical trials have demonstrated the effectiveness of these treatments in reducing mortality, it is unclear how these advancements have affected patient outcomes in routine clinical settings.

To synthesise contemporary evidence on health outcomes in heart failure patients, I searched Pubmed for reports published from 1 January 2012 to 15 February 2019 that included “heart failure” and “mortality” in their title, reviewed references of clinical practice guidelines and consulted with experts for relevant studies.

Mortality risk steadily increases after a new diagnosis of heart failure. Based on the Framingham Heart Study, 30-day mortality is around 10%, 1-year mortality is 20–30%, and 5-year mortality is 45–60%.[25,62] Hospitalisation adversely impacts prognosis. A recent study from the UK among patients diagnosed in primary care settings reported one-year survival rates of 81.2% versus 68.8% in patients not admitted to hospital and admitted to hospital, respectively. Stewart and colleagues suggested that heart failure was more ‘malignant’ than cancer in a study of over 30,000 patients hospitalised for heart failure, myocardial infarction, or four common cancers in Scotland; with the exception of lung cancer, heart failure was associated with the worst 5-year adjusted mortality.[63] Numerous studies have also investigated mortality following a hospital admission for heart failure, a measure that is relevant for secondary care service planning but does not inform about the long-term course of the condition. For a chronic condition, such as heart failure, survival rates after initial diagnosis are more relevant to patients and policy makers.

In an attempt to compare various reports, I selected studies that reported 1-year mortality rates following a new diagnosis of heart failure and (i) referred to European or North American cohorts, (ii) included at least 1,000 patients, (iii) were not restricted to clinical trials, special care management programmes, certain age-groups or associated conditions, and (iv) reported trends over time. I found that 1-year mortality rates were substantially higher in hospitalised patients than in outpatients, were higher in men than women, but differed little between patients with reduced ejection fraction and those with preserved ejection fraction. As for temporal trends of mortality rates, I found those to be generally declining up to the mid-2000 years and stable thereafter, despite the introduction of new treatments, in particular beta-blockers, in the early 2000s (**table 2.3**).

Most studies confined investigations to all-cause mortality in heterogeneous cohorts, without investigating underlying patterns, such as changes by sub-group or cause-specific mortality. Only one study, from the Olmsted county cohort,[1] distinguished between cardiovascular and non-cardiovascular mortality and hospitalisations, yet was limited by its sample size and did not examine cause-specific outcomes by individual disease or disease cluster. In-depth analyses investigating how specific causes of morbidity and mortality and changes in patient characteristics contribute to overall trends may provide valuable clues for the development of more targeted therapies or public health strategies, but are not available.

Table 2.3: Selected studies reporting mortality rates following incident heart failure

Study	Country	Data collection period	Size	Design	Case identification	1-year mortality rates			Comments
						All (trend)	Stratified (trend)		
Taylor 2019[54]	UK	2000 2017	55,959	Retrospective cohort	General practice consultation	25.8% 19.2% (🡻)			The study reports modest improvements in survival (6.6% over 17 years).
Taylor 2017[4]	UK	1998-2012	54,313	Retrospective cohort	General practice consultation	18.7% (🡘)			The study presents crude mortality rates.
Gerber 2015 (Olmsted County)[1]	US	2000-2010	2,762	Prospective cohort	Outpatient and hospital discharge records	20.2% (🡘)	**CVD** 9% (🡘)	**Non-CVD** 11% (🡘)	The study reports temporal trends with no decline in mortality rates over time.
Yeung 2012[64]	Canada	1997 2007	419,551	Retrospective cohort	Outpatient and hospital discharge records	27% 25% (🡻)	**Inpatients** 36% 34% (🡘)	**Outpatients** 18% 16% (🡻)	Mortality rates presented are age-sex-standardised to the 1991 Ontario population aged > 20 years, and risk-adjusted to patients' comorbidity profiles.
Gomez-Soto 2011[37]	Spain	2000 2007	4,793	Prospective cohort	Diagnosis by GP or hospital admission	31%* 29%* (🡻)	**Men** 35% 34% (🡻)	**Women** 27% 24% (🡻)	Risk-adjusted mortality rates accounting for age at incidence, comorbidities, type of heart failure, and source of incident diagnosis (inpatient vs. outpatient).
Roger 2004 (Olmsted County)[23]	US	1979-1984 1985-1990 1991-1995 1996-2000	4,537	Prospective cohort	Outpatient and hospital discharge records	25%* 23%* 23%* 19%* (🡻)	**Men** 30% 26% 25% 21% (🡻)	**Women** 20% 19% 20% 17% (🡻)	Mortality estimates after onset of heart failure among men and women aged 75 years. Trends compare the last to the first reporting period.
Levy 2002 (Framingham)[25]	US	1950–1969 1970–1979 1980–1989 1990–1999	1,075	Prospective cohort	Population based screening	29%* 35%* 30%* 26%* (🡻)	**Men** 30% 41% 33% 28% (🡻)	**Women** 28% 28% 27% 24% (🡻)	Mortality rates presented refer to men and women aged 65 to 74 years, and are adjusted for age. Trends are adjusted for age, type of heart failure and comorbidities. Trends compare the last to the first reporting period.

***Abbreviations**: HF = Heart Failure, GP = General Practice, UK = United Kingdom, US = United States of America, CVD = Cardiovascular Disease. Trends: 🡘 indicates stable trend, 🡻 indicates declining trend, and O indicates trends are not reported. * Overall rates are not reported; To allow overall comparison, I present estimates as the average of men and women rates.*

3. DATA SOURCES

The research presented in this thesis has been carried out using electronic health records data from the Clinical Practice Research Datalink (CPRD) database. This chapter presents background information on electronic health records data and detailed information about the CPRD and linked data sources.

3.1 Electronic health records

Electronic health records (EHR) refer to a systematised collection of medical information from individual patients and providers, generally captured during a health care encounter, in a digital format.[65,66] They can contain various types of data, including structured data of prescriptions that includes dosages and dates captured in e-prescribing systems, to unstructured free-text in clinical notes.[66] Data that are captured in EHR systems are primarily intended to serve clinical and administrative purposes (e.g. quality of care monitoring).[66]

Electronic health records databases further represent a valuable source of information for research purposes, as they offer rich longitudinal health data on large geographically, socioeconomically, and culturally diverse populations at low-cost.[65] Major areas of population health EHR research so far have included re-evaluating prior findings; exploiting large sample sizes to analyse subgroups and to study rare diseases or multiple diseases simultaneously; social and environmental epidemiology; research on stigmatised conditions; predictive modelling; and exploiting natural experiments.[65]

Accessibility, functionality and research application of EHRs have increased markedly over the past decade. This increased use is partly in response to the increasing difficulties associated with traditional epidemiological methods (e.g. large-scale randomised controlled trials and prospective cohort studies), where cost, time, resources, and low response rates are key limiting factors .[65,67] EHRs represent a cost-effective way to conduct research on data that are already

collected in routine clinical encounters, incurring significantly less cost than prospective data collection, requiring less time to complete, involving larger and more generalisable populations, and having fewer limitations to follow-up (**table 3.1**).[65,68] EHR data can also be used alongside clinical trial data to provide a full clinical picture for the recruited patients.[5]

Major advantages of using EHR data for health research lie in very large sample sizes, long-term follow-up, and the richness of information they provide. EHR data that are made available for research purposes are generally automatically extracted and consolidated across large populations and several years of follow-up, allowing detailed analyses of associations and estimating risk associations with higher precision than would be possible when using data sources based on small sample sizes. This makes them particularly valuable for the study of rare exposures and diseases.[5] The largely unselected provision of data presents the further advantage that cohorts are representative of certain sub-groups of the population with specific attributes, e.g. US Medicare beneficiaries,[69] or even of national populations, as is the case with datasets from the UK or Denmark for example.[5,70] The breadth of information provided by EHR data is also of great interest, as it can contain the patient's entire health record, including diagnoses, tests and treatments, and provides data that are often not captured completely in traditional observational studies. Furthermore, data are often integrated across various health services (e.g. primary and secondary care), hence, provide fine-grained longitudinal health profiles, facilitating cohort-wide investigations and knowledge discovery on an unprecedented scale.[66,71] Longitudinal research is made possible by using the dates associated with specific EHR entries. Doing so allows researchers to study not only disease onset, but also disease severity and progression, so that EHR data are also an ideal data source to identify cases with chronic conditions that require ongoing care.[65] Although the quality of the data recorded will vary across data sources, practitioner-recorded data are generally considered more accurate and reliable than self-reported data.[65]

Despite the many benefits, the use of EHRs for epidemiology requires careful consideration of unique issues related to study population definition, population attrition, and disease/case definition.[65] Unlike standardised primary data collection in epidemiologic research, EHR data are

collected for the purposes of the clinical encounter. Rather than being driven by research needs, the data collected are directly influenced by patients' health status, by how and when they seek care, and by variation in physician care practices and documentation. Accordingly, the patient and physician, not the researcher, stipulate the amount of time a patient is under observation (person-time), which impacts calculation of prevalence, incidence, and risk ratios.[1] Reliable estimates of incidence rates must hence use data sources that provide a clear delimitation of patients' observation time, as is the case with some datasets from the UK, Denmark or the USA.[5,70,72] Consistency and quality of EHR data, including missing data, incorrect data, differences in recording of data over time, or differences within and between different practitioners present further challenges. There are, however, practical approaches to dealing with the disadvantages of EHRs. For example, imputation of EHR data, specifically blood pressure, cholesterol, body mass index, and smoking status, is a viable solution to use in cardiovascular risk prediction.[73] It has also been shown that case identification can be improved substantially by combining multiple EHR sources, or by using advanced algorithms and/or more specific diagnostic codes.[74,75] Finally, careful consideration must be given to the validity of diagnoses (for example, by performing or referring to independent validation studies) and to changes in care practices over time or by practice/region, by studying relevant guidelines or health system changes and by performing judicious sensitivity analyses.

This thesis aims to address important knowledge gaps in heart failure epidemiology that pertain to the disease's incidence and prevalence, its management in routine clinical practice, and its associated health outcomes (see section **1.2 'Aims of this thesis'**). Previous studies have relied on prospective cohorts (e.g. Framingham study)[25], registries (e.g. ESC registry)[47], as well as EHR data (e.g. Olmsted county study)[1], and have been limited by the size of the cohort, its representativeness and generalisability to other populations, the breadth of information available, and the ability to study long-term trends (see sections **2.2 'Prior evidence on incidence and prevalence'**, **2.3 'Prior evidence on clinical practice gaps'**, and **2.4 'Prior evidence on prognosis'**). To advance scientific knowledge in this field, my research relies not only on original analyses and high-quality work, but also on a rich dataset, with longitudinal information

about diagnoses, investigations, prescriptions, hospitalisations and mortality, from a large and representative patient population. After carefully considering various possible sources of data, such as prospectively collected cohorts and registries, EHR data appeared as the most appropriate data source that could provide the richness, breath and long-term perspective required for this study.

Table 3.1: Comparison of traditional and EHR epidemiology studies

Study feature	Traditional study	EHR study
Original purpose of data collection	Research; requires primary data collection.	Clinical care or administration; research relies on secondary data.
Cost	More expensive, primarily government-funded.	Less expensive; data collection primarily funded by health care system.
Common study design	Prospective cohort, nested case-control, cross-sectional.	Retrospective or prospective cohort, nested case-control; cross-sectional less common because longitudinal data are available.
Study population	Based on recruitment; may involve incentives or suffer from healthy volunteer effects; low response rate.	Based on patient use of a specific health system. Often very large number of participants. EHR data can also be used to pre-screen patients for eligibility. Various population designs are available, e.g. primary care patients, specialty cohorts.
Consent	Informed consent must be obtained before participant can be enrolled in the study	'Opt-out' models include all patients except those that specifically express their wish not to share data; whereas 'opt-in' models require participants to consent to share their clinical records.
Follow-up	Scheduled; continues as long as supported by funding, often with standardised timing between visits.	Occurs during health care encounters; in general, will have more unique encounters, with variable timing between visits.
Data collection and storage	Established protocol; generally robust approach to data collection; often with primary focus in one area of epidemiology with specialised measurements, e.g. exposure assessment, genetics; biosamples stored for future analysis.	Recorded during health care encounter with varying levels of detail based on provider practices; stored in clinical diagnoses, laboratory results, current medications and medication orders, problem list, and notes; biosamples rarely banked.
Conditions captured	Any outcomes and all severities as specified at the beginning of the study by investigators as long as ascertainment can be validly operationalised.	Only those outcomes requiring care by a physician; data missing on mild, self-resolving, or short-lived conditions.
Outcome ascertainment	Consistent outcome definitions, identified in the same way for each participant; investigators can specify in advance outcomes to study and how to measure.	Based on physician-specific clinical diagnosis, identified from a variety of locations in EHR, diagnosis enriched with other clinical information, e.g. laboratory tests, medications.
Covariate ascertainment	Prespecified variables.	Entire health record, tests, and treatments are available, but not random, and perhaps confounded by disease severity and other factors.
Community conditions e.g. social, built, and food environments	Measured with GIS, or sometimes by direct observation if a small number of communities are under study.	Sometimes assigned GIS-based indicator, generally for a large number of participants spanning large geographies. Sometimes patient-level socioeconomic factors captured as part of EHR (e.g. socioeconomic status linked to patient address)

Adapted from Casey et al.[65] Abbreviations: HER = electronic health record; GIS = geographic information systems.

3.2 The Clinical Practice Research Datalink and linked datasets

3.2.1 Background

The Clinical Practice Research Datalink (CPRD)

The CPRD is a research service supporting public health and clinical studies using electronic health records. CPRD is jointly sponsored by the Medicines and Healthcare products Regulatory Agency and the National Institute for Health Research, as part of the Department of Health and Social Care.[76] CPRD collects de-identified patient data from a network of primary care practices across the UK, alongside linkages to a range of other health related data sources.[76] The CPRD, previously called GPRD for General Practice Research Database, has evolved from an early general practice information system. Free computing equipment was supplied in return for standardised data recording and provision of patient-level data into a central database to be used for health research.[77,78] Over 30 years later this concept has developed into one of the largest and most utilised verified primary care database in the world.[5,78]

As of March 2019, the full CPRD database contained anonymised patient data from over 35 million individual patient records, with approximately 11 million actively registered patients.[76] The 'CPRD-GOLD' (herein referred to as CPRD) data are derived from 674 general practices that use the Vision electronic health record system software,[5,78] and covers approximately 7% of the current UK population. The data has been shown to be broadly representative of the UK population by age, sex and ethnicity, and has been validated for epidemiological research for a broad range of conditions.[5,79] The CPRD has recently released the 'CPRD-Aurum' database that is different from the 'CPRD-GOLD' data used in this thesis; 'CPRD-Aurum' contains data from the Egton Medical Information Systems electronic record system (EMIS-Web) software, and refers to different architecture, coding systems and patient cohorts than CPRD-GOLD.[80] The CPRD has been used in over 2,000 scientific publications,[76] including large observational studies on the association between blood pressure and cardiovascular disease,[81] the association between body-mass-index and cancer,[82] or to disprove the link between measles, mumps and rubella vaccination and autism.[83] The dataset has contributed to the exponential growth in the use of primary care databases in publications since the early 1990s.[84] The CPRD contains data on a wide

range of variables, including diagnoses, prescriptions, investigations and vaccinations.[76] As data are prospectively recorded as part of routine care, they are not subject to certain types of bias inherent in traditional observational studies, such as recall bias or non-response bias.[85]

The UK healthcare system

In the UK, healthcare is provided by the National Health Service (NHS) and is free at the point of delivery for all residents.[86] The system relies on general practitioners (GPs) as the cornerstone of medical care. GPs act as the first point of contact for any non-emergency health-related issue, provide primary healthcare and coordinate referrals to further services as necessary. Hospitals then provide specialist services, as well as direct access to Accident and Emergency (A&E) departments. Secondary care teams feedback information to GPs about their patients, including diagnoses and prescribed medications.[5] Community pharmacies are privately owned but have contracts with the relevant health service to supply prescription drugs. Over 98% of the UK population are registered with a primary care general practitioner (GP).[5] Patient data are routinely recorded onto computers by practice staff, against a unique patient NHS number.[5] Thus prospective follow up of individuals is possible via the healthcare records of the GP, and it is for this reason that primary care databases offer such opportunities for research.[78]

3.2.2 Structure of the CPRD

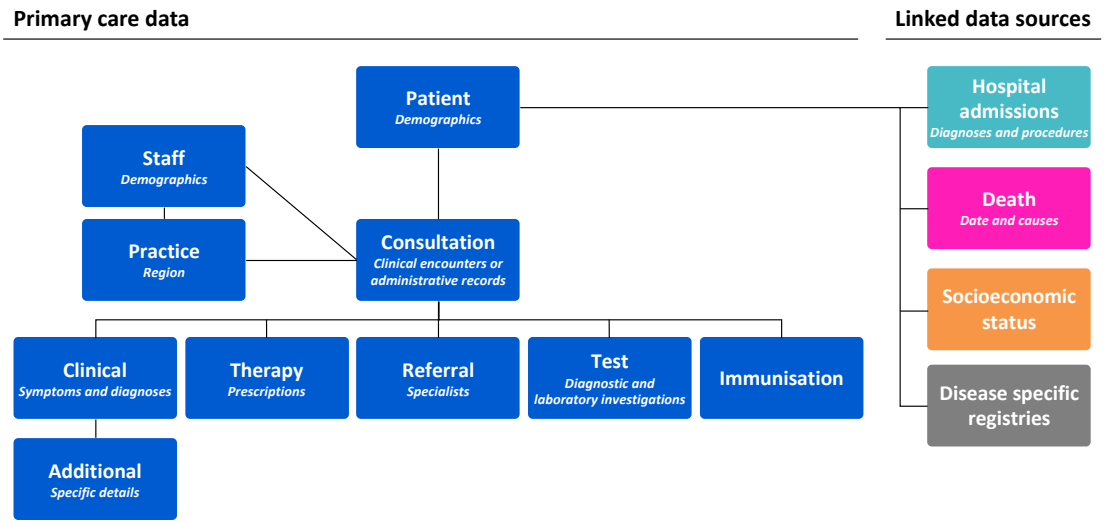
CPRD is structured as a main dataset that contains patients' health information as recorded by their primary care provider during routine clinical encounters, with the exception of any patient-identifiable information (e.g. name or address) and any free text notes which are removed for privacy reasons. For those primary care practices that participate in the CPRD linkage scheme, data are linked at patient-level to further health-related information, such as secondary healthcare records, the national death registry, or socioeconomic status data.

Clinical information in the CPRD is structured in a relational format and organises data in different tables, which each refer to one set of information or 'topic' and can be linked with each other via unique identifiers (see **figure 3.1**, further details provided in section **4.1 'Data extraction and processing'**).

Data are recorded via a standard clinical terminology system, named 'Read' coding system after its creator Dr. James Read. Read codes allow the recording of diagnoses, similarly to diagnosis coding systems such as the International Classification of Diseases (ICD), as well as a broad range of patient related features and clinical concepts including: occupation; social circumstances; ethnicity and religion; clinical signs, symptoms and observations; laboratory tests and results; diagnostic, therapeutic or surgical procedures performed; and a variety of administrative items.[87] Therapeutic information includes prescriptions using codes from the Prescription Pricing Authority, with the corresponding date, dosage and method of administration. Additional information is provided on vaccinations, weight and blood pressure measurements, laboratory test results and on some aspects of lifestyle. All information is entered by practice staff and is anonymised prior to central collection.[88]

All variables used in this thesis are described in detail in **Chapter 4** to provide enough detail for studies in this thesis to be replicated.

Figure 3.1: Overview of the CPRD data structure



Simplified overview of the relational data structure of CPRD and linked data sources. Patients consult with practice staff, where clinical, therapy, referral, test and immunisation information are recorded. Adapted from Herrett et al.[5]

3.2.3 Linked databases

The CPRD has established a substantive and unique linkage program has enabled access to a broad range of additional healthcare-related information.[78] The CPRD is able to link patients' primary care records with secondary care records (Hospital Episode Statistics (HES)), and mortality data from national death registry (Office for National Statistics (ONS)) as well as socioeconomic data (Index of Multiple Deprivation (IMD)). It is also linked to disease-specific registries such as the Myocardial Infarction National Audit Project, that have not been used in this thesis. Linkage is only available for English practices, due to the differences in NHS admission datasets created in Wales, Scotland and Northern Ireland.[76] In the dataset provided by CPRD for use in this thesis, linkage was available for 75% of English practices covering approximately 50% of all patients in CPRD.

Hospital episode statistics

The Hospital Episode Statistics (HES) dataset contains details of all admissions to English NHS health care providers, including acute hospital trusts, primary care trusts and mental health trusts. HES also covers admissions to independent sector providers (private or charitable hospitals) paid for by the NHS, and it is estimated that 98–99% of hospital activity in England is funded by the NHS.[89] Specifically, the data set used in this thesis relates to the 'Admitted Patient Care (APC)', which includes any secondary care-based activity that requires a hospital bed (including day cases). However HES APC does not cover accident and emergency (A&E, emergency department) attendances or outpatient bookings, which are held in separate HES databases.[89] Data are available at the person level for admitted patients, and provides information about admission and discharge dates as well as diagnoses recorded during the admission. Several diagnoses may be recorded during each admission, and the first recorded diagnosis is considered as the 'primary' diagnosis.[90] Diagnoses are coded using International Classification of Diseases and Health-Related Problems, Tenth Edition (ICD-10, herein referred to as ICD). Although some instances of HES APC data provide data relating to procedures, these were not available in our data cut.

Office of National Statistics mortality data

The Office for National Statistics (ONS) mortality data contains information related to a person's death taken from the death certificate for all deaths registered in England and Wales. All deaths are recorded with date of death, a primary cause of death, and up to 15 secondary causes of death. Causes of death are recorded using diagnostic codes from the ICD-10 system.[91]

Index of Multiple Deprivation

Index of Multiple Deprivation (IMD) is the official measure of relative deprivation for small residential areas (or neighbourhoods) in England.[92] IMD is a composite measure based on various social and economic characteristics of neighbourhoods, and is used as a proxy for the socioeconomic status of individuals who live there. The index ranks every small area in England from 1 (most deprived area) to 32,844 (least deprived area). Quintiles are calculated by ranking the 32,844 small areas in England from most deprived to least deprived and dividing them into five equal groups. These small areas, also known as lower-layer super output areas, contain an average population of 1500 people, and their boundaries remain fixed over time allowing the study of temporal trends.[92] The linkage provided by CPRD is established by matching the patient's postcode to the neighbourhood it refers to. To ensure patient anonymity, CPRD provides information about deprivation quintiles, but not the ranks themselves. IMD scores are updated every few years, and the dataset used in this thesis relied on the 2015 version.[93]

3.2.4 Representativeness and validity

Representativeness

The CPRD patient cohort has been shown to be broadly representative of the UK population in terms of age and sex, ethnicity, and body mass index distribution.[5,79,94] However, the CPRD may not be representative of all practices in the UK based on geography and size.[5]

Data validity

The validity of research based on EHR data depends on the quality and completeness of data recorded. The CPRD has established a consistent approach to ensure data provided adhere to the standards required for research purposes.

General practices contributing to the CPRD, are required to record (i) each episode of illness, or new occurrence of a symptom, and (ii) all significant morbidity events, e.g. all significant clinical contacts, all significant diagnoses and abnormal test results, all referrals to outpatient clinics and hospital admissions.[88] Prescription data in the CPRD are known to be well documented: practitioners use the computer to create prescriptions and these are automatically recorded.[88] The therapy file is therefore virtually complete, except for prescriptions issued in secondary care and for drugs that are purchased over the counter.[88,95] In contrast, new diagnoses must be manually recorded on the computer and although all significant diagnoses should be included, they may be incomplete. Additionally, conditions may be misdiagnosed or miscoded in GP records.[88]

The CPRD carries out a series of ongoing checks to ensure that the data are 'up to standard'; these checks comprise an assessment of both patient data (age, gender, registration details and event dates) and the completeness, continuity and plausibility of electronic data recording in key areas at the practice level (for example, ensuring a minimum specified percentage of deaths have cause of death recorded, a minimum referral rate per 100 patients, and a minimum number of prescriptions per patient per month).[88] For each contributing practice, time periods for which data are considered to be of continuous 'high quality' and appropriate to be used for research purposes are marked by an 'up to standard' (UTS) data field. It is based on two central concepts: assurance of continuity in data recording (gap analysis), and avoidance of use of data for patients which have transferred out and dead patients (death recording). Individual patient records are further labelled as 'acceptable' for use in research (or not) by a process that identifies and excludes patients with non-continuous follow up or patients with poor data recording that raises suspicion as to the validity of that patient record (for example an empty or invalid first registration date, absence of a record for a year of birth, etc.).[96] Data used in the thesis have been restricted to each practices' 'up to standard' period as well as individual patient records flagged as 'acceptable' for research purposes.

The research presented in this thesis was first and foremost reliant on the accuracy of diagnoses recorded by physicians in primary care, as part of a consultation, or secondary care, as part of a

hospital admission, particularly as pertains to heart failure but other conditions as well. A large number of independent validation studies have been performed and provide support for the validity of clinical diagnoses recorded in CPRD. Three studies are of major importance. First, a systematic review, published in 2010, has identified 212 studies that investigated the validity of 183 conditions.[88] Studies used various methods to assess the validity of diagnoses. Independent specialist review of patients' health record or of additional medical information provided by general practitioners was most commonly used. Comparisons of disease incidence rates recorded in CPRD to an external source was another commonly used approach. Overall, quantitative estimates of validity were high (median 89% of cases confirmed) and qualitative evidence from external rate comparisons and sensitivity analyses supported the validity of diagnoses.[88] Second, a study specifically investigating heart failure diagnoses, which despite it being conducted before the introduction of national care monitoring programmes, has reported a positive predictive value of 82% for heart failure diagnoses recorded in CPRD.[97] Third, a more recent study investigating the validity of chronic obstructive pulmonary disease (COPD), another major chronic condition managed in primary care, has reported an accuracy of 87% compared with specialist assessment.[98] Finally, as part of this thesis, I have performed a range of investigations on case ascertainment, including sensitivity analyses and rate comparisons, which provided additional evidence of a high validity of diagnoses (details presented in **Chapter 5**, section **5.4.6 'Sensitivity analyses'**)

3.2.5 Ethical considerations and data protection

Ethical approval

Scientific approval for the research in this thesis was given by the CPRD Independent Scientific Advisory Committee (ISAC) (protocol number 15_125R2 and 16_049R). The CPRD Group has ethical approval from a National Research Ethics Service Committee (NRES) for all purely observational research using anonymised CPRD data; namely, studies that do not include patient involvement, which is the case of the work presented here, and hence no separate ethical approval was required.[99]

Patient anonymity and consent

The CPRD collects data from general practices who opt-in and patients in these practices who have not opted-out. Each practice can also choose whether they consent for their data to be linked with additional sources, such as hospital episodes statistics.[100] Patient confidentiality is respected by ensuring that all information entered by practice staff and is anonymised by a trusted third party (NHS Digital, the statutory body in England legally permitted to receive patient identifiable data) prior to central collection.[100] Anonymisation undergoes a rigorous process which ensures that the data do not contain the name, address, or date of birth of patients or their healthcare professionals, and that information provided exclusively refers to numbers, dates, and clinical codes (no free text fields). Scientists using these data for research purposes have no access to identifiers or key codes, and are not able to link the information back to individuals.[5]

Data protection

Recital 26 of the General Data Protection Regulation (GDPR) leaves open the interpretation that record-level personal data can be considered anonymised if subject to sufficient de-identification, and hence whether it is to be considered 'personal data'. To take the most cautious approach, the data has been handled as 'personal data' under the GDPR and processed following the principles outlined in Article 5 of the GPRD. Appropriate safeguards have been taken to ensure the data was stored and processed exclusively in secure environments (data server on the university network, or a personal computer with hard disk encryption and password protection); access to the data was restricted to those persons directly involved in the research; data was used exclusively for the purpose of the proposed study and will be kept only for as long as it has been set in the ISAC agreement.

3.2.6 External influencers of data quality

Clinical practice changes over time due to a number of external factors, for example, when new evidence or clinical guidelines become available, or following implementation of government policies. Such changes also influence data recorded in CPRD and need to be carefully evaluated and considered.

In the UK, two national clinical audit programmes are of particular importance for the research undertaken in this thesis: the 'quality and outcomes framework' (QOF) that applies to primary care, and the 'national heart failure audit' (NHFA) that applies to secondary care.

The 'quality and outcomes framework' was introduced in 2004, and incentivises general practitioners to follow evidence-based care practices and monitors over 100 indicators across a range of conditions, including heart failure.[101] Achievements rates are monitored at practice level and made publicly available in a yearly report. Primary care practices who achieve set target rates receive a financial contribution.[101] The UK's 'quality and outcome framework' primary care scheme is one of the largest implementations of healthcare pay-for-performance in the world and has been regarded as a model for other countries.[102] Data recording and health outcomes are expected to improve after the introduction of QOF, yet its impact on quality of care is still subject to much debate.[102] The definition of QOF indicators and incentives are re-evaluated each year. Beyond its impact on clinical practice, changes to QOF also impact recording practices because achievement data is automatically extracted from EHR.

The 'national heart failure audit' was established in 2007 to monitor and improve the care and treatment of patients hospitalised for acute heart failure in England and Wales. The audit encourages the implementation of evidence-based and guideline-recommended practices, collects data on selected clinical indicators, and produces yearly reports on patient demographics, clinical practice and outcomes.[7] Initially, participating hospitals were asked to provide a subset of data (at least the first 10 patients with a primary death or discharge diagnosis of heart failure in each month); this requirement has steadily increased and, from 2012, all hospitals in England and Wales were expected to report all unscheduled admissions due to heart failure to the audit.[103]

For the present research, which is essentially focussed on heart failure, both national clinical audit programmes safeguard a stable quality of clinical coding practices and provide a solid support for the validity of recorded diagnoses. Indeed, these programmes report that approximately 90% of recorded heart failure diagnoses in England are referred for echocardiography, specialist assessment, or B-type natriuretic peptide (BNP) measurement.[45,104]

Clinical guidelines present as another important influence on data quality. Guidelines for the diagnosis and management of heart failure from the National Institute for Clinical Excellence (NICE)[12,38] provide additional consistency over the study period. Indeed, guidelines are largely consistent in regard to diagnostic criteria and recommended investigations. One important change is the availability of natriuretic peptides testing and the variability in assay accuracy. However, its testing is mainly used to exclude suspected cases, as opposed to confirming diagnoses, and therefore unlikely to impact disease incidence rates.[12,38]

After carefully considering results from independent validation studies and sensitivity analyses, alongside the influence of national care monitoring programmes and clinical guidelines, and after consulting with clinical and statistical experts, I have considered the validity of diagnoses in CPRD as appropriate for the defined research objectives.

4. METHODS

This chapter provides details on methods common to the analyses presented in chapter 5, chapter 6 and chapter 7. Additional information that is specific to each analysis is provided in the methods sections of respective chapters.

4.1 Data extraction and processing

4.1.1 Background

One of the core challenges of using the CPRD for research is that EHR data are not in a format appropriate for analysis. The structure of the database reflects the primary purpose of data collection, which is essentially administrative and clinical. Data are present in a longitudinal format across different tables within and across data sources, and need to be combined appropriately to create a single flat file that can be used for analysis. This process is complex and requires careful evaluation of variable definitions, linkage eligibility, and relational keys but also of the varying levels of detail and specificity within and between health care settings or health care providers.

Except for the most common demographic information, variables are generally not readily available and need to be extracted from the longitudinal data. For example, typical study data will provide a list of study participants, alongside their baseline date and baseline measurements, such as smoking, body mass index or blood pressure. When working with CPRD, researchers will first need to identify the relevant study population (e.g. identify all patients with a new diagnosis of heart failure), define and extract individual's baseline date(s) (e.g. the date of incident diagnosis), and associated baseline characteristics (e.g. age, sex, blood pressure, smoking status, comorbidities, etc.). Relevant measurements may or may not be recorded. Also, most records will not coincide with the baseline date and some measurements may have been

recorded several times in the months before/after baseline, so that an algorithm needs to be defined to extract, select and/or combine the different measurements.

4.1.2 Relational structure

Clinical information in the CPRD is structured in a relational format and organises data in different tables (see also **figure 3.1**). Each table refers to one set of information or 'topic' (e.g. the 'patient' table contains patients' demographic information), and is composed of rows or 'records' (e.g. individual patients) and columns that list individual attributes (e.g. year of birth, sex, etc.). Each row in a table has its own unique key (e.g. 'patient id'), and rows in one table can be linked to rows in other tables via these unique identifiers (e.g. the patient table will list the patients' 'practice id', which can in turn be linked to the 'practice' table to retrieve information about the practice (e.g. region).

4.1.3 Clinical and diagnostic codes

In line with its relational structure, information in CPRD is coded. For example, the 'patient' table lists sex as a numeric variable (1|2|3) and a separate lookup table lists its description (1=male | 2=female | 3=indeterminate). Similarly, various clinical measurements are coded as 'entities' that refer to different types of tests (e.g. entity type =1 refers to blood pressure measurements whereas entity type =13 refers to measures of weight). This structured coding system facilitates operations, ensures data integrity, avoids duplication, and reduces required storage space. More complex clinical concepts, such as symptoms, diagnoses, procedures, are also coded, and these typically present with a very large breadth of codes and descriptors. In UK primary care, clinical concepts are represented by 'Read' codes (in the CPRD, Read codes are mapped to 'medcodes'), and in secondary care settings (including HES and ONS data linked to CPRD), ICD-10 codes are used.

4.1.4 Phenotyping

Health data scientists commonly refer to 'phenotyping' as the process of identifying patients with a certain condition or characteristics based on the information provided by electronic health records. This involves identifying relevant codes for demographics, symptoms, diagnoses,

procedures or therapies, often in combination with each other, alongside relevant data sources (e.g. primary care, secondary care or mortality data) that are most appropriate for the condition or characteristics investigated. This process needs to be thought through very carefully and adjusted to the study design and objectives. For example, to identify patients with hypertension, one could rely on records of hypertension in patients' primary care record. To improve sensitivity, one could also include patients diagnosed with hypertension in secondary care, consider any patient with two or more blood pressure measurements above a certain threshold, or those prescribed anti-hypertensive medications. Alternatively, if the research question relies on identifying hypertension with high specificity, one might only want to consider patients with both a diagnosis of hypertension and recorded high blood pressure readings. There is currently no widely accepted framework to guide this process, nor are there standards for how these phenotypes are described in the literature, even for commonly used databases like the CPRD.[75] In this thesis, I have taken a systematic approach for phenotyping diseases and other clinical characteristics, which I present in the remainder of this chapter.

Phenotyping conditions

Phenotyping conditions such as for defining diagnoses or identifying clinical signs, presents specific challenges. In routine clinical practice data, the basis for making a diagnosis is not always transparent or documented; and quantitative measures that would confirm or refute a diagnosis are often not recorded. A fine balance between sensitivity and specificity of clinical definitions is required and must be carefully evaluated in line of study objectives. Any inaccuracies in this process are also very likely to significantly impact study outcomes.

In this thesis, phenotyping of conditions was restricted to the use of diagnostic codes (Read codes for primary care data and ICD codes for hospital data). In sensitivity analyses, additional use of procedures and prescription data to identify cases of heart failure was explored, and showed that these had little impact on identification of diagnoses. Because evidence on the validity of diagnoses relying on procedures and prescription codes is limited, it was deemed more appropriate to focus on formal diagnoses.

To collate diagnostic codes, I have used the following approach, which I have adapted from Davé and Petersen[105].

Scoping

- Define a set of key words and synonyms commonly used to describe the condition of interest;
- Search and extract all Read and ICD codes in the respective code dictionaries that contain at least one of the selected key words;
- Compare and complement this list to previous literature[1,36], related work performed within the department, online clinical code repositories[84,106] as well as codes used in the National Heart Failure Audit[45] and the Quality and Outcomes Framework[104] to ensure completeness.

Screening

- Screen initial list of codes and exclude clearly irrelevant codes;
- If the study relies on accurate distinction of 'new' diagnoses or 'incident' cases, differentiate between codes that refer to a pre-existing condition and codes that may indicate a new diagnosis;
- Perform two independent reviews under consideration of the study's research question and special requirements for specificity and sensitivity - reviews are to be performed by clinicians with knowledge of relevant specialty, general practice and electronic health records data;
- Synthesise reviews and seek advice from an independent expert with speciality knowledge where there is disagreement.

Calibration

- For each code, extract number and frequency of occurrence within the population of interest;
- Review and revise code list in light of occurrence information to ensure validity and completeness.

Heart failure phenotyping

Given that heart failure was the primary focus of this thesis, a considerable amount of time was spent on the phenotyping of heart failure. Medical codes were compiled following the approach described above, and led to a selection of 147 clinical codes. Of those, 107 were categorised as possibly referring to first diagnosis, and 40 codes referred to a pre-existing diagnosis (**table 4.1** and **table 4.2** respectively). Those codes referring to a pre-existing diagnosis were used to

identify prevalent heart failure diagnoses and to exclude patients with a pre-existing condition from incidence calculations. Key words and synonyms included ‘heart failure’, ‘cardiac failure’, ‘ventricular failure’, ‘ventricular dysfunction’, ‘LVD’, ‘LVSD’, ‘cardiomyopathy’, ‘pulmonary oedema’, ‘New York heart association classification’, ‘NYHA’. The final code list includes codes used in the UK quality of care management programmes (the Quality and Outcomes Framework for primary care, and the National Heart Failure Audit for secondary care), and additional codes identified through medical dictionary keyword searches, previously published literature,[1,36] and online clinical code repositories.[84] Clinical reviews were performed by Prof. Rahimi and Dr. Tran, and independent advice was sought from Prof. Cleland for selected codes. Codes were further labelled as ‘HF with reduced ejection fraction’ (HF-REF) if they clearly referred to reduced ejection fraction or left ventricular systolic dysfunction (e.g. “585f.00 Echocardiogram shows left ventricular systolic dysfunction”), otherwise they were labelled as ‘non HF-REF or unspecified HF’ (HF-UNS).

Table 4.1: Diagnostic codes that refer to a new diagnosis of heart failure

A. ICD-10 codes used in hospital discharge records

Code	Description	HF Type	Comment
I50.0	Congestive heart failure	HF-UNS	NHFA
I50.1	Left ventricular failure	HF-UNS	NHFA
I50.9	Heart failure, unspecified	HF-UNS	NHFA
I42.0	Dilated cardiomyopathy (Congestive cardiomyopathy)	HF-REF	NHFA
I42.9	Cardiomyopathy, unspecified	HF-UNS	NHFA
I11.0	Hypertensive heart disease with (congestive) heart failure	HF-UNS	NHFA
I25.5	Ischaemic cardiomyopathy	HF-REF	NHFA
I13.2	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	HF-UNS	
I13.0	Hypertensive heart and renal disease with (congestive) heart failure	HF-UNS	

B. Read codes used in general practice records

Medcode	Read Code	Description	HF Type	Comment
884	G581.00	Left ventricular failure	HF-UNS	QOF HF
2062	G58..00	Heart failure	HF-UNS	QOF HF
2906	G580.11	Congestive cardiac failure	HF-UNS	QOF HF
398	G580.00	Congestive heart failure	HF-UNS	QOF HF
8966	G5yy900	Left Ventricular Systolic Dysfunction	HF-REF	QOF LVSD
3204	G55..00	Cardiomyopathy	HF-UNS	
11284	585f.00	Echocardiogram shows left ventricular systolic dysfunction	HF-REF	QOF LVSD
1223	G58..11	Cardiac failure	HF-UNS	QOF HF
5942	G581.13	Impaired left ventricular function	HF-REF	QOF HF
7251	33BA.00	Impaired Left Ventricular Function	HF-REF	
9913	1O1..00	Heart failure confirmed	HF-UNS	
12550	G5yyA00	Left Ventricular Diastolic dysfunction	HF-UNS	
8010	G551.00	Hypertrophic obstructive cardiomyopathy	HF-REF	
5695	G41z.11	Chronic cor pulmonale	HF-UNS	
4024	G58z.00	Heart failure NOS	HF-UNS	QOF HF
11351	585g.00	Echo shows LVDD	HF-REF	
7535	G554400	Primary dilated cardiomyopathy	HF-REF	
13189	662g.00	New York Heart Association classification - class II	HF-UNS	QOF HF
5255	G581000	Acute left ventricular failure	HF-UNS	QOF HF
10079	G580.12	Right heart failure	HF-UNS	QOF HF
3499	G554300	Hypertrophic non-obstructive cardiomyopathy	HF-REF	
16383	1O1..00	Heart failure confirmed	HF-UNS	
9524	G580.14	Biventricular failure	HF-UNS	QOF HF
7320	G343.00	Ischaemic cardiomyopathy	HF-REF	
17278	G58z.12	Cardiac failure NOS	HF-UNS	QOF HF

Medcode	Read Code	Description	HF Type	Comment
19066	662h.00	New York Heart Association classification - class III	HF-UNS	QOF HF
27964	G582.00	Acute heart failure	HF-UNS	QOF HF
22993	G55z.00	Cardiomyopathy NOS	HF-UNS	
107397	G5yyD00	Left ventricular cardiac dysfunction	HF-REF	QOF LVSD
18853	662f.00	NYHA class f - i	HF-UNS	QOF HF
101138	G583.00	Heart failure with normal ejection fraction	HF-UNS	
32671	G580100	Chronic congestive heart failure	HF-UNS	QOF HF
4915	G555.00	Alcoholic cardiomyopathy	HF-REF	
10154	G580.13	Right ventricular failure	HF-UNS	QOF HF
9402	G55y.11	Secondary dilated cardiomyopathy	HF-REF	
27884	G580200	Decompensated cardiac failure	HF-UNS	QOF HF
32898	8H2S.00	Admit heart failure emergency	HF-UNS	
21852	G554200	Familial cardiomyopathy	HF-UNS	
106897	G583.12	Heart failure with preserved ejection fraction	HF-UNS	QOF HF
104275	G584.00	Right ventricular failure	HF-UNS	QOF HF
5141	G554000	Congestive cardiomyopathy	HF-UNS	
11424	G580300	Compensated cardiac failure	HF-UNS	QOF HF
97780	G559.00	Arrhythmogenic right ventricular cardiomyopathy	HF-REF	
101137	G583.11	HFNEF - heart failure with normal ejection fraction	HF-UNS	QOF HF
106008	8CMW800	Heart failure clinical pathway	HF-UNS	
94870	G580400	Congestive heart failure due to valvular disease	HF-UNS	QOF HF
27683	G558100	Cardiomyopathy in myotonic dystrophy	HF-UNS	
70648	Gyu5M00	Other hypertrophic cardiomyopathy	HF-REF	
22262	G1yz100	Rheumatic left ventricular failure	HF-UNS	QOF HF
51214	662i.00	New York Heart Association classification - class IV	HF-UNS	QOF HF
106198	661M500	Heart failure self-management plan agreed	HF-UNS	
103732	8CMK.00	Has heart failure management plan	HF-UNS	
62718	G21z100	Hypertensive heart disease NOS with CCF	HF-UNS	
52127	G211100	Benign hypertensive heart disease with CCF	HF-UNS	
21837	G232.00	Hypertensive heart & renal dis with (congestive) heart failure	HF-UNS	
105542	8CeC.00	Preferred place of care for next exacerbation HF	HF-UNS	

***Abbreviations**: 'HF-REF' = heart failure with reduced ejection fraction (highlighted in blue); 'HF-UNS' = heart failure with unspecified ejection fraction. 'NHFA' identifies those codes used by the National Heart Failure Audit to identify patients with a heart failure diagnosis from hospital discharge records. 'QOF HF' identifies those codes used by the 2014 Quality and Outcomes Framework to identify patients with a heart failure diagnosis from general practice records. 'QOF LVSD' refers to codes used by the 2014 Quality and Outcomes Framework to identify patients with a left ventricular systolic dysfunction diagnosis from general practice records.*

Table 4.2: Diagnostic codes that refer to pre-existing heart failure

Code Type	Medcode	Readcode	Description
READ	95021	9N4s.00	Did not attend practice nurse heart failure clinic
READ	24503	8B29.00	Cardiac failure therapy
READ	95835	679X.00	Heart failure education
READ	26115	8HHb.00	Referral to heart failure nurse
READ	5155	23E1.00	O/E - pulmonary oedema
READ	90935	9hH..00	Exception reporting: heart failure quality indicators
READ	30749	9hH0.00	Excepted heart failure quality indicators: Patient unsuitable
READ	34213	9h1..00	Exception reporting: LVD quality indicators
READ	11613	9h11.00	Excepted from LVD quality indicators: Patient unsuitable
READ	28649	9h12.00	Excepted from LVD quality indicators: Informed dissent
READ	15058	14A6.00	H/O: heart failure
READ	46912	14AM.00	H/O: Heart failure in last year
READ	83502	662p.00	Heart failure 6-month review
READ	12366	662T.00	Congestive heart failure monitoring
READ	30779	662W.00	Heart failure annual review
READ	32945	8CL3.00	Heart failure care plan discussed with patient
READ	17851	8HBE.00	Heart failure follow-up
READ	70619	8HHz.00	Referral to heart failure exercise programme
READ	71235	8Hk0.00	Referred to heart failure education group
READ	64062	9hH1.00	Excepted heart failure quality indicators: Informed dissent
READ	32911	9Or..00	Heart failure monitoring administration
READ	19380	9Or0.00	Heart failure review completed
READ	90193	9Or1.00	Heart failure monitoring telephone invite
READ	90192	9Or2.00	Heart failure monitoring verbal invite
READ	72965	9Or3.00	Heart failure monitoring first letter
READ	72386	9Or4.00	Heart failure monitoring second letter
READ	89650	9Or5.00	Heart failure monitoring third letter
READ	18793	9On..00	Left ventricular dysfunction monitoring administration
READ	60710	9On0.00	Left ventricular dysfunction monitoring first letter
READ	60721	9On1.00	Left ventricular dysfunction monitoring second letter
READ	72341	9On2.00	Left ventricular dysfunction monitoring third letter
READ	92305	9On3.00	Left ventricular dysfunction monitoring verbal invite
READ	96484	9On4.00	Left ventricular dysfunction monitoring telephone invite
READ	100784	2126400	Heart Failure Resolved
READ	102585	8HgD.00	Discharge from heart failure nurse service
READ	106680	8HTL000	Referral to rapid access heart failure clinic
READ	106836	8IB8.00	Referral to heart failure exercise programme not indicated
READ	106894	8IE1.00	Referral to heart failure exercise programme declined
READ	107981	8IE0.00	Referral to heart failure education group declined
READ	42999	12CR.00	FH: Hypertrophic obstructive cardiomyopathy

Phenotyping comorbidities

Phenotyping of comorbidities relied on previously published work. Essentially, code lists were compiled from previous literature, previous research within the department, and online clinical repositories, and then reviewed and adapted following the previously described approach. Analyses of comorbidities essentially relied on investigating the prevalence of chronic conditions among patients with heart failure, and codes that indicated that a condition was inactive, treated or resolved, were excluded from these code lists. Code lists were reviewed by Prof. Rahimi and Dr. Tran. Patients without diagnosis were assumed to be free from that condition. Diagnosis code lists for the extraction of each condition were adapted from the CALIBER code repository.[106] An **online supplement**, accessible under https://www.researchgate.net/profile/Nathalie_Conrad3, was set up to make code lists available for other researchers to download and re-use in a computer-ready format. Space constraints prohibited the inclusion of code lists for individual comorbidities in the supplementary appendix of this thesis.

4.2 Study setting

The dataset available to us included primary care data from 1 January 1985 to 31 December 2015. Linkage to secondary care and mortality data was provided from 1 January 1998 to 30 September 2015. Because comprehensive identification of individuals relies on the use of linked datasets,[75] this study was restricted to periods for which linkage to secondary care records was available. Furthermore, the comprehensiveness of clinical records has been shown to be of consistent and comparable quality from the early 2000s onwards.[5] Therefore, to allow for a sufficient 'look-back' period for the extraction of medical history and prevalent diagnoses, the study period was set to start on 1 January 2002. To allow for the comparison of complete years (i.e. for each year to include data from January to December), the study period was set to end on 31 December 2014.

4.3 Eligible participants

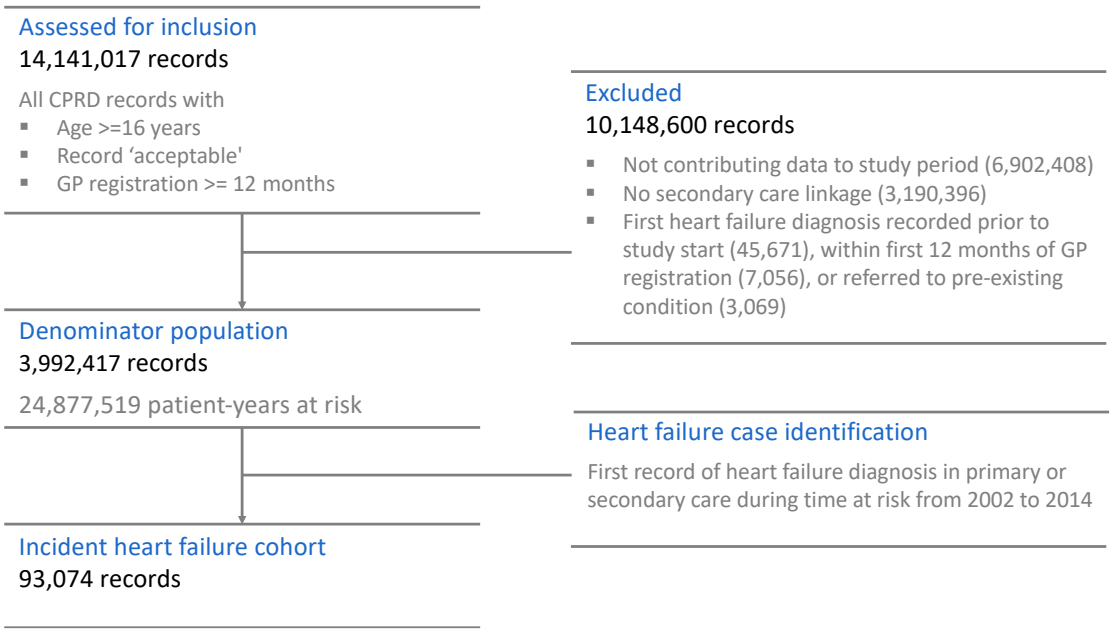
Patients were considered for inclusion in the study if they were aged 16 and over, registered with a general practice for at least 12 months, their record labelled as 'acceptable' by CPRD quality control (see **Chapter 3**, in **'Representativeness and validity'**), and eligible for linkage to secondary care, mortality and socioeconomic status data. To ensure consistent data quality, patients' observation time was further restricted to practice's up-to-standard periods (see **Chapter 3**, in **'Representativeness and validity'**). Only patients contributing to data during the study period (1 January 2002 to 31 December 2014) were considered for inclusion.

4.4 Study population

Heart failure diagnosis was defined as the first record of heart failure in primary care or hospital admission records from any diagnostic position, using a total 147 diagnostic codes (**tables 4.1 and 4.2**).

For incidence calculations, I excluded all individuals who had a diagnosis of heart failure before the study start date (Jan 1, 1985, to Jan 1, 2002, in primary care records and Jan 1, 1998, to Jan 1, 2002, in secondary care records), or within the first 12 months of registration with their general practice, or those whose first record of heart failure referred to a pre-existing condition (**table 4.2**). Time at risk was defined to start on the latest date of: study the start date (1 January 2002), 12 months after a patient's current practice registration date ('crd'), and practice's up-to-standard date ('uts'); and to end on the earliest date of: the study end date (31 December 2014), patients' transfer out of practice date ('tod'), practice's last collection date ('lcd'), and patient death ('dod'). A total of 4,048,213 patients contributed data between 1 January 2002 to 31 December 2014. After excluding individuals who had a diagnosis of heart failure before the study start date (45,671 records) or within the first 12 months of registration with their general practice (7,056 records), or whose first record of heart failure referred to a pre-existing condition (3,069), a total of 3,992,417 eligible patients were identified and contributed to 24,877,519 patient-years at risk. Of those patients, 93,074 developed incident heart failure during the study period (**figure 4.1**).

Figure 4.1: Flowchart of patients included in the study



***Abbreviations**: CPRD = Clinical Practice Research Datalink; GP = General Practice.*

4.5 Baseline co-variates

In the following paragraphs, I describe how individual variables have been extracted from CPRD and linked data sources. To assist readability, I refer to patients' primary care record for the actual CPRD database, secondary care records in reference to linked HES data, mortality records in references to linked ONS data, and socioeconomic data in reference to linked Index of Multiple Deprivation (IMD) quintiles.

4.5.1 Demographics

Age (at baseline)

Patients' year of birth (CPRD does not provide exact date of birth to protect patient anonymity) is listed in primary care records' 'patient' table. Age at baseline was calculated by subtracting patient's year of birth from the year of incident heart failure diagnosis. In some analyses age was further categorised into age groups.

Sex

Sex was extracted from primary care records' 'patient' table, with 1=male, 2=female. There were no patients with indeterminate gender in the data cut used in this thesis.

Socioeconomic status

The IMD quintiles were provided in linked socioeconomic data tables ('patient_imd2015.txt') at patient level. The dataset used in this thesis refers to the 2015 version of IMD scores, and 1=least deprived fifth and 5=most deprived fifth. Although lack of deprivation does not necessarily equate to affluence, to assist readability, this thesis refers to "least deprived" and "most affluent" interchangeably. Similarly, although the IMD quintiles refer to small neighbourhoods rather than individuals, this thesis refers to "most deprived/affluent" as a reference to "living in most deprived/affluent areas".

Ethnicity

Ethnicity recordings are provided both in primary care as well as secondary care records. In primary care records ethnicity is recorded via Read codes and may be recorded several times, in which case the latest available record of ethnicity was used. In secondary care records, ethnicity is recorded as a variable named 'ethnos' in the 'patient' table.[79] When ethnicity differed between primary and secondary care records, secondary care data was used. The majority of ethnicity extracted was 'white' (88% of non-missing entries) or 'unknown', and was missing for about 30% of the study population. To assist readability, ethnicity was grouped into two categories, 'white' and 'other'.

Region

Each practice is assigned to one of 13 geographical regions (primary care records, 'practice' table). Regions correspond to the former geographical division of the National Health Service in 10 strategic health authorities in England (which are similar to administrative regions, with the exception of the large South East England region which is divided into two: South Central and South East Coast)[107], alongside Northern Ireland, Scotland and Wales. In this thesis, analyses were restricted to patients eligible for linkage to secondary care, mortality and socioeconomic data, which is only available for English practices, so that data from Northern Ireland, Scotland and Wales was not included. Patients were assigned to their practice's region through the unique patient-practice link (every patient record is linked to one and only one practice).

4.5.2 Clinical measurements

Baseline clinical measurements where extracted from patients' primary care records, as part of the 'additional' table. For each patient and each measure investigated, the latest measurement within the two years before incident heart failure was used. If no measurement took place within that time frame, the measure was considered missing.

Body mass index

Body mass index (BMI) was extracted using 'enttype=13' which refers to weight measurements, and the column 'data3', which refers to recorded BMI. Readings were considered invalid if BMI<10 or BMI>70. BMI was stratified according to the World Health Organization (WHO) categories: 'underweight' (<18.5 kg/m2), 'normal' (18.5-24.9 kg/m2), 'overweight' (25-29.9 kg/m2), and 'obese' (≥30 kg/m2) [181]. Read or ICD codes for categories of BMI were not used to extract BMI as a clinical variable.

Blood pressure

Blood pressure was extracted using 'enttype=1' which refers to blood pressure measurements, and the columns 'data1' and 'data2', which respectively refer to diastolic blood pressure (DBP) and systolic blood pressure (SBP). All readings were assumed to be in mmHg. Readings were considered invalid if SBP<50, SBP>250, DBP<40, or DBP>150.

Smoking

Smoking was extracted using the 'enttype=4', which refers to smoking, and the column 'data1', which refers to smoking status. Smoking status was categorised into 'Yes' (data1=1), 'Ex' (data1=3), 'No' (data1=2) or 'Missing' (data1=0).

4.5.3 Diagnostic investigations

Diagnostic investigations were extracted as recorded in primary care records within ± 6 months of incident heart failure diagnosis. Investigations considered in this thesis were: (i) echocardiogram; (ii) electrocardiogram (ECG); and (iii) plasma natriuretic peptides (B-type natriuretic peptide [BNP] or N-terminal-pro-BNP [NT-pro-BNP]), as well as (iv) cardiology specialist assessment. For each investigation, general practitioners record the 'type' of

investigation (recorded in the variable 'enttype') as well as a descriptor (recorded as a 'Read' code). Extracting information about investigations and referrals therefore relies first and foremost on a comprehensive list of codes describing the given investigations.

To compile an appropriate list of clinical codes, I have used a similar yet simplified approach to the one used to phenotype conditions:

1. Define a set of key words and synonyms commonly used to describe the procedure of interest;
2. Extract all 'enttypes' and 'Read' codes in the code dictionary that contain at least one of the key words selected under step 1;
3. Complement the list obtained in step 2 with codes used in the UK's general practice pay for performance scheme (the 'quality and outcomes framework') and relevant scientific literature;
4. Review the broad list of codes established in step 3 and manually select those that appropriately refer to the procedure of interest. This last step must be performed by one (or several) clinicians with specialty knowledge. In this case, my supervisor Prof. Rahimi who is a cardiologist has kindly helped out with this task.

The resulting lists of clinical codes used to identify diagnostic tests and referrals in this thesis are presented in **table S1**. Diagnostic investigations (echocardiogram, electrocardiogram and natriuretic peptides tests) were extracted from the 'test' table, if their entity type and descriptor matched any of those listed in table S1. Referrals were extracted from both the 'clinical' and the 'referral' tables, if their descriptor matched any of those listed in table S1.

4.5.4 Drug prescriptions and intolerances

Information relating to drug prescription data is provided in primary care records' 'therapy' table. Each prescription relates to one drug (described with a 'prodcode' number), a quantity ('qty', or the number of tablets prescribed), a numeric daily dose ('ndd', i.e. the number of tablets to be taken per day), and tablet strength (the active dose contained in each tablet). Other descriptors are also provided but have not been used in this thesis (e.g. pack size or type of the prescribed product). A product dictionary details the specific formulation of each drug and alongside the British National Formulary classification, the pharmaceutical reference book in the UK.[108]

Drug prescription data were extracted for the three main treatment classes recommended by guidelines for the management of heart failure with reduced ejection fraction: (i) angiotensin-converting-enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB); (ii) beta-blockers; (iii) mineralocorticoid receptor antagonists (MRA).

Specifically, the information was extracted using the following terms:

- ACE-inhibitors: BNF chapter 2.5.5.1 and any of the following drug substances: Captopril, Cilazapril, Enalapril, Fosinopril, Lisinopril, Perindopril, Quinapril, Ramipril, or Trandolapril;
- ARBs: BNF chapter 2.5.5.2 and any of the following drug substances: Candesartan, Losartan, or Valsartan;
- Beta-blockers: BNF chapter 2.4 and any of the following drug substances: Bisoprolol, Carvedilol, Metoprolol succinate, Metoprolol tartrate, or Nebivolol;
- MRAs: BNF chapter 2.2.3 and any of the following drug substances: Eplerenone or Spironolactone.

Intolerances to certain drugs or drug classes were extracted from patients' primary care record ('clinical' table). A list of clinical codes referring to a contra-indication or intolerance to any of the studied drug classes was established using a similar approach to the one used for diagnostic codes. The resulting lists of clinical codes used in this thesis are presented in **table S2**.

4.5.5 Comorbidities

To describe comorbidities, 17 common chronic conditions were selected. These included anaemia, asthma, atrial fibrillation, cancer, chronic kidney disease, chronic obstructive pulmonary disease, dementia, depression, diabetes, dyslipidaemia, hypertension, ischaemic heart disease, obesity, osteoarthritis, peripheral arterial disease, stroke, thyroid disease. To establish this list of conditions, my supervisor Prof. Rahimi and I reviewed the list of conditions included in the UK primary care reporting and incentives scheme (the 'Quality and Outcomes Framework'), which aims to include those chronic conditions that most commonly affect the UK population. We selected those conditions that were most relevant to the largely elderly heart failure patient population (e.g. we excluded 'learning disabilities' and 'epilepsy') and added anaemia and dyslipidaemia, because of their importance in heart failure. For each condition,

baseline prevalence was defined as the record of a diagnosis in either primary care or secondary care, at any time prior to incident heart failure diagnosis and in any diagnostic position. Diagnosis code lists for the extraction of each condition were adapted from the CALIBER code repository,[106] and are reported in the **online supplementary material**.

4.5.6 Hospital admissions

Information relating to hospital admissions is provided by the linked secondary care (hospital episodes statistics admitted patient care, HES APC) dataset, which includes data on all admissions to NHS hospitals in England.[89] Different data tables are provided allowing researchers to investigate data with different levels of granularity (for example some tables detail individual episodes of care within each hospital admission), and in this thesis only tables summarising information at admission level were used. Reports of hospital admissions experienced by patients after a diagnosis of heart failure considered records of primary admission diagnoses ('HES_primary_diag_hosp.txt' table) and was restricted to admissions with overnight stay. When secondary care data was used to extract information about diagnoses (heart failure and associated comorbidities), data from all diagnostic positions were considered ('HES_diagnosis_hosp.txt' table) and no restriction was made in regard to overnight stay. Discharge date ('discharged' variable) was used to define the date of hospitalisation or diagnosis.

4.5.7 Mortality

Mortality information is provided by the linked death registry (Office for National Statistics, ONS) data ('death_patient.txt' table) and contains information about date of death, alongside up to 15 causes of death. Patient's primary care record also contains information about death date ('deathdate' in the 'patient' table). Sensitivity analyses were performed and showed that death dates differed significantly (i.e. differed by more than two months) in about 3% of patients. Data from the national death registry is considered more accurate and was used as the reference for all mortality related information in this thesis.

5. INCIDENCE AND PREVALENCE

5.1 Introduction

Adequate public health and service delivery planning requires reliable information about contemporary population-level disease epidemiology. Two measures provide valuable and complementary information for policy makers – incidence and prevalence. Incidence refers to the number of individuals newly diagnosed with a specific disease or who experience a specific health-related event during a particular time period (such as a month or year). Prevalence, on the other hand, refers to the total number of individuals in a population who have a disease or health condition at a specific period of time, usually expressed as a percentage of the population.[109]

Both measures can be presented as either crude or standardised estimates, and each have different meaning and utility.

Crude estimates reflect the total number of cases in the population of interest. Estimates can also be presented as rates, in which case estimates are divided by the at-risk population. Crude estimates describe the disease's impact on the population and services of interest and are helpful in determining disease burden and specific health services' needs for a given population. However, they are influenced by the underlying age and sex distribution of the population, which can change over time and differ by geographic areas, and hence are not useful when it comes to compare disease incidence or prevalence from one year to another, or between one geographic area and another.

Standardised rates compute hypothetical rates based on a common age-sex distribution and reflect the rates that are to be expected if the population presented with a standard age-sex distribution. This method relies on the computation of age-sex-specific rates of disease and a standard age-sex distribution. Standardised estimates provide a useful way to compare health

status or outcomes among populations that may have different age (and sex) distributions, and hence allows us to understand how a disease itself affects certain groups of people or changes over time, independently of differences in age and sex distributions.

For heart failure, estimates of incidence rates and their temporal trends, even in high-income countries, are scarce and inconsistent.[1,22–25,110] Previous studies have frequently been based on selected cohorts[1,23–25] which may or may not be representative of the general population. Other studies have restricted case identification to general practice consultations[36] or hospitalisations.[111,112] However, it is only by considering presentations across the whole spectrum of acute and chronic care that the full burden of disease can be captured and an accurate distinction made between incident and prevalent cases. Moreover, previous reports have differed in their approach to age-standardisation - some studies presenting crude rates,[20,22] others standardising to census populations,[1,23,24] or simply adjusting for differences in the denominator population.[25,26] Very few studies have referred to a standard population, rendering comparisons amongst studies challenging. Consequently, reported incidence rates have varied tenfold across studies (for a detailed literature review refer to section **2.2 'Prior evidence on incidence and prevalence'** and **table 2.1**).

As for the absolute number of incident heart failure cases, country-specific estimates are rarely reported. For instance, in the United Kingdom (UK), although several national programmes generate heart failure statistics, reliable information about the absolute number of new cases is not available. The UK's annual 'quality and outcomes framework' reports prevalence estimates based on general practice consultations but incidence is not recorded.[104] National heart statistics and the national heart failure audit report annual numbers of inpatient episodes of heart failure and are limited in their ability to distinguish between first and recurrent presentations.[45,113] More generally, both national and international quantification of the absolute number of incident heart failure cases are absent from global heart failure reviews.[62,114] In addition, long-term trends on the heterogeneity of incident heart failure in the general population overall and by important features such as age or socioeconomic status are scarce.[115]

To address these knowledge gaps, the present work relies on a large longitudinal database of linked primary and secondary care from a representative sample of the UK population,[5] assessed trends in crude and standardised heart failure incidence and prevalence by sex, age, socioeconomic status and region, and investigated the comorbidity profile of patients over more than a decade.

Parts of this chapter have been published in *the Lancet* at http://dx.doi.org/10.1016/S0140-6736(17)32520-5. This publication benefitted from the input of several co-authors as well as my thesis supervisors. My role consisted in designing the study, conducting the literature searches, the data extraction, all statistical analyses, and writing the first draft of the manuscript.

5.2 Aims

The research presented in this chapter aimed to evaluate heart failure incidence and prevalence in a large, representative, general population cohort, in the United Kingdom, and to investigate variation over time, age, sex, socioeconomic status and region.

5.3 Methods

5.3.1 Data source

The study was conducted using linked electronic health records from the Clinical Practice Research Datalink (CPRD), a cohort that is broadly representative of the UK population in terms of age, sex and ethnicity. Primary care records from CPRD were linked to secondary care admission records from Hospital Episodes Statistics (HES) Admitted Patient Care data. Primary care data was available from 1 January 1985 to 30 September 2015, and linkage was available from 1 January 1998 onwards (for a detailed description of the dataset refer to **Chapter 3**).

5.3.2 Eligible participants

Patients eligible for inclusion in the study were men and women aged 16 and over, contributing data during the period 1 January 2002 to 31 December 2014, registered with their general

practice for at least 12 months, and whose record was labelled as 'acceptable' by CPRD quality control[5] and approved for CPRD and HES linkage (4,048,213 records).

5.3.3 Case identification

Heart failure diagnosis was defined as the first record of heart failure in primary care or hospital admission records from any diagnostic position, using a total 147 diagnostic codes. These include codes used in the UK quality of care management programmes (the 'quality and outcomes framework' for primary care, and the 'national heart failure audit' for secondary care), as well as further codes identified through medical dictionary keyword searches, previous literature,[1,36] and on-line clinical code repositories[84,106] (refer to section **4.4 'Study population'** for further description).

5.3.4 Study population

Incidence calculations were based on disease-free individuals. All individuals who had a diagnosis of heart failure before the study start date (45,671 records) or within the first 12 months of registration with their general practice (7,056 records), or whose first record of heart failure referred to a pre-existing condition (3,069) were excluded. A total of 3,992,417 patients were included in the incidence analysis.

Prevalence calculations included all eligible individuals alive and registered with an up-to-standard general practice on the sampling date.

5.3.5 Study design

This study describes temporal trends of incidence and prevalence in a retrospective population-based cohort.

5.3.6 Patient characteristics

For those with incident heart failure, baseline characteristics (systolic and diastolic blood pressure, smoking status, and body mass index (BMI)) were abstracted from electronic health records as the most recent measurement within 2 years prior to heart failure diagnosis,

alongside information on comorbidities, socioeconomic status, ethnicity, and region (for a detailed description of covariates refer to **Chapter 4**).

5.3.7 Statistical analyses

Baseline characteristics are presented as frequencies (%) for categorical data, medians and interquartile range (IQR) for non-normally distributed continuous data, or means and standard deviation (SD) for normally distributed continuous data, over the whole heart failure patient cohort and stratified by sex, socioeconomic quintile, and period of diagnosis. Number and percentage of records with missing data are displayed for variables with missing entries. For categorical variables, frequencies refer to complete cases.

Observed age-, sex-, and year-specific incidence rates were computed by dividing the number of incident cases by the number of patient-years in the cohort. Time at risk was defined as to start on the latest date of the study start date (1 January 2002), 12 months after a patient's current practice registration date ('crd'), and practice's up-to-standard date ('uts'); and to end on the earliest date of the study end date (31 December 2014), patients' transfer out of practice date ('tod'), practice's last collection date ('lcd'), and patient death ('dod').

Observed age-, sex-, and year-specific prevalence rates were computed considering all patients ever diagnosed with heart failure (numerator) among patients alive, aged 16 or over, and registered with a general practitioner during an UTS period (denominator) on June 30th in each year. I assumed no heart failure incidence for patients aged 15 or under and report total incidence and prevalence over all ages (>0 years).

Standardised rates were computed by applying direct age and sex standardisation[116] to the 2013 European Standard Population[27] using 5-year age bands up to 90 years of age. The European Standard Population is an artificial population structure, designed and published by the statistical office of the European Union (Eurostat), to allow the calculation of age- and sex-standardised rates that are comparable across regions and time.[27]

Crude rates were inferred by applying year-, age- and sex-specific incidence rates to UK census mid-year population estimates, using 5-year age bands up to 90 years of age.

Impact of socioeconomic differences was estimated by comparing the estimated absolute number of incident cases with a hypothetical absolute incidence based on rates from the most affluent group (i.e. applying age-sex-specific incidence rates from the most affluent group to the total population).

Poisson regression models were used to examine overall and category-specific incidence rate ratios (IRR) and corresponding 95% confidence intervals (CI). Models were adjusted for calendar year of diagnosis, age, sex, region and socioeconomic status, where applicable.

Study findings are reported in accordance with the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) recommendations.[117] Statistical analyses were performed in R, version 3.3 (R Foundation for Statistical Computing, Vienna, Austria).

5.3.8 Sensitivity analyses and additional analyses

I have performed several sensitivity analyses to address some of the limitations associated with routinely-collected electronic health records, as well as additional exploratory analyses to investigate categorisation of heart failure by type of ejection fraction.

5.4 Results

5.4.1 Incidence

Among the 3,992,417 individuals included in the study, a total of 93,074 incident heart failure cases were identified between 1 January 2002, and 31 December 2014. Patient characteristics stratified by sex, socioeconomic status, and time period categories are shown in **table 5.1**. The mean (SD) age at heart failure diagnosis was 76.7 (12.6) years, 49% were women, and 79% had three or more comorbidities. From 2002 to 2014, mean age at diagnosis increased from 76.5 to 77.0 years (adjusted difference [95% CI]: 0.79 years [0.37,1.20]). Males and most deprived individuals had higher prevalence rates of smoking, as well as a BMI in the overweight or obese range at baseline.

Table 5.1: Baseline characteristics of patients with incident heart failure by sex, socioeconomic status and year of diagnosis

Characteristic	All cases (n=93,074)	Sex		Socioeconomic status (SES)		Time period	
		Women (n=45,647, 49%)	Men (n=47,427, 51%)	SES 1 (affluent) (n=18,371, 20%)	SES 5 (deprived) (n=16,270, 18%)	2002-2004 (n=21,943, 24%)	2012-2014 (n=20,804, 22%)
Age [years], mean (SD)	76.7 (12.6)	79.4 (11.8)	74.0 (12.7)	77.8 (12.1)	74.5 (13.3)	76.5 (12.0)	77.0 (12.9)
Women, no. (%)	45647 (49%)			8694 (47%)	8278 (51%)	10889 (50%)	10163 (49%)
Ethnicity, no. (%)							
White	45550 (97%)	22247 (98%)	23303 (97%)	9108 (98%)	8330 (96%)	10588 (98%)	13618 (96%)
Missing	46278 (50%)	22875 (50%)	23403 (49%)	9096 (50%)	7560 (46%)	11175 (51%)	6651 (32%)
Socioeconomic-status (IMD 2015 quintile), no. (%)							
1 (least deprived)	18371 (20%)	8694 (19%)	9677 (20%)			4177 (19%)	4344 (21%)
2	20073 (22%)	9737 (21%)	10336 (22%)			4680 (21%)	4600 (22%)
3	20052 (22%)	9818 (22%)	10234 (22%)			4769 (22%)	4500 (22%)
4	18308 (20%)	9120 (20%)	9188 (19%)			4387 (20%)	3941 (19%)
5 (most deprived)	16270 (17%)	8278 (18%)	7992 (17%)			3930 (18%)	3419 (16%)
Systolic blood pressure							
Mean (SD) [mmHg]	133 (21)	134 (21)	131 (21)	132 (20)	132 (21)	137 (24)	130 (19)
Missing, no. (%)	5195 (6%)	2716 (6%)	2479 (5%)	922 (5%)	1057 (6%)	2601 (12%)	645 (3%)
Diastolic blood pressure							
Mean (SD) [mmHg]	74 (12)	75 (12)	74 (12)	74 (11)	74 (12)	77 (12)	73 (11)
Missing, no. (%)	5195 (6%)	2716 (6%)	2479 (5%)	922 (5%)	1057 (6%)	2601 (12%)	645 (3%)
BMI category, no. (%)							
Underweight	2193 (4%)	1541 (6%)	652 (2%)	389 (4%)	424 (4%)	329 (3%)	592 (4%)
Normal	17381 (31%)	8413 (33%)	8968 (29%)	3665 (35%)	2967 (29%)	3000 (31%)	4368 (30%)
Overweight	18786 (34%)	7060 (28%)	11726 (38%)	3741 (35%)	3220 (31%)	3434 (36%)	4629 (32%)
Obese	17644 (32%)	8222 (33%)	9422 (31%)	2789 (26%)	3793 (37%)	2910 (30%)	4784 (33%)
Missing	37070 (40%)	20411 (45%)	16659 (35%)	7787 (42%)	5866 (36%)	12270 (56%)	6431 (31%)

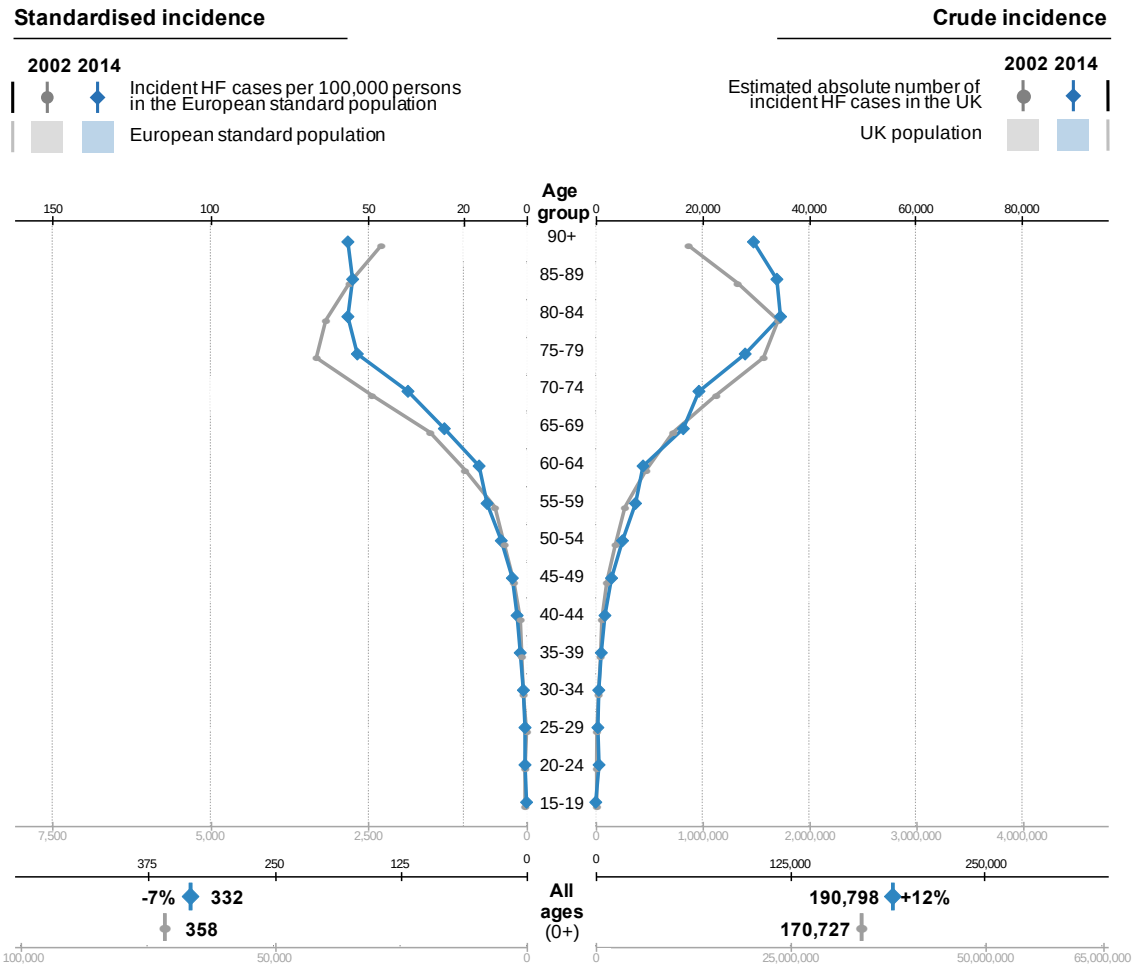
Characteristic	All cases (n=93,074)	Sex		Socioeconomic status (SES)		Time period	
		Women (n=45,647, 49%)	**Men** (n=47,427, 51%)	**SES 1** (affluent) (n=18,371, 20%)	**SES 5** (deprived) (n=16,270, 18%)	**2002-2004** (n=21,943, 24%)	**2012-2014** (n=20,804, 22%)
Smoking, no. (%)							
No	29551 (41%)	17603 (53%)	11948 (31%)	6394 (46%)	4496 (34%)	5081 (41%)	7023 (41%)
Ex	32572 (45%)	11604 (35%)	20968 (54%)	6248 (45%)	5838 (45%)	5192 (42%)	7949 (47%)
Yes	9596 (13%)	3929 (12%)	5667 (15%)	1146 (8%)	2755 (21%)	2031 (17%)	2065 (12%)
Missing	21355 (23%)	12511 (27%)	8844 (19%)	4583 (25%)	3181 (20%)	9639 (44%)	3767 (18%)
Atrial fibrillation, no. (%)	36950 (40%)	18309 (40%)	18641 (39%)	7711 (42%)	6044 (37%)	6990 (32%)	9460 (45%)
Chronic kidney disease, no. (%)	22762 (24%)	11912 (26%)	10850 (23%)	4325 (24%)	3956 (24%)	1363 (6%)	7542 (36%)
Chronic obstructive pulmonary disease, no. (%)	17896 (19%)	8199 (18%)	9697 (20%)	2670 (15%)	4343 (27%)	3782 (17%)	4494 (22%)
Diabetes, no. (%)	20531 (22%)	9363 (21%)	11168 (24%)	3489 (19%)	4238 (26%)	3893 (18%)	5366 (26%)
Dyslipidaemia, no. (%)	25958 (28%)	11516 (25%)	14442 (30%)	5062 (28%)	4948 (30%)	3361 (15%)	8024 (39%)
Hypertension, no. (%)	62419 (67%)	32117 (70%)	30302 (64%)	12230 (67%)	11008 (68%)	11940 (54%)	15766 (76%)
Ischaemic heart disease, no. (%)	45584 (49%)	19408 (43%)	26176 (55%)	8745 (48%)	8317 (51%)	10279 (47%)	10341 (50%)
Osteoarthritis, no. (%)	40176 (43%)	23040 (50%)	17136 (36%)	7828 (43%)	7186 (44%)	7962 (36%)	10277 (49%)
3 or more comorbidities, no. (%)	73610 (79%)	37338 (82%)	36272 (76%)	14188 (77%)	13236 (81%)	14876 (68%)	18040 (87%)

Number and percentage of records with missing data are displayed for variables with missing entries. Category percentages refer to complete cases. Socioeconomic status (SES) refers to Index of Multiple Deprivation (IMD) 2015 quintile, with SES 1 referring to the most affluent and SES 5 to the most deprived quintile. Number of comorbidities refers to any of the 17 conditions investigated (see Methods).

Comparisons of overall and age-specific incidence of heart failure in 2002 and 2014 are shown in **figure 5.1**. In age-sex-standardised models, incidence decreased by 7%, from 358 per 100,000 persons in 2002 to 332 per 100,000 persons in 2014 (adjusted incidence rate ratio (IRR) [95% CI]: 0.93 [0.91,0.94]) (**figure 5.1, left panel**). In contrast to the declining standardised incidence, crude incidence rates increased by 2% from 288 per 100,000 persons in 2002 to 295 per 100,000 persons in 2014, and the estimated absolute number of yearly new diagnoses of heart failure increased by 12% from 170,727 in 2002 to 190,798 in 2014, due to population growth, especially in older age groups (**figure 5.1, right panel**). For comparison, I aggregated the number of new cases of the four most common causes of cancer (lung, breast, bowel and prostate) reported by the UK cancer statistics in 2014, and found these totalled 189,136.[118]

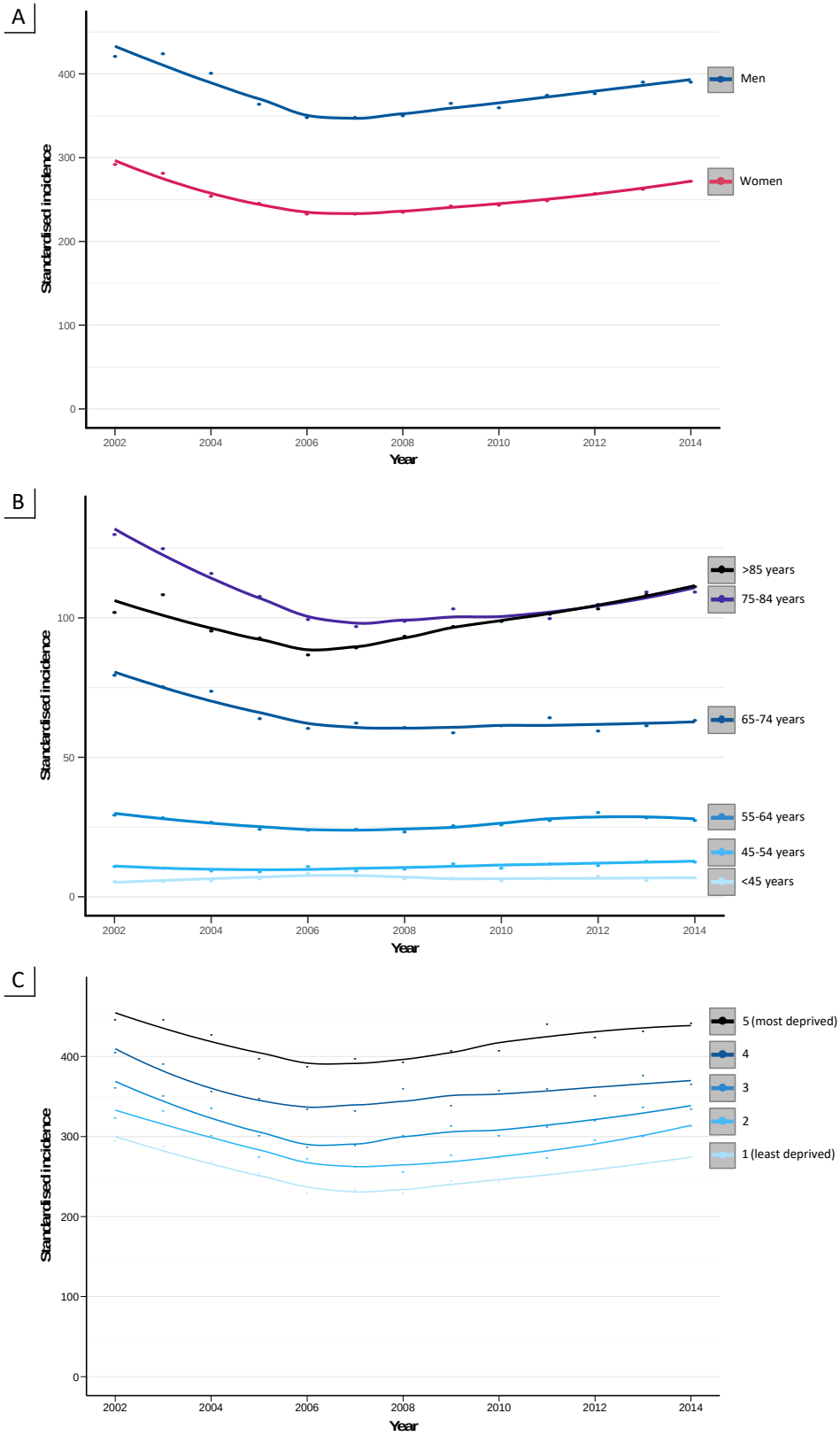
Temporal trends in heart failure incidence further presented a nadir in the years 2006-2007, which were visible across both sexes, most age-groups and all socioeconomic quintiles (**figure 5.2**).

Figure 5.1: Overall and age-stratified heart failure incidence in 2002 versus 2014



Standardised heart failure (HF) incidence (left panel) presents cases in 100,000 persons from the European standard population. Crude incidence (right panel) presents estimated number of cases in the United Kingdom (UK) population (census mid-year estimates) in 2002 and 2014.

Figure 5.2: Temporal trends in age-standardised incidence from 2002 to 2014, (A) by sex; (B) by age group; (C) by socioeconomic status quintile

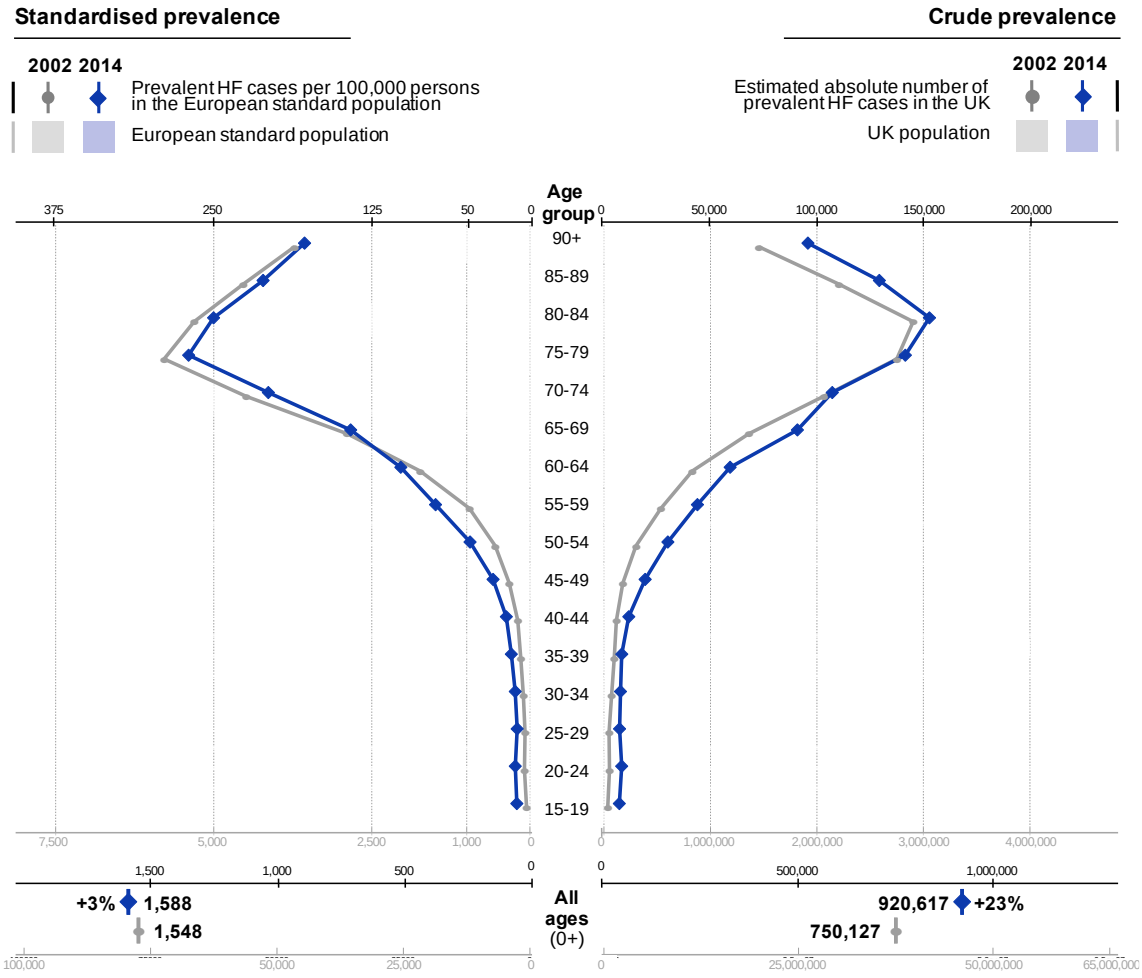


Standardised heart failure incidence refers to expected cases in 100,000 persons from the European standard population. Socioeconomic status refers to Index of Multiple Deprivation 2015 quintiles.

5.4.2 Prevalence

Age-sex-standardised heart failure prevalence rates remained relatively stable over the study period, ranging from 1.5% in 2002 to 1.6% in 2014 (adjusted rate ratio (RR) [95% CI]: 1.03 [1.02,1.05]). Nonetheless, the absolute number of people living with heart failure in the UK increased by 23% over the study period from 750,127 in 2002 (1.3% of the total population) to 920,616 in 2014 (1.4% of the total population) (**figure 5.3**).

Figure 5.3: Overall and age-stratified heart failure prevalence in 2002 versus 2014

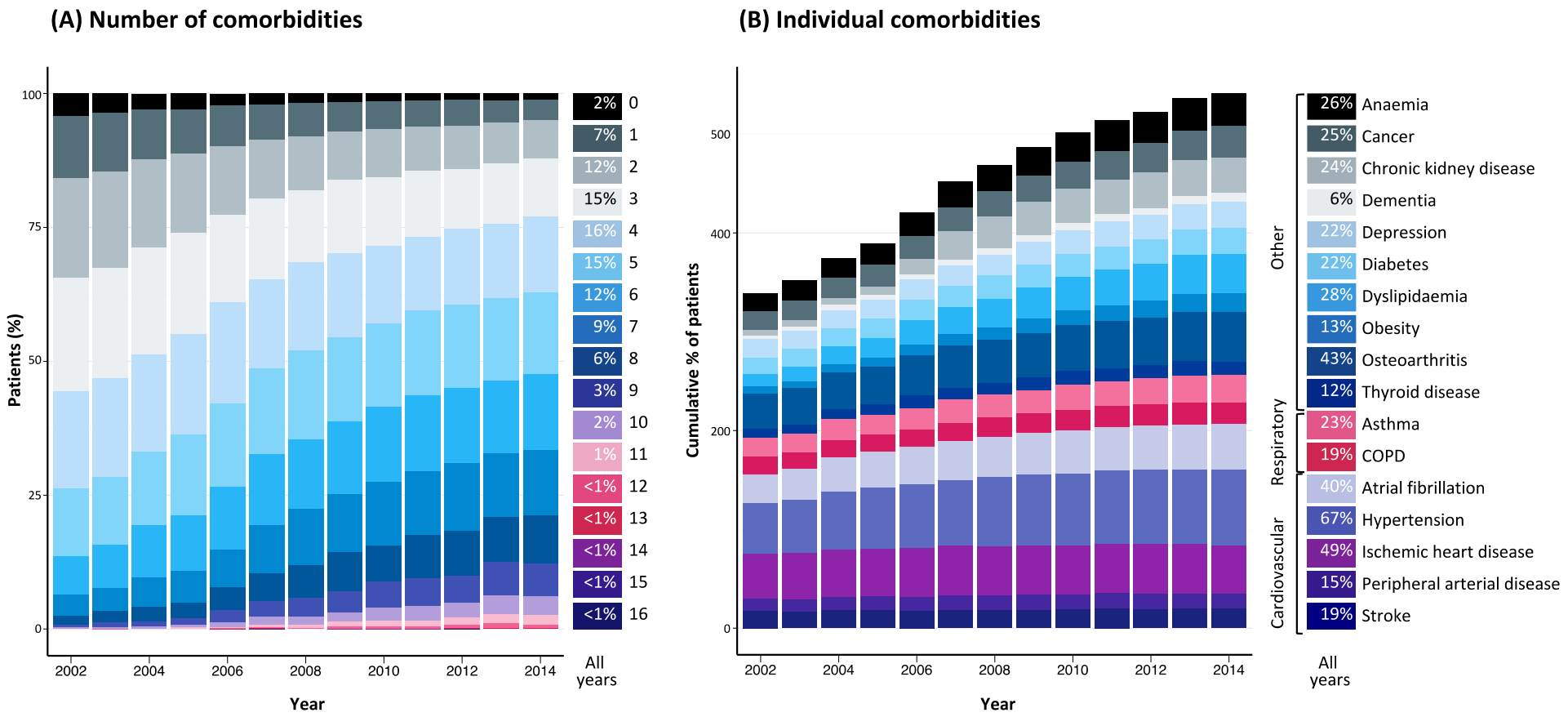


Standardised heart failure (HF) prevalence (left panel) presents cases in 100,000 persons from the European standard population. Crude prevalence (right panel) presents estimated number of cases in the United Kingdom (UK) population (census mid-year estimates) in 2002 and 2014.

5.4.3 Comorbidities

The number of comorbidities at or prior to incident heart failure diagnosis was high (mean (SD) 4.5 (2.4)) and increased over time from 3.4 in 2002 to 5.4 in 2014 (age-,sex-, and socioeconomic-status-adjusted difference 2.0 [1.9,2.1]) (**figure 5.4**). Overall 79% of patients had three or more comorbidities, increasing from 68% to 87% between 2002 and 2014. The most common comorbidities preceding a diagnosis of heart failure were hypertension (67%), ischaemic heart disease (49%), osteoarthritis (43%), and atrial fibrillation (40%). Anaemia (26%), chronic kidney disease (24%), diabetes (22%), chronic obstructive pulmonary disease (19%), stroke (19%), and peripheral arterial disease (15%) were other common preceding (or concomitant) diagnoses.

Figure 5.4: Temporal trends in comorbidities among patients with incident heart failure from 2002 to 2014



(A) Number of comorbidities affecting patients with incident heart failure out of 17 major conditions, over time.

(B) Percentage of patients affected by individual comorbidities, over time.

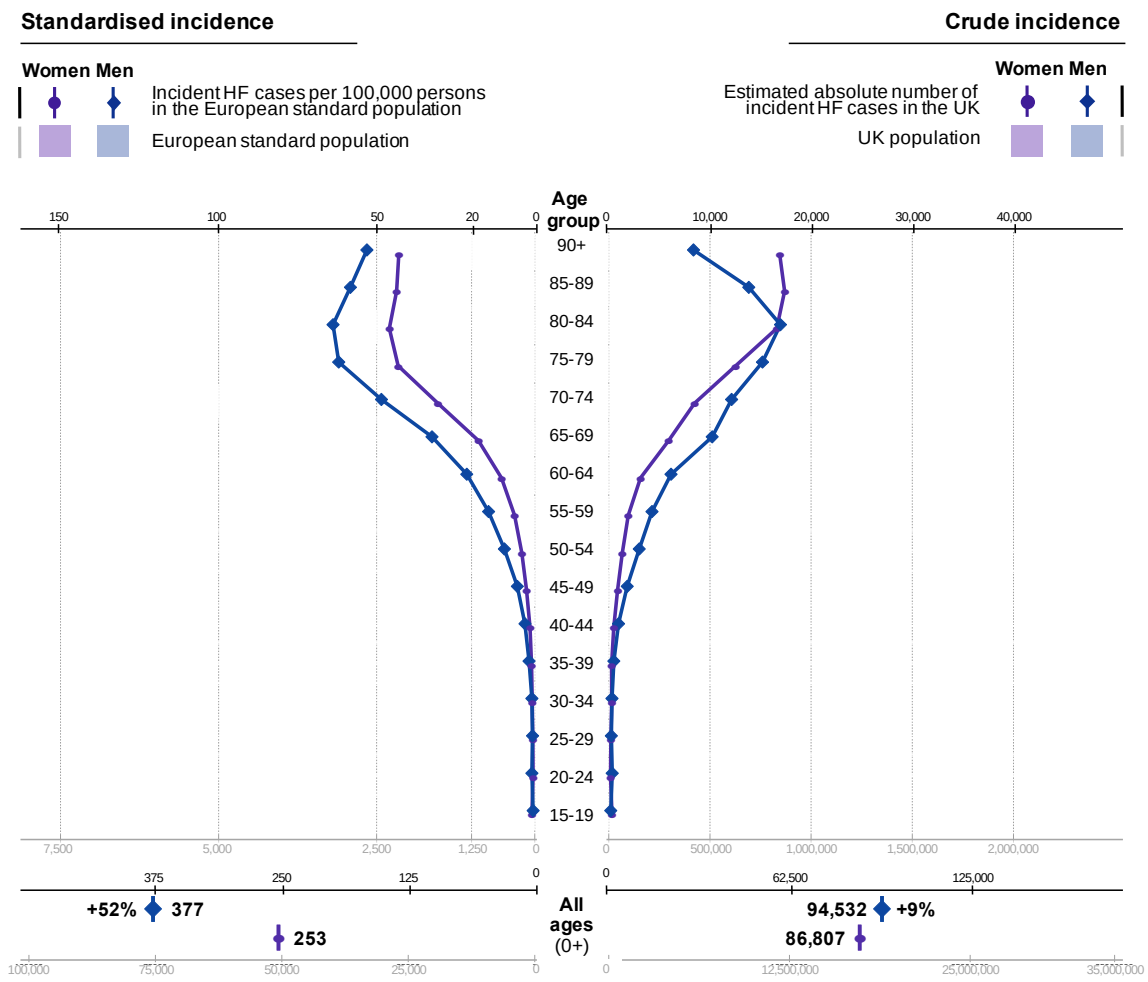
5.4.4 Age differences

Heart failure incidence gradually increased with age, and represented 13 cases per 100,000 persons among those aged less than 45 years and 5,650 cases per 100,000 persons among those aged 90 years or more. The observed decline in heart failure incidence was consistent across most age groups (**figure 5.2.B**), and the greatest reduction was observed among those aged 70-79. However, there was an increase in rates in the very elderly (85 years or more), and in those less than 55 years the rates appeared too low for a meaningful contribution to the overall burden.

5.4.5 Sex differences

Age-standardised incidence of heart failure was higher in men than women (IRR: 1.52 [1.50,1.54]), particularly in younger age groups (IRR for the 45-54 years age group: 2.23 [2.08,2.39]). However, the total number of incident cases was only 9% higher in men, due to the greater number of women in the older age groups (**figure 5.5**). Men were also younger at diagnosis than women (mean age at diagnosis 74.0 vs. 79.5 years; adjusted difference: -5.51 [-5.67, -5.35]) and more likely to be smokers (69% of current or former smokers in men compared with 47% in women). In time trend analyses, the rate of decline in age-standardised incidence was similar for men and women from 2002 to 2014 (**figure 5.2A**). A similar pattern was seen in patients with prevalent heart failure; standardised prevalence rate was higher in men than women (1.8% in men vs. 1.2% in women, RR: 1.52 [1.51, 1.53]).

Figure 5.5: Overall and age-stratified heart failure incidence for women and men



Standardised heart failure (HF) incidence (left panel) presents cases in 100,000 persons from the European standard population. Crude incidence (right panel) presents estimated absolute number of cases in the United Kingdom (UK) population (2014 census mid-year estimates). Incidence rates were calculated over all years from 2002 to 2014.

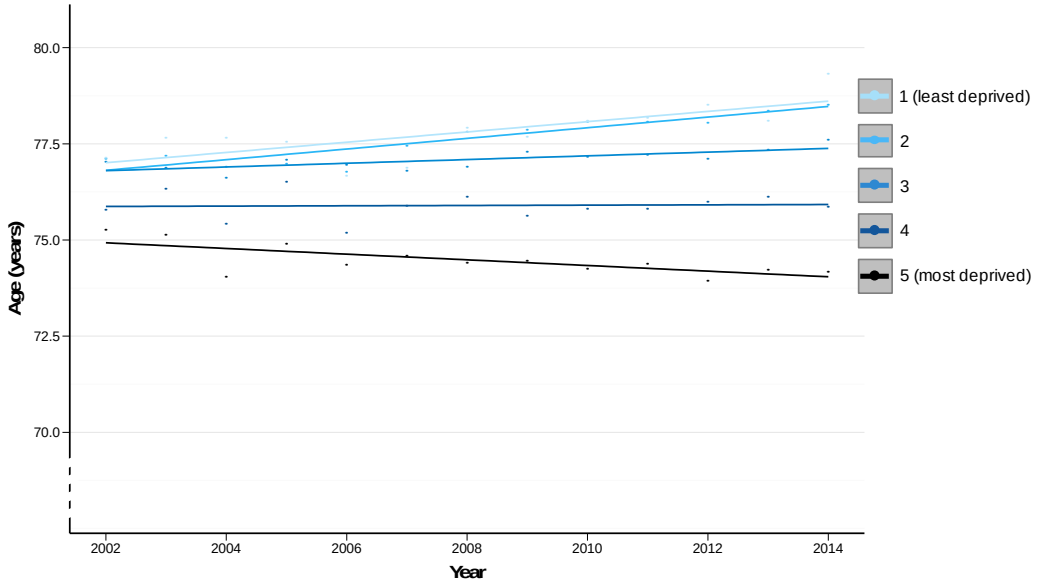
5.4.6 Socioeconomic differences

At same age and sex, patients in the most deprived socioeconomic quintile were 61% more likely to experience incident heart failure (IRR: 1.61 [1.58,1.64]). Socioeconomic inequalities were apparent across all age groups and both sexes but were more pronounced in younger age groups (IRR: 2.56 [2.30-2.85] in the 45-54 years age group vs. 1.17 [1.13,1.22] in the 85+ age group). A similar disparity pattern was observed in age-sex-standardised prevalence rates (2.0% in most deprived vs. 1.2% in least deprived, RR: 1.57 [1.55, 1.58]).

In stratified time-trend analyses, there was no evidence to suggest that the overall decline in age-sex-standardised incidence rates differed by socioeconomic quintiles (**figure 5.2C**). However, age at which heart failure was diagnosed differed by socioeconomic status and this gap in age widened over time. Over the whole study period, patients from the most deprived socioeconomic quintile were about 3.5 years younger at diagnosis than those from the least deprived (mean age at diagnosis 74.5 for most deprived vs. 77.8 for most affluent group; adjusted difference [95% CI]: -3.51 years [-3.77,-3.25]). From 2002 to 2014, age at diagnosis increased by 2.45 years [1.58, 3.32] amongst the most affluent, but tended to decrease amongst the most deprived (adjusted difference -0.44 years [-1.50, 0.61]) (**figure 5.6**). Socioeconomic inequalities were also visible in comorbidity rates, and the proportion of patients presenting with three or more comorbidities ranged from 81% to 77% for the most vs. least deprived group.

To estimate the absolute impact of socioeconomic inequalities, I investigated how absolute incidence would change if incidence rates from the most affluent group were to apply to all patients, and found that socioeconomic disparities accounted for 31,810, or approximately 18%, excess heart failure cases in the UK each year.

Figure 5.6: Temporal trends in age at incident heart failure diagnosis from 2002 to 2014, by socioeconomic status quintile

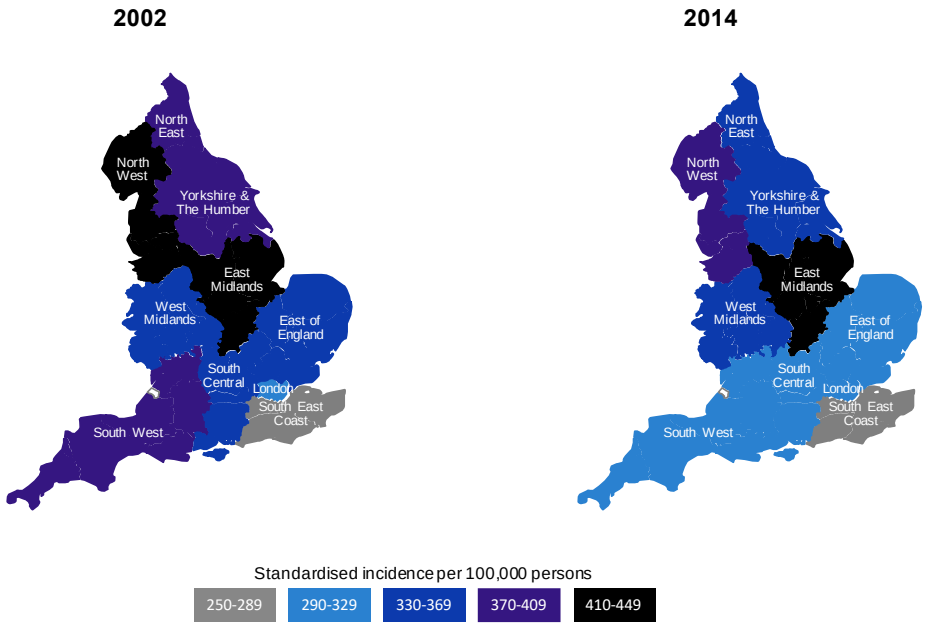


Mean age at incident heart failure diagnosis by year and socioeconomic quintile is presented with fitted linear regression lines and 95% confidence intervals in grey. Socioeconomic quintile refers to Index of Multiple Deprivation (IMD) 2015 quintile.

5.4.7 Regional differences

Heart failure incidence rates presented with substantial regional variation even after adjusting for age, sex, and socioeconomic differences. Age-sex-standardised incidence rates ranged from 268 per 100,000 patient-years in the 'South East Coast' region to 393 per 100,000 patient-years in the 'North West' region (IRR: 1.35, [1.32,1.38]). However, these overall regional differences attenuated over the study period, so that IRR between the highest and lowest incidence regions decreased from 1.44 [1.31,1.58] in 2002 to 1.26 [1.15,1.38] in 2014. Regions with highest heart failure incidence rates were those located in the North of England (North West, East Midlands, North East, Yorkshire and the Humber, West Midlands) (**Figure 5.7**).

Figure 5.7: Age-sex-standardised heart failure incidence by English regions in 2002 and 2014



Incidence rates are standardised to the European standard population. Geographical division refers to the information provided by the Clinical Practice Research Datalink (CPRD).

5.4.8 Sensitivity analyses

I have performed several sensitivity analyses to confirm the validity of heart failure cases included in the study cohort.

Case identification restricted to diagnostic codes included in national care monitoring programmes. Diagnostic codes used for main analyses were intentionally expanded from the national audit programmes list (the 'quality and outcomes framework' and the 'national heart failure audit') with additional codes indicating a heart failure diagnosis, so as to ensure completeness. In sensitivity analyses I found that 97% of patients included in the main study had a record heart failure used in the national clinical audit programmes and that restricting diagnostic codes to those used in the national audit programmes led to no significant changes in the reported temporal trends and sub-group comparisons. In light of these findings, it appeared reasonable to assume that the selection of diagnostic codes used in this study is both accurate and comprehensive, and that the resulting analyses are robust.

Case identification restricted to diagnoses recorded in secondary care, or referred for specialist assessment or echocardiography. In sensitivity analyses, I further found that 92% of patients included in the main analyses either had a heart failure diagnosis recorded in secondary care, or had been referred to a specialist cardiology service or for an echocardiography (at any point in time). While that proportion increased moderately over time, I found no significant change by sex or socioeconomic status. These findings are supportive of the validity of diagnoses underlying the present study.

For a comprehensive assessment of the validity of heart failure diagnoses documented in routine clinical practice records, I further investigated the scientific literature, healthcare reporting programmes and clinical guidelines. I found that more than 200 independent validation studies have been performed in CPRD over a broad range of conditions, including heart failure[97], with an average positive predictive value of 89%.[88] In addition, two national clinical audit programmes (the 'quality and outcomes framework' introduced in 2004 for primary care, and the 'national heart failure audit' introduced in 2007 for secondary care) ensure a stable quality of clinical coding practices and provide a solid support for the validity and consistency of recorded diagnoses of heart failure over the study period (refer to section **3.2.4 'Representativeness and validity'** for further information).

5.4.9 Additional analyses on heart failure with reduced ejection fraction

In exploratory analyses, I categorised cases as 'heart failure with reduced ejection fraction' (HF-REF) if their record included a diagnostic code with a clear reference to reduced ejection fraction within 1 year of their index diagnosis (**table 4.1**). Patients without reference to reduced ejection fraction were categorised as 'heart failure with preserved or unspecified ejection fraction' (HF-UNS). Measures of ejection fraction from echocardiography reports were not available to confirm or refute categorisation. Diagnostic classification used by hospital records did not allow reliable distinction by ejection fraction, so that most HF-REF categorisations relate to a primary care consultation.

A total of 12,101 incident heart failure diagnoses were categorised as HF-REF, and represented 22.0% of diagnoses recorded by a general practitioner. The proportion of HF-REF diagnoses differed by sex, 25% and 17% of heart failure diagnoses were classified as HF-REF in men and women, respectively (age-standardised). The proportion of HF-REF diagnoses did not differ by socioeconomic status (age-sex-standardised). Over time, the proportion of diagnoses categorised as HF-REF increased from 8% in 2002 to 30% in 2014 (RR: 3.81 [3.36, 4.25]), with a sharp increase in 2004. The temporal trend affected men and women similarly. Patients classified as HF-REF were significantly younger than those in the HF-UNS group (mean age at diagnosis: 68.5 vs. 77.3, adjusted difference: - 8.15 years [-7.86,8.45]).

5.5 Discussion

5.5.1 Summary of main findings

This comprehensive, contemporary analysis suggests that the overall age and sex standardised incidence rate of heart failure has declined by 7% between 2002 and 2014. The decline occurred in both sexes, across all regions, and in each socioeconomic group. However, because of the changing age structure of the population, the total number of incident cases in the UK increased by 12% and now exceeds that for new cases of breast, prostate, lung and bowel cancer combined.[118] The prevalence of heart failure has increased even more substantially during the same period; despite the relatively stable standardised prevalence rates, the absolute number of people living with heart failure in the UK increased by 23% from 750,127 in 2002 to 920,616 in 2014. Multimorbidity in patients with incident heart failure was common and increased in parallel to the increasing age of incident heart failure patients. In addition, significant sex, socioeconomic and regional differences were apparent and persisted over time.

5.5.2 Comparison with existing literature

This study presents an important complement to the inconsistent knowledge-base of heart failure incidence (**table 2.1**).[1,22–26,110] Many of the previous studies refer to limited data sources – either from general practice consultations[36] or hospitalisations[111,112] – whereas it is only by considering both in- and outpatient care that one can fully capture the burden of the disease

and accurately distinguish between incident and prevalent cases. Perhaps unsurprisingly reported incidence rates of heart failure vary from 60 per 100,000 in a UK-based study of primary care data[36] to 538 per 100,000 in a large-scale study from Canada that considers diagnoses recorded by general practitioners, specialists, and hospital discharges.[24]

Among those studies that covered both inpatient and outpatient diagnoses, two US-based studies are particularly relevant in light of the depth of analyses they provide and the long time-span they refer to: the Framingham cohort[25] and the Olmsted county studies.[1,23] Limitations of these studies relate to the restricted populations they refer to and the comparatively small sample size which may reduce the generalisability of their findings. Quantitative comparison of incidence rates across studies is further hindered by standardisation methods that do not refer to a publicly available standard population. For illustrative purposes, I observe that with an incidence rate of 332 per 100,000, the results from this thesis are slightly above those reported by the recent Olmsted study, and slightly below those reported by the Framingham study for the 1990-1999 period.

Temporal trends reported within studies are more interesting and comparisons are relevant. The declining age-standardised incidence of heart failure reported in this thesis is consistent with previous studies, although the magnitude of decline appeared to be less pronounced than in data from the US, Canada, or Sweden from the same period.[1,24,26] The higher age-standardised incidence rate ratio for men is consistent across heart failure incidence studies, although reports vary in proportions[1,22,25]. While previous studies have reported stronger age-standardised decline in women[1,25], results from this thesis present similarly declining rates for both men and women.

5.5.3 General discussion of findings

Incidence and prevalence

The age-sex-standardised incidence rate of heart failure declined modestly in comparison with myocardial infarction where incidence rates have declined by about one third over a similar time period in England, as in many other countries.[119] The comparatively small reduction in

standardised heart failure incidence rate might be due to higher survival rates amongst patients with post-myocardial infarction ventricular dysfunction as a result of improvements in medical treatment.[119–121] Further insights into these trends come from stratified analyses. Although the declines in rates were largely consistent for both sexes, across all socioeconomic groups and regions, the age-stratified analyses show some discordant trends. The standardised incidence rates appeared to have *increased* in the very elderly (>85 years) despite declining rates for myocardial infarction in the same age category.[119,122]

The rise in incidence of heart failure in older people may reflect less effective control of cardiovascular risk factors in those age groups. Alternative explanations include policy interventions for better diagnosis and management of patients in the community[104] and investments into specialist heart failure services which may have led to higher diagnosis rates, in particular among the elderly. Such national policy interventions and investments in services could also explain the observed nadir in the number of new heart failure diagnoses in the years 2004 to 2006, which coincides with the introduction of a national care monitoring programme, the 'quality and outcomes framework'. However, such modest short term variations have also been observed in other long-term heart failure incidence studies[1,23] and may reflect random variation.

Standardised trends are necessary for comparing changes in disease burden over time and place, but to service payers, providers and researchers, it is also important to know the absolute numbers of patients requiring treatment. Despite a modest decline in standardised incidence rates, there has been a 12% *increase* in the total number of new cases of heart failure cases. This is substantial, and, by comparison, is now similar to the total number of new cases of breast, prostate, lung and bowel cancer combined.[118] The predominant reason for the rise in incidence is the increasing number of older people in the UK, a demographic change reflected in many other countries. More specifically, the number of people aged 65-69 years has increased by 36%, representing the post-war 'baby-boom' generation that is now reaching the age at higher risk of heart failure.

The prevalence of heart failure has increased even more substantially than its incidence, possibly as a result of longer survival after heart failure diagnosis. Overall, despite a relatively stable standardised prevalence rates, the absolute number of people living with heart failure has increased by 23%.

Comorbidities

The number of comorbidities associated with heart failure was high and increased between 2002 and 2014 in parallel with increasing age at onset. This suggests that in addition to the growing number of patients with heart failure, their clinical management is becoming more complex, further increasing the burden on health services and demand for specialist cardiology input in multi-disciplinary care teams.

The increasing number of comorbidities is likely to be influenced by several factors, and further research is needed to understand its determinants. Two factors appear to be of particular importance. First, the declining incidence of heart failure suggests that disease onset has been prevented in certain, most likely healthier, patients. Hence over time the cohort of patients with incident heart failure has become smaller, concentrating a more comorbid and older population. This assumption is supported by the increasing age of the cohort, and the association between age and incidence of multi-morbidity is well established.[123] Second, changing clinical guidelines, improved physicians' awareness, screening programmes, technological advances or improved availability of diagnostic tests, may have influenced recording rates for certain conditions, hence reducing historic under-diagnosis. Studies have suggested this to be the case for diabetes[124] and CKD[125]. Dyslipidaemia may present similar patterns in line with more common cholesterol screening. Finally, one cannot exclude that for certain conditions, the observed increasing prevalence is due to increasing incidence of the disease because of clinical, environmental or life style risk factors.

Observed prevalence rates of key comorbidities are broadly consistent with those reported in clinical trials. For example, rates of atrial fibrillation are consistent with rates observed in the PARADIGM-HF trial, the largest and most recent heart failure trial.[126] As for ischaemic heart disease, observed prevalence rates fall within the range of previous trials, accounting for the

difference in underlying prevalence of coronary artery disease between heart failure with reduced ejection fraction (HF-REF) and heart failure with preserved ejection fraction (HF-PEF) (ischaemic aetiology in ATMOSPHERE 56%, PARADIGM-HF 60% and I-Preserve 25%; coronary heart disease in TOPCAT 59%) and epidemiological/registry reports (e.g. 28% in the Olmsted county cohort [23] or 55% a the recent Swedish study[26]).

Beyond the number of comorbidities, the nature of comorbidities observed in this study reveals interesting patterns. Given that heart failure is a common complication of several cardio-metabolic conditions, the high prevalence of such diseases is not surprising. Yet, non-cardiovascular comorbidities also make a significant contribution to multi-morbidity in heart failure and these have been increasing over time. Some of these, such as chronic obstructive pulmonary disease, could be due to shared risk factors, such as smoking.[127] However, the particularly common occurrence of osteoarthritis, which in this study was the third most frequent comorbidity, has not been described and is perhaps less expected. This may simply be due to co-occurrence of two common chronic diseases that show a highly age-dependent burden. However, one could also speculate that some heart failure events are caused or precipitated by osteoarthritis or non-steroidal anti-inflammatory drugs that are commonly used to treat its symptoms.[128,129] Future appropriately designed studies could investigate this question further.

Sex differences

Differences in incidence and prevalence of heart failure by sex provides valuable insights for clinical management and future research. The findings from this study confirm previous reports of considerably higher age-standardised incidence in men than women, but also shows that in practice, due to the higher number of women among older age groups, the total number of patients affected is actually similar for both sexes. Moreover, differences in age at diagnosis between men and women and prevalence of smoking are clearly identifiable. These findings suggest that appropriate management of heart failure is equally important for women and men. Important differences in baseline characteristics and risk factors by sex deserve further

investigation and may need to be considered for more tailored prevention and management strategies.

Socioeconomic differences

Achieving equity in access to essential health care has been a goal of many health care systems and is now a specific target of the United Nation's Sustainable Development Goal 3. Previous studies have shown that in countries where the human development index (a composite measure of gross national income per capita, life expectancy, and education) is low, patients present with heart failure at a much younger age.[3] Likewise, at the country-level, socioeconomic deprivation is associated with an increased incidence of heart failure.[36,130] The present study extends these earlier findings by showing that lower socioeconomic status is not only associated with higher standardised incidence of heart failure, but also an earlier disease onset and higher comorbidity rates. Time-trend analyses further show that there has been no substantial convergence of the incidence rates by socioeconomic status and in fact the age-gap between the most and least deprived groups has widened by almost 2.5 years over the study period. The present study was not designed to investigate the causal role of socioeconomic status or pathways through which it affects heart failure incidence. However, previous research has shown that the variability in heart failure incidence by socioeconomic gradient is likely to be explained by several biological, environmental and behavioural risk factors, including but not exclusively, known cardiovascular risk factors such as smoking, obesity or blood pressure.[130,131] Thus, achieving equity in outcomes is likely to require additional population-level and individual-level interventions. The persistent and partly widening gaps in disparities in a healthcare system with equality of access to healthcare also raises questions about how, when and where more deprived patients seek care and, whether additional efforts are necessary to achieve equity in health care use (as well as access).

Regional differences

The English 'North-South' inequality in health has been widely reported,[132–134] with cardiovascular diseases as the largest factor behind health inequalities.[135,136] Previous studies have also shown inequalities to remain persistent after adjustment for socioeconomic

deprivation[134] and only partly explained by common cardiovascular risk factors such as systolic blood pressure, body mass index, or smoking[137]. Many other factors might plausibly explain the excess heart failure incidence in the north of England. These include concomitant medical conditions and their treatments (e.g. respiratory diseases, depression, musculoskeletal affections, or infections) often linked to environmental (e.g. working conditions or air pollution) and lifestyle (e.g. diet or drug prescription habits) factors. Observed disparities offer potential opportunities to design more targeted and equitable prevention strategies, and suggest that prevention measures in England may need to prioritise northern regions to reduce inequalities. Further research is needed to understand the determinants of geographical disparities.

Heart failure with reduced ejection fraction

Because measures of ejection fraction are not routinely recorded in the CPRD database, this thesis restricted analyses of heart failure with reduced ejection fraction (HF-REF) to exploratory analyses. As a proxy for ejection fraction measurements, I used information provided by diagnostic codes to identify patients with reduced ejection fraction. This approach is also the one used by the 'quality and outcomes framework' to monitor and incentivise evidence-based heart failure management in the UK. Because most diagnostic codes are unspecific in regard to the type of ejection fraction sub-group, this approach is likely to strongly underestimate the true number of HF-REF cases. Indeed, available data suggest that heart failure with reduced ejection fraction (HF-REF) represents 40-50% of all heart failure cases[62,110,138], with a higher proportion of cases in men than women[1]. In this study, rates were somewhat lower (in 2014 HF-REF cases represented 30% of heart failure diagnoses recorded in primary care), but consistent with accounts from the 'quality and outcomes framework' which reports that 30% of prevalent heart failure cases seen in primary care are due to left ventricular systolic dysfunction in 2014.

Nevertheless, the evolution of case categorisation over time provides interesting insights in regard to changing clinical practices and characteristics of the HF-REF sub-group which are likely to be indicative of the true HF-REF population. For example, the sharp increase in HF-REF diagnoses in 2004 corresponds to the introduction of 'quality and outcomes framework'

guidelines which require practices to produce a register of patients with left ventricular dysfunction so that the observed increase is likely due to improved coding practices.

5.5.4 Strengths and limitations

A major strength of this study is the selection of a large representative cohort across primary and secondary care, with a sufficient number of cases in each sex, age, socioeconomic, and regional category to allow overall and sub-population analyses. This population-based approach increases the generalisability of findings compared with surveys that select partipants.[81] Moreover, given the similarity of trends in cardiovascular disease and population ageing from the UK with other European countries, North America and Australasia[139,140], findings from this thesis are likely to be broadly applicable to much of the rest of the developed world.

One of the key limitations of this study was the incomplete clinical information contained in the electronic health records available. In particular, left ventricular ejection fraction values were not available, meaning that it was not possible to identify the exact type of heart failure.

Geographical analysis in this thesis was also limited to the 10 regions provided by the CPRD dataset, which varied in size and included between 12 and 94 general practices. More granular geographical information would have allowed more precise investigations of intra-regional variability, but was not available.

Research using electronic health records data is further reliant on the accuracy of clinical coding input by physicians. While the reliable diagnosis of heart failure can be challenging, particularly among elderly and in primary care settings, several elements support the validity of clinical diagnoses this study relies on. First, in the United Kingdom, echocardiography and specialist diagnosis of heart failure are incentivised and monitored by the 'quality and outcomes framework' (QOF), which was announced in 2002 and formally introduced in 2004.[141] QOF reports indicate that at least 95% of all heart failure patients diagnosed in primary care were referred for echocardiography or specialist assessment, since its introduction.[142] In secondary care settings, the 'national heart failure audit' introduced in 2007 reports that approximately 90% of recorded heart failure diagnoses in England are referred for echocardiography, specialist

assessment, or B-type natriuretic peptide (BNP) and ensure a stable quality of clinical practices. My own sensitivity analyses further confirm these numbers and show that 92% of patients included in the study cohort had a heart failure diagnosis recorded in secondary care, or a record of either specialist cardiology service or echocardiography referral. More generally, the validity of clinical diagnoses recorded in CPRD has been investigated for a wide range of diseases, including heart failure[97] and other common chronic conditions[98], with an average positive predictive value of 89%[88] and 92% completeness, compared with national registry data[75] (refer to section **3.2.4 'Representativeness and validity'** for further information). Finally, even though diagnoses in particular patient groups, such as elderly persons, may be more prone to misclassification by specialists or non-specialists, no evidence suggests that such errors would have substantially changed over time, so that it was deemed reasonable to assume the reported temporal trends were unlikely to be affected.

Validity of diagnoses presents as an essential trade-off that has to be made in the design of incidence studies. At the one end, investigators may decide on a smaller cohort for the ability to better validate diagnoses according to specific criteria, such as the Olmsted county studies.[1] Such studies have the advantage of better differentiation between the two main types of heart failure and treatment specific to each of them. On the other end, very large-scale studies, in particular when representative of a whole nation, enable assessment of relative as well as absolute disease rates overall and in several subgroups (e.g. by age, socioeconomic status and time), and precisely because they are based on routinely reported diagnoses they are more likely to capture the burden of disease as diagnosed by physicians and covered by health services. These two types of studies are complementary, and as such, the present study presents one piece of evidence on the incidence of heart failure that is to be considered within the broader scientific literature.

5.5.5 Policy and practice implications

These results present policy makers with important elements to address the impact of heart failure in developed countries, and to rethink management strategies, underlying guidelines, as well as reprioritisation of resources in the following areas:

- **Research prioritisation** on the determinants of heart failure incidence. Most importantly investigating the reasons behind sex, socioeconomic and geographic disparities in heart failure incidence rates is essential for the development of better prevention measures.
- **Prevention strategies** to address inequalities. Current prevention strategies have been insufficient to reduce the burden equally among socioeconomic groups and regions, and need to be reassessed to accommodate the demographic shift and improve their reach to less affluent populations.
- **Resource allocation** that plans for the increasing number of cases. Further resources will likely need to be allocated to diagnostic and management services outside hospitals; for example, by extending the availability of natriuretic peptides testing in the community to ease the burden on echocardiography services, or by setting up IT-supported home monitoring programmes.
- **Models of care** that are scalable, adaptive, and multidisciplinary, to the increasing, diverse and largely multi-morbid patient population. Current primary and secondary care models for diagnosis and management of heart failure might not be sufficiently scalable for this emergent burden or ready for the complex management of such patients, and will need to be adapted. This situation calls for more patient-centric approaches that enable identification and management of potentially competing patient needs.

5.5.6 Future research

The description of temporal trends in the incidence of heart failure reveals several surprising results that deserve further investigation. A major finding relates to the fact that heart failure incidence has not declined as much as other cardiovascular disorders over the same period, and seems to have declined less so in the UK than in recent US based studies. Yet perhaps the most important finding relates to the magnitude of regional and socioeconomic disparities. All these suggest that a lot remains to be done to address the partly preventable nature of heart failure.

The present study was designed to be descriptive and not to investigate causality between risk factors and incidence of heart failure. Although various other studies have investigated this subject, disparities by socioeconomic, region and sex affecting the incidence of heart failure are only partly understood and deserve further investigation. A comprehensive understanding of risk factors is crucial to support the design and implementation of more appropriate prevention strategies and ultimately reduce the incidence and prevalence of the condition.

Similarly, this study highlights a high prevalence of comorbidities at the time of new-onset heart failure. Some of these conditions and associated treatments, such as ischaemic heart disease or cancer, are known to be on the causal pathway of heart failure. Others, in particular non-cardiovascular disorders present with surprisingly high prevalence and their association with new-onset heart failure has not been studied comprehensively. Further appropriately designed studies are warranted to investigate whether some of these conditions or associated therapies, for example as pertains to osteoarthritis or other inflammatory conditions, actively contribute to the development of heart failure.

5.6 Conclusion

These findings have important implications for health care resource planning and preventive strategies. The decline in standardised heart failure incidence rates, in particular in the 60 to 79 years age group, suggests that heart failure prevention has improved, probably due to a combination of environmental changes, public health measures and improvements in clinical care. However, the increase in the absolute number of incident and prevalent cases of heart failure is placing an increasing burden on healthcare. The profile of patients with heart failure is diverse and evolving over time - with a trend towards an older age and a substantial increase in the number of associated comorbidities - indicating that both prevention and management are becoming more complex. The observed disparities in heart failure incidence by sex, socioeconomic status and region point to potential opportunities for more targeted and equitable prevention strategies.

5.7 Research in context

5.7.1 Evidence before this study

I searched Pubmed for reports published from 1 January 2000 to 30 April 2017 that included “heart failure” and “incidence” in their title, reviewed references of clinical practice guidelines and consulted with experts for relevant studies.

Estimates of heart failure incidence rates, trends over time, and association with patient features were scarce and inconsistent. Studies frequently referred to restricted populations or to

limited data sources, either from general practice consultations or hospitalisations. In an attempt to compare reports of heart failure incidence, I selected a subset of studies that (i) referred to a community-based cohort, (ii) included outpatient diagnoses in their case identification, (iii) presented incident rates in the general population (all ages and sexes), and (iv) considered all types of heart failure. I found that reports differed in their approach to age-standardisation, rendering comparisons amongst studies challenging, and that reported incidence rates varied tenfold across studies (**table 2.1**). No study presented both crude and standardised rates overall and by subgroups.

5.7.2 Added value of this study

This study provides important new information on the contemporary incidence of heart failure and insights into its variation over time, by age, sex, region and socioeconomic status.

Crude and standardised incidence rates are derived from a large, representative, general population cohort, and set a baseline for international comparison, monitoring of prevention strategies and informed design of public health policies.

This research provides evidence that, in the UK, the burden of heart failure is increasing due to population growth and ageing, and is similar to the combined incidence of breast, prostate, lung and bowel cancer. Many high-income countries present with similar population structures and temporal changes, and are likely to experience a similar burden.

Finally, results highlight important changes in patients' profile over time - with a trend towards an increasing age at first presentation and an substantial rise in the number of associated comorbidities - and quantifies the magnitude of socioeconomic disparities in heart failure, showing that these are not only affecting incidence, but also age at first presentation and comorbidity rates.

5.7.3 Implications of all the available evidence

In Western countries, improvements in heart failure prevention have been achieved but remain modest compared with other cardiovascular diseases. Population growth and ageing, observed

in many high-income countries, have been shown to overcome these improvements leading to an increasing absolute burden of heart failure.

Heart failure incidence is similar to the four most common causes of cancer (lung, breast, bowel and prostate) combined, and requires reinforced public health action in prevention, resource planning, as well as efficient and effective care delivery.

The profile of patients with heart failure, while mostly elderly, male, multi-morbid, and deprived individuals, remains diverse and is changing over time. Socioeconomic disparities in disease incidence, age at onset, as well as associated comorbidities point to a potentially preventable nature of heart failure that still needs to be tackled.

6. DELIVERY OF CARE

6.1 Introduction

6.1.1 Quality of care

Quality of health care is commonly defined as 'the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge', as described by the US 'Institute of Medicine' (now named 'National Academy of Medicine').[143] This definition establishes six important components of a health care system that provides high quality care to individuals: the system is safe, effective, patient-centred, timely, efficient and equitable.[143]

Until the 1990s, professional judgment was relied upon to ensure that patients received high-quality care; and the monitoring of and improvement in quality were viewed as the responsibility of individual clinicians.[144] However, as evidence has emerged regarding wide and inexplicable variations in practice patterns as well as quality, interest has grown in collecting and assessing objective measures.[145]

Assessing health care quality objectively is a difficult and controversial task, and developing a 'measure' for its assessment is often viewed as an "elusive" goal.[146,147] Health care is made up of diverse components of services, varying from mammography screening for breast cancer to performing surgery and to counselling for depression.[146] To break down the measurement challenge into manageable units, the conceptual framework proposed by Avedis Donabedian is often used. This framework identifies three dimensions of quality: 1) structure, 2) process, and 3) outcome.[147] Structural data are characteristics of physicians and hospitals (e.g. a physician's specialty or the ownership of a hospital). Process data are the components of the encounter between a health care professional and a patient (e.g. diagnostic tests ordered). Outcome data refer to the patient's subsequent health status (e.g. an improvement in symptoms or

mobility).[144] Different groups in the health care system also have different issues of concern regarding the quality of health care and are interested in different measures of performance.[146] Physicians generally view quality in health care as the application of evidence-based medical knowledge to the particular needs and wishes of individual patients. Some patients may place more importance on how clinicians communicate with them, or how long they are kept waiting for appointments, whereas private healthcare payers may prioritise patient satisfaction, and public health care payers may place particular focus on the use of preventive services.[146]

Due to the high complexity and various different perspectives on the matter, quality of care measures are often controversial. The most criticised aspects are that measures are typically based on easily measured, intermediate endpoints, such as risk-factor control or care processes, not on meaningful, patient-centred outcomes; and their use interferes with individualised approaches to clinical complexity which may lead to gaming, overtesting, and overtreatment.[148] There is also limited evidence that many quality measures - including those tied to incentives and those promoted by health insurers and governments - lead to improved health outcomes.[148]

Recent perspectives view the multifaceted nature of the quality of care as a critical component for the implementation of health interventions. Indeed, increased uptake of health services requires not only better technical quality, but also better acceptability and patient-centeredness – across the continuum of care. Perceptions of quality are shaped by interconnected community, the health system and individual factors; the quality of care may not be understood fully without some appreciation of the social norms, relationships, values and trust within the communities and societies where care is provided.[149]

Taking into account different perspectives and complexities, the present study does not attempt to define ‘quality of care’. Instead, the study was designed to examine different, important aspects of heart failure management that could help identify gaps in care, and provide valuable information as a basis for health services to improve the care received by heart failure patients. Specifically, the objective was to establish a framework that describes patient-centred trajectories of care and indicators that appropriately reflect clinical practice guidelines for the management of heart failure. Rather than comparing individual physicians or regions, the study

set out to investigate trends over time, allowing not only one-time measurements but understanding how different aspects of care have changed over time. In essence, the study was designed to go beyond the much investigated and one-dimensional question 'are physicians prescribing evidence-based therapy?', and to examine whether patients receive appropriate care in a timely, continuous and equitable manner, and whether care has improved over time.

6.1.2 Assessment of heart failure care

The past 25 years have witnessed remarkable developments in clinical interventions that improve symptoms, quality of life, and prognosis in patients with heart failure. However, effective clinical care involves a complex process of investigations, step-wise initiation of medicines, and dose-titration that often takes place in different care settings over several months, and can be difficult to implement consistently. Although clinical guidelines provide a valuable tool to support physicians in the management of heart failure patients,[6,12,38–42] ensuring optimal use of evidence-based therapies in routine clinical practice remains a major concern and challenge to health services worldwide.[2,3]

In the UK, two major programs have been introduced to improve physicians' adherence to evidence-based practices: the 'Quality and Outcomes Framework' (QOF),[43] a healthcare reporting and incentives schemes that applies to primary care physicians and was initiated in 2004; and the 'National Heart Failure Audit' (NHFA),[7] a large-scale reporting scheme for secondary care launched in 2007. Each scheme individually produces yearly reports on selected heart failure care indicators with very high rates of adherence to clinical guidelines.[44,45] Yet, programs only consider the clinical setting for which they were designed and have not assessed their broader impact on patient care across the continuum of primary and secondary services, which chronic conditions, such as heart failure, rely on. More generally, similar limitations apply to studies that have investigated heart failure care in Western countries. So far, studies have been largely confined to specific clinical settings, selected cohorts, and limited follow-up information, with no ability to describe and compare patient trajectories following a new diagnosis of heart failure. Finally, little is known of variations in care practices by important

patient characteristics, such as age or sex. (For a detailed literature review refer to section **2.3 'Prior evidence on clinical practice gaps'** and **table 2.2**).

To address these knowledge gaps, I used a database of linked primary and secondary healthcare records in the UK,[5] and performed a longitudinal assessment of outpatient care, covering diagnosis, follow-up, diagnostic investigations, treatment initiation, and dosages in patients with incident heart failure. I further sought to investigate temporal trends and variation by important patient characteristics such as age, sex, and socioeconomic status.

Parts of this chapter have been published in *PLOS Medicine* at

https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002805. This publication benefitted from the input of several co-authors as well as my thesis supervisors. My role consisted in designing the study, conducting the literature searches, the data extraction, all statistical analyses, and writing the first draft of the manuscript.

6.2 Aims

The research presented in this chapter aimed to investigate the clinical care received by heart failure patients across a broad range of indicators, from diagnosis up to one year later, and to examine any variation over time, age, sex, and socioeconomic status.

6.3 Methods

6.3.1 Data source

The study was conducted using electronic health records from the Clinical Practice Research Datalink (CPRD), a cohort that is broadly representative of the UK population in terms of age, sex and ethnicity. Primary care records from CPRD were linked to secondary care admission records from Hospital Episodes Statistics (HES) Admitted Patient Care data. Primary care data was available from 1 January 1985 to 31 December 2015, and linkage was available from 1 January 1998 to 30 September 2015 (for a detailed description of the dataset refer to **Chapter 3**).

6.3.2 Eligible participants

Patients eligible for inclusion in the study were men and women aged 16 and over, contributing data during the period 1 January 2002 to 31 December 2014, registered with their general practice for at least 12 months, and whose record was labelled as 'acceptable' by CPRD quality control[5] and approved for CPRD and HES linkage (4,048,213 records).

6.3.3 Case identification

Heart failure diagnosis was defined as the first record of heart failure in primary care or hospital admission records from any diagnostic position, using a total 147 diagnostic codes (refer to section **4.5 'Study population'** for further description).

Patients were categorised as having 'heart failure with reduced ejection fraction' (HF-REF) if their record included a diagnostic code with a clear reference to reduced ejection fraction within one year of their index diagnosis (table 3.1). Patients without reference to reduced ejection fraction were categorised as 'heart failure with preserved or unspecified ejection fraction' (HF-UNS). Diagnostic classification used by hospital records did not allow reliable distinction by ejection fraction, so that most HF-REF categorisations relate to a primary care consultation.

6.3.4 Study population

A total of 93,074 patients newly diagnosed with heart failure between 2002 and 2014 were identified following the methods described in **Chapter 5**.

6.3.5 Study design

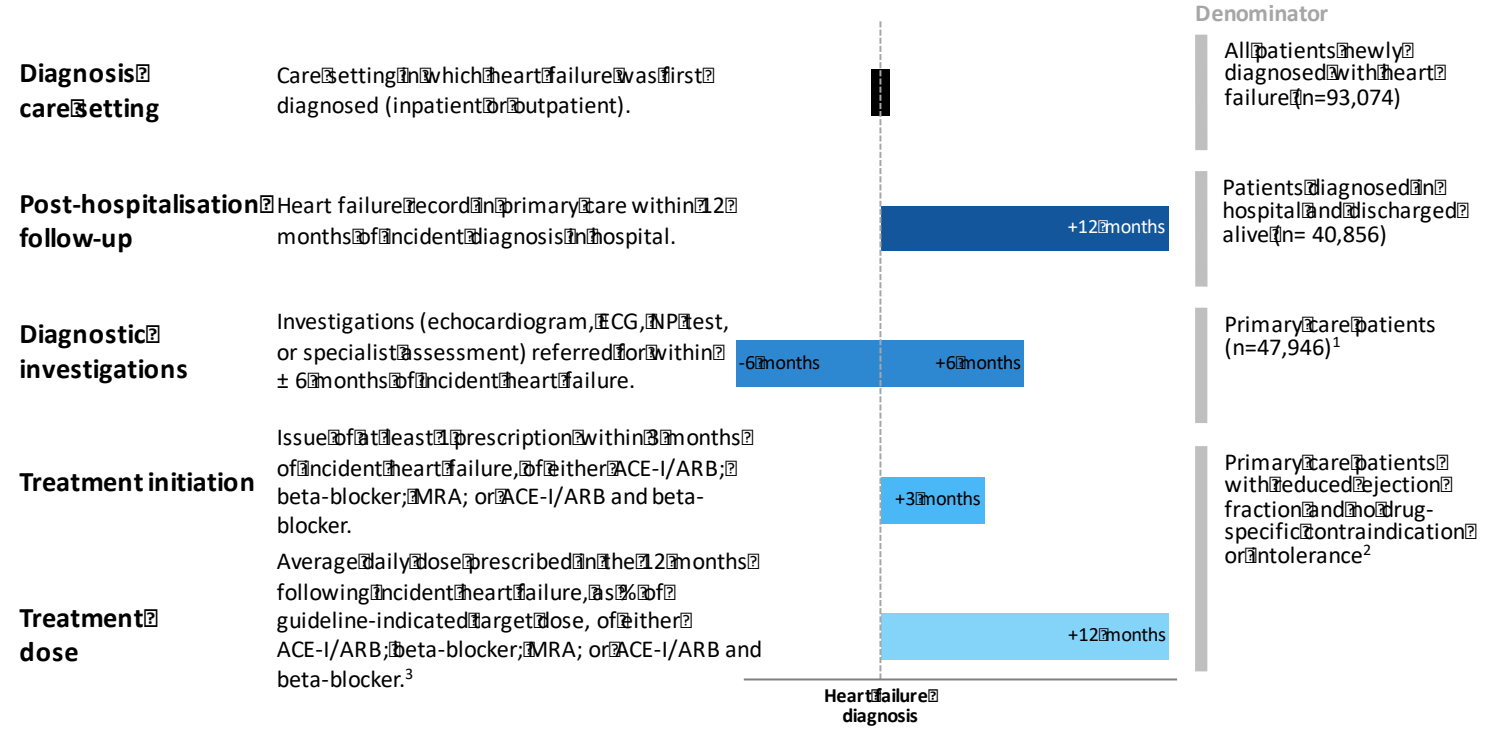
The study uses a descriptive design and a retrospective, observational population-based cohort.

6.3.6 Study outcomes

Five aspects of care across the disease trajectory of patients with heart failure were investigated: (i) diagnosis care setting, (ii) post-hospitalisation follow-up, (iii) diagnostic investigations, (iv) prescription of essential medicines, and (v) treatment dosages. Data about diagnostic investigations and prescriptions were only available in primary care records, so that indicators (iii), (iv) and (v) were restricted to patients whose heart failure was recorded in primary care

(n=47,925). Analysis of guideline-recommended drug treatment was further restricted to patients with reduced ejection fraction (n=11,040) with no record of drug-class-specific contraindications or intolerance (**table S1**). **Figure 6.1** provides an overview of study outcome measures with further details provided below.

Figure 6.1: Definitions of essential care indicators



[1] Primary care patients include all outpatient diagnoses and inpatients with post-hospitalisation follow-up. [2] For ACE-I/ARB n=9,920; for beta-blocker n=8,430; for MRA n=10,896; for ACE-I/ARB and beta-blocker n=7,768. [3] In sub-group analyses we further investigated the average daily dose prescribed in the 3 months preceding diagnosis.

***Abbreviations**: ECG = electrocardiogram, NP = natriuretic peptides, ACE-I = angiotensin-converting-enzyme inhibitor, ARB = angiotensin receptor blocker, MRA = mineralocorticoid receptor antagonists.*

The care setting in which heart failure was first diagnosed was categorised as either inpatient or outpatient. Inpatient diagnoses were further categorised based on whether heart failure was listed in primary or secondary diagnostic position. Outpatient diagnoses refer to diagnoses first recorded in primary care with no prior hospitalisation, and are likely to reflect both outpatient consultations by specialists and direct diagnoses by general practitioners.

The potential for primary care follow-up after diagnosis in hospital (in short follow-up) was defined as the documentation of heart failure in primary care records within 12 months of diagnosis, with the rationale that documentation of diagnosis is a prerequisite for subsequent disease monitoring and management (see section **6.4.4 'Sensitivity analyses'**).

Diagnostic investigations included tests recommended as "essential" by the European Society of Cardiology (ESC) guidelines:[42] (i) echocardiogram; (ii) electrocardiogram (ECG); and (iii) plasma natriuretic peptides (B-type natriuretic peptide [BNP] or N-terminal-pro-BNP [NT-pro-BNP]), as well as (iv) cardiology specialist assessment, within ± 6 months of incident heart failure diagnosis. Diagnostic tests were considered individually and as a composite of any of the four tests. The list of diagnostic codes used to identify diagnostic tests are presented in **table S2**.

Drug treatment patterns were investigated for the three main treatment classes indicated in the management of heart failure with reduced ejection fraction by the ESC guidelines[42]: (i) angiotensin-converting-enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB); (ii) beta-blockers; and (iii) mineralocorticoid receptor antagonists (MRA).

For each of the three drug classes, I report treatment initiation as the proportion of eligible patients who received at least one prescription in the first three months following their heart failure diagnosis. A composite treatment initiation indicator was defined as prescriptions for the two treatment classes indicated in all patients with heart failure with reduced ejection fraction, which are ACE-I or ARB, and beta-blockers.

Calculations further included the average daily dose prescribed to eligible patients over all days alive and registered with their general practice, in the first 12 months following incident heart failure (see section **6.3.7 'Method for the calculation of average daily doses'**). Average daily

doses are presented as a fraction of the drug-specific guideline-recommended dose. Daily doses were calculated for all eligible patients, irrespective of receipt of treatment, as an estimate of population-level of treatment. The guideline recommended doses were defined as the minimal target dose recommended by the latest ESC guidelines available during the study period (**table S3**). Average daily dose was analysed as a continuous variable, as a binary variable (<50% or ≥50% of recommended dose), as well as categorised into 0%, 1-24%, 25-49%, 50-74%, and ≥75% of the recommended dose. Because drugs used for treatment of heart failure are also used for other indications, the average daily dose prescribed in the 3 months preceding diagnosis was also investigated.

6.3.7 Method for the calculation of average daily doses

For each prescription issued, I calculated *prescription duration* by dividing the prescribed quantity by the daily number of tablets. Prescriptions were considered active from the date they were recorded up to the end of their duration or a more recent prescription of the same drug class was made (whichever came first, so that at any time point a maximum of one prescription was valid). If on the same day two or more prescriptions were issued with the same duration and dosage, durations were aggregated. Further, if on the same day two or more prescriptions were issued with the same duration and different dosages, dosages were aggregated. If on the same day two or more prescriptions were issued with the different duration and dosages, the prescription with the strongest dose and the highest quantity was considered active.

For each prescription issued, I also calculated the *prescribed daily dose (PDD)* by multiplying the prescribed number of tablets per day and the tablet strengths in mg. Where the number of tablets per day was not recorded, it was assumed for the patients to take the number of tablets recommended by guidelines (two tablets per day for Carvedilol, Valsartan, Ramipril, and Enalapril; three tablets per day for Captopril; and one tablet per day for all other drugs).

Finally, for every day that a patient was alive and registered with a participating general practice in the first 12 months following diagnosis, I calculated the *average daily dose (ADD)*.

The *average daily dose* was expressed as a fraction of the drug-specific guideline-recommended dose based on European Society of Cardiology guidelines for the treatment of heart failure effective during the study period (**table S3**), taking the lower target dose when a range was offered.

6.3.8 Patient characteristics

For those with incident heart failure, baseline characteristics (systolic and diastolic blood pressure, smoking status, and body mass index (BMI)) were abstracted from electronic health records as the most recent measurement within 2 years prior to heart failure diagnosis, alongside information on comorbidities, socioeconomic status, ethnicity, and region (for a detailed description of covariates refer to **Chapter 4**).

6.3.9 Statistical analyses

Baseline characteristics are presented as frequencies (%) for categorical data, medians and interquartile range (IQR) for non-normally distributed continuous data, or means and standard deviation (SD) for normally distributed continuous data, over the whole heart failure patient cohort and stratified by place of diagnosis as well as record of ejection fraction. Number and percentage of records with missing data are displayed for variables with missing entries. For categorical variables, frequencies refer to complete cases.

For binary or categorical outcome variables, I computed age, sex, socioeconomic, and year-specific risks as the proportion of eligible patients who received care within a defined time-frame of incident heart failure diagnosis. To assist readability, I further refer to risks, proportions and rates interchangeably. For continuous outcome variables, I computed means and standard deviations.

To examine changes over time and by sub-groups, I used Poisson or linear regression models with robust error variance, and report risk ratios (RR) or adjusted mean differences alongside corresponding 95% confidence intervals (CI). All models were adjusted for year of diagnosis, age (categorised as <45, 45-54,55-64,65-74, and ≥75 years) sex, region, and socioeconomic status. As a measure of temporal trend, p-values modelled by including year as a continuous variable are

also reported. Selected graphical representations were smoothed using local polynomial regression and labelled as such in the figure caption.[150,151]

I performed several sensitivity analyses to assess the robustness of my results towards differences in follow-up duration, 30-day mortality, or prevalence of comorbidities, over time and by sub-groups (see section **6.4.4 'Sensitivity analyses'**).

Study findings are reported in accordance with the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) recommendations.[117] Analyses were prospectively specified in the study protocol and all statistical analyses were performed in R, version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

6.4 Results

A total of 93,074 patients newly diagnosed with heart failure between 2002 and 2014 were included in the study. Patient characteristics stratified by sex, socioeconomic status, and time period categories have been previously published.[152] Patients characteristics varied depending on where they were first diagnosed; those diagnosed in hospital were older, had more comorbidities, and were more likely to be women (**table 6.1**). Patients with a record of reduced ejection fraction were more likely to be younger, male, and presented fewer comorbidities than those where ejection fraction was preserved or unspecified (**table 6.2**).

Table 6.1: Baseline characteristics of patients with incident heart failure, by care setting

Characteristic	All patients (n=93,074)	Diagnosis care setting		
		Inpatient (HF primary cause) (n=11,578, 12%)	Inpatient (HF secondary cause) (n=40,789, 44%)	Outpatient (specialist or primary care) (n=40,707, 44%)
Age [years], mean (SD)	76.7 (12.6)	78.1 (12.6)	77.6 (12.4)	75.4 (12.7)
Women, no. (%)	45,647 (49%)	6,054 (52%)	20,844 (51%)	18,749 (46%)
Ethnicity, no. (%)				
White	56,011 (88%)	6,974 (88%)	25,259 (88%)	23,778 (87%)
Missing	*29,122 (31%)*	*3,609 (31%)*	*12,132 (30%)*	*13,381 (33%)*
Socioeconomic status, no. (%)				
1 (least deprived)	18,371 (20%)	2,182 (19%)	7,889 (19%)	8,300 (20%)
2	20,073 (22%)	2,492 (21%)	8,600 (21%)	8,981 (22%)
3	20,052 (22%)	2,479 (21%)	8,697 (21%)	8,876 (22%)
4	18,308 (20%)	2,307 (20%)	8,122 (20%)	7,879 (19%)
5 (most deprived)	16,270 (17%)	2,118 (18%)	7,481 (18%)	6,671 (16%)
Systolic blood pressure				
Mean (SD) [mmHg]	133 (21)	133 (21)	132 (20)	133 (201)
Missing, no. (%)	*5,195 (6%)*	*654 (6%)*	*2,656 (7%)*	*1,885 (5%)*
Diastolic blood pressure				
Mean (SD) [mmHg]	74 (12)	74 (12)	74 (11)	75 (12)
Missing, no. (%)	*5,195 (6%)*	*654 (6%)*	*2,656 (7%)*	*1,885 (5%)*
BMI category, no. (%)				
Underweight	2,193 (4%)	284 (4%)	1,107 (5%)	802 (3%)
Normal	17,381 (31%)	2,164 (33%)	7,657 (32%)	7,560 (30%)
Overweight	18,786 (34%)	2,067 (31%)	7,818 (33%)	8,901 (35%)
Obese	17,644 (31%)	2,139 (32%)	7,162 (30%)	8,343 (33%)
Missing	*37,070 (40%)*	*4,924 (43%)*	*17,045 (42%)*	*15,101 (37%)*
Smoking, no. (%)				
No	29,551 (41%)	3,787 (44%)	12,647 (40%)	13,117 (41%)
Ex	32,572 (45%)	3,683 (43%)	14,299 (46%)	14,590 (46%)
Yes	9,596 (13%)	1,082 (13%)	4,360 (14%)	4,154 (13%)
Missing	*21,355 (23%)*	*3,026 (26%)*	*9,483 (23%)*	*8,846 (22%)*

Characteristic	All patients (n=93,074)	Diagnosis care setting		
		Inpatient (HF primary cause) (n=11,578, 12%)	Inpatient (HF secondary cause) (n=40,789, 44%)	Outpatient (specialist or primary care) (n=40,707, 44%)
Comorbidities				
Atrial fibrillation, no. (%)	36,950 (40%)	5,199 (45%)	17,325 (42%)	14,426 (35%)
Chronic kidney disease, no. (%)	22,762 (24%)	3,233 (28%)	11,336 (28%)	8,193 (20%)
Chronic obstructive pulmonary disease, no. (%)	17,896 (19%)	2,113 (18%)	9,276 (23%)	6,507 (16%)
Diabetes, no. (%)	20,531 (22%)	2,952 (25%)	9,412 (23%)	8,167 (20%)
Dyslipidaemia, no. (%)	25,958 (28%)	3,281 (28%)	12,524 (31%)	10,153 (25%)
Hypertension, no. (%)	62,419 (67%)	8,226 (71%)	28,776 (71%)	25,417 (62%)
Ischaemic heart disease, no. (%)	45,584 (49%)	5,804 (50%)	22,247 (55%)	17,533 (43%)
Osteoarthritis, no. (%)	40,176 (43%)	5,029 (43%)	18,227 (45%)	16,920 (42%)
3 or more comorbidities, no. (%)	73,610 (79%)	9,567 (83%)	34,904 (86%)	29,139 (72%)

Number and percentage of records with missing data are displayed for variables with missing entries. Category percentages refer to complete cases. Socioeconomic status refers to Index of Multiple Deprivation (IMD) 2015 quintile, with 1 referring to the most affluent and 5 to the most deprived quintile. Number of comorbidities refers to any of the 17 conditions investigated (see Methods). ***Abbreviations****: HF = heart failure.*

Table 6.2: Baseline characteristics of patients with incident heart failure, by record of ejection fraction

Characteristic	All patients (n=93,074)	Ejection fraction record	
		Reduced ejection fraction (n= 11,040, 12%)	Preserved or unspecified ejection fraction (n= 82,034, 88%)
Age [years], mean (SD)	76.7 (12.6)	69.2 (13.7)	77.8 (12)
Women, no. (%)	45,647 (49%)	3,853 (35%)	41,794 (51%)
Ethnicity, no. (%)			
White	56,011 (88%)	7,067 (86%)	48,944 (88%)
Missing	*29,122 (31%)*	2,819 (26%)	26,303 (32%)
Socioeconomic status, no. (%)			
1 (least deprived)	18,371 (20%)	2,366 (21%)	16,005 (20%)
2	20,073 (22%)	2,450 (22%)	17,623 (21%)
3	20,052 (22%)	2,360 (21%)	17,692 (22%)
4	18,308 (20%)	2,061 (19%)	16,247 (20%)
5 (most deprived)	16,270 (17%)	1,803 (16%)	14,467 (18%)
Systolic blood pressure			
Mean (SD) [mmHg]	133 (21)	129.6 (19.5)	133.1 (20.6)
Missing, no. (%)	*5,195 (6%)*	390 (3%)	4,805 (6%)
Diastolic blood pressure			
Mean (SD) [mmHg]	74 (12)	75.1 (11.2)	74.4 (11.5)
Missing, no. (%)	*5,195 (6%)*	403 (3%)	4,792 (6%)
BMI category, no. (%)			
Underweight	2,193 (4%)	151 (2%)	2,042 (4%)
Normal	17,381 (31%)	2,117 (28%)	15,264 (32%)
Overweight	18,786 (34%)	2,835 (37%)	15,951 (33%)
Obese	17,644 (31%)	2,524 (33%)	15,120 (31%)
Missing	*37,070 (40%)*	3,413 (31%)	33,657 (41%)
Smoking, no. (%)			
No	29,551 (41%)	3,575 (38%)	25,976 (42%)
Ex	32,572 (45%)	4,520 (48%)	28,052 (45%)
Yes	9,596 (13%)	1,382 (15%)	8,214 (13%)
Missing	*21,355 (23%)*	1,563 (14%)	19,792 (24%)

Characteristic	All patients (n=93,074)	Ejection fraction record	
		Reduced ejection fraction (n= 11,040, 12%)	Preserved or unspecified ejection fraction (n= 82,034, 88%)
Comorbidities			
Atrial fibrillation, no. (%)	36,950 (40%)	3,681 (33%)	33,269 (41%)
Chronic kidney disease, no. (%)	22,762 (24%)	1,961 (18%)	20,801 (25%)
Chronic obstructive pulmonary disease, no. (%)	17,896 (19%)	1,456 (13%)	16,440 (20%)
Diabetes, no. (%)	20,531 (22%)	2,080 (19%)	18,451 (22%)
Dyslipidaemia, no. (%)	25,958 (28%)	3,420 (31%)	22,538 (27%)
Hypertension, no. (%)	62,419 (67%)	6,464 (59%)	55,955 (68%)
Ischaemic heart disease, no. (%)	45,584 (49%)	5,420 (49%)	40,164 (49%)
Osteoarthritis, no. (%)	40,176 (43%)	4,012 (36%)	36,164 (44%)
3 or more comorbidities, no. (%)	73,610 (79%)	7,555 (68%)	66,055 (81%)

Ejection fraction classification as recorded in patients' primary care record. Number and percentage of records with missing data are displayed for variables with missing entries. Category percentages refer to complete cases. Socioeconomic status refers to Index of Multiple Deprivation (IMD) 2015 quintile, with 1 referring to the most affluent and 5 to the most deprived quintile. Number of comorbidities refers to any of the 17 conditions investigated (see Methods).

6.4.1 Temporal trends of essential care indicators

Setting of heart failure diagnosis

Between 2002 and 2014, a diagnosis of heart failure was first recorded during a hospitalisation in 56% of cases (12% as a primary diagnosis and 44% as a secondary diagnosis), and in an outpatient setting in 44% (**table 6.3**). Among secondary inpatient diagnoses of heart failure, about a third of primary causes for admission were cardiac and a fifth respiratory disease.

Whilst the proportion of patients diagnosed in hospital with primary heart failure diagnosis remained stable at 12%, there were opposing trends for secondary inpatient diagnoses vs outpatient diagnoses. Rates of outpatient diagnoses showed a 36% relative decline over time (from 56% in 2002 to 36% in 2014, risk ratio (RR) [95% CI]: 0.64 [0.62, 0.67]), and were offset by a 67% relative increase in secondary inpatient diagnoses (from 31% in 2002 to 52% in 2014, RR: 1.67 [1.60, 1.74]) (**table 6.3**).

Primary care follow-up after hospitalisation

Amongst heart failure inpatients who survived the index hospitalisation, only 17% had their heart failure diagnosis recorded by their primary care physician in the subsequent 12 months, with rates declining over time (20% in 2002 vs 14% in 2014; RR: 0.73 [0.65, 0.82]). Follow-up rates were higher for patients with a primary discharge diagnosis of heart failure (31%) than secondary diagnosis (12%) (**table 6.3**).

Diagnostic tests

Among patients with a recorded diagnosis of heart failure in primary care, the use of diagnostic investigations increased substantially over time. In 2014, 82% of patients had at least one of the following tests: natriuretic peptide (8%), an ECG (37%), an echocardiogram (51%) or specialist assessment (28%), compared with 37% in 2002 (RR: 2.24 [2.15, 2.34]) (**table 6.3**).

Treatment initiation and dosages over time

Amongst patients with a diagnosis of heart failure recorded in primary care, reduced ejection fraction, and no contraindications or intolerances, prescriptions of essential drugs within three

months of incident diagnosis differed by drug class. In 2014, prescription rates were high for ACE-I or ARB (80%) and beta-blocker (72%) but lower for MRA (28%) (**table 6.3**).

Average daily doses prescribed over the 12 months following diagnosis remained below the recommended target doses throughout the study period (2014 values: 42% for ACE-I or ARB, 29% for beta-blocker, 22% for MRA). When taken combined, the overall dose of beta-blocker and ACE-I / ARB prescribed to patients changed little over time (adjusted difference from 2002 to 2014: +6% [+2%, +10%]), although patterns differed by individual drug classes and declined for ACE-I or ARB (adjusted difference from 2002 to 2014: -7% [-13%, -2%]) (**table 6.3**).

Figure 6.2 provides a graphical overview of care delivery indicators and diverging temporal trends.

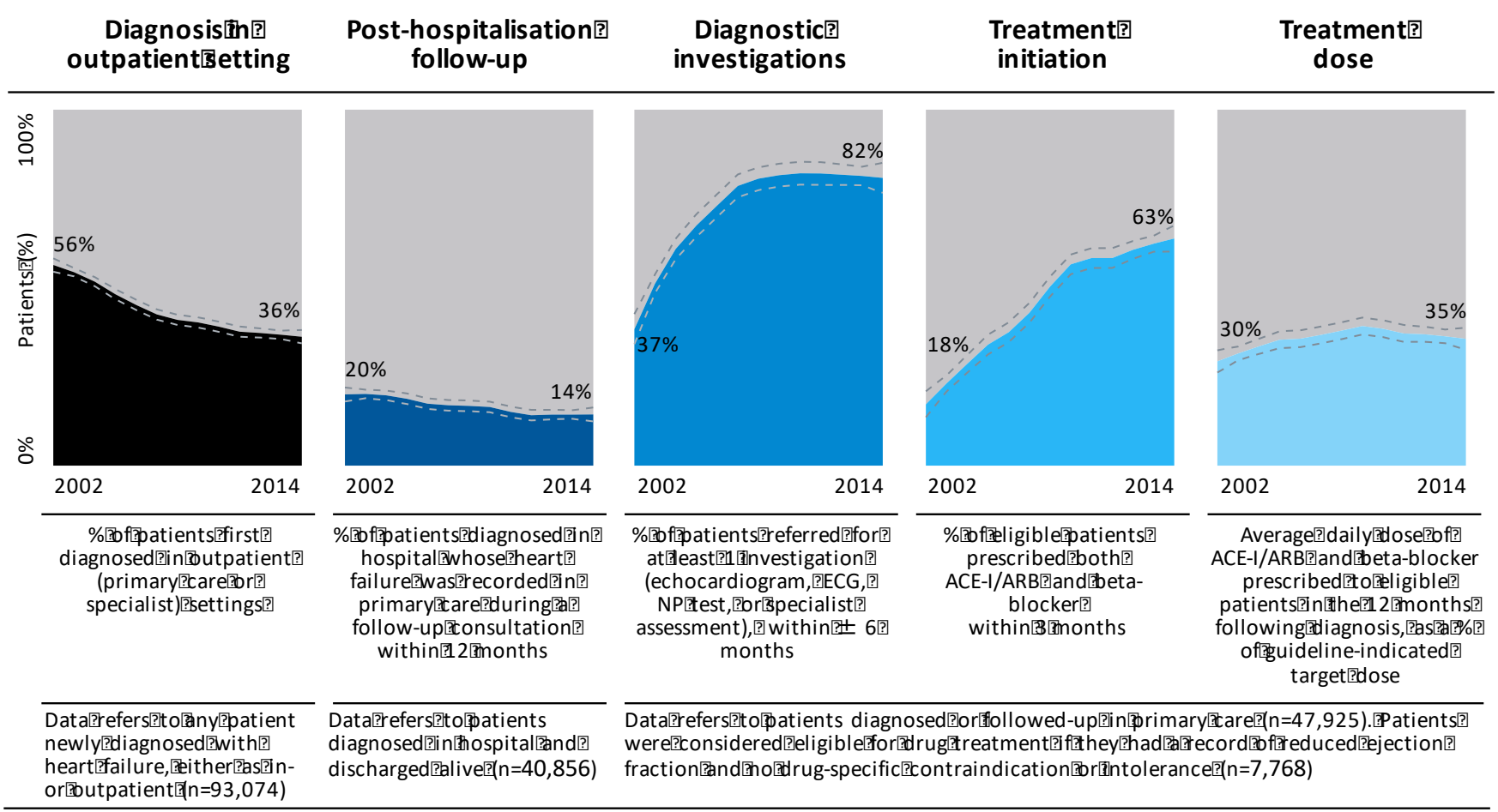
Table 6.3: Temporal trends in essential care indicators following incident heart failure, by year of diagnosis

	Denominator cohort (n)	2002-2014	2002	2014		P for trend
Diagnosis care setting	All patients with heart failure (93,074)	**n (%)**	**n (%)**	**n (%)**	**Risk ratio [95% CI]**	
Inpatient (HF primary cause)		11,578 (12%)	912 (12%)	740 (12%)	0.94 [0.86, 1.03]	0.02
Inpatient (HF secondary cause)		40,789 (44%)	2,277 (31%)	3,242 (52%)	1.67 [1.6, 1.74]	<0.001
Outpatient (specialist or primary care)		40,707 (44%)	4,120 (56%)	2,260 (36%)	0.64 [0.62, 0.67]	<0.001
Post-hospitalisation follow-up		**n (%)**	**n (%)**	**n (%)**	**Risk ratio [95% CI]**	
All inpatients	Inpatients, discharged alive (40,856)	6,807 (17%)	489 (20%)	459 (14%)	0.73 [0.65, 0.82]	<0.001
Inpatient (HF primary cause)	Primary inpatients, discharged alive (9,195)	2,854 (31%)	228 (32%)	174 (29%)	0.95 [0.80, 1.12]	0.209
Inpatient (HF secondary cause)	Secondary inpatients, discharged alive (31,661)	3,953 (12%)	261 (15%)	285 (11%)	0.73 [0.62, 0.85]	<0.001
Diagnostic investigations	Patients diagnosed or followed-up in primary care (47,925)	**n (%)**	**n (%)**	**n (%)**	**Risk ratio [95% CI]**	
Echocardiogram		24,649 (51%)	796 (17%)	1,693 (62%)	3.56 [3.36, 3.78]	<0.001
Electrocardiogram		17,928 (37%)	995 (21%)	1,090 (40%)	1.83 [1.71, 1.96]	<0.001
Natriuretic peptide test		4,177 (9%)	NA	616 (23%)	NA	NA
Specialist assessment		14,046 (29%)	563 (12%)	847 (31%)	2.5 [2.27, 2.75]	<0.001
At least 1 diagnostic investigation		33,660 (70%)	1,683 (37%)	2,248 (82%)	2.24 [2.15, 2.34]	<0.001

	Denominator cohort (n)	2002-2014	2002	2014		P for trend
Treatment initiation	Patients diagnosed or followed-up in primary care, reduced ejection fraction (11,040), and no drug-specific contra-indication	**n (%)**	**n (%)**	**n (%)**	**Risk ratio [95% CI]**	
ACE-I / ARB	9,920	7,748 (78%)	285 (75%)	586 (80%)	1.06 [0.99, 1.13]	<0.001
Beta-blocker	8,430	4,661 (55%)	72 (22%)	490 (72%)	3.27 [2.65, 4.03]	<0.001
MRA	10,896	1,999 (18%)	59 (14%)	207 (26%)	1.88 [1.45, 2.44]	<0.001
Beta-blocker and ACE-I / ARB	7,768	3,759 (48%)	56 (18%)	403 (63%)	3.48 [2.72, 4.43]	<0.001
Treatment dose	Patients diagnosed or followed-up in primary care, reduced ejection fraction (11,040) and no drug-specific contra-indication	**mean (SD)**	**mean (SD)**	**mean (SD)**	**Adjusted difference [95% CI]**	
ACE-I / ARB	9,920	48% (45%)	50% (44%)	42% (41%)	-7% [-13%, -2%]	<0.001
Beta-blocker	8,430	25% (30%)	11% (22%)	29% (32%)	19% [15%, 22%]	<0.001
MRA	10,896	18% (39%)	16% (36%)	20% (37%)	5% [1, 9%]	<0.001
Beta-blocker and ACE-I / ARB	7,768	36% (30%)	30% (26%)	35% (29%)	6% [2%, 10%]	<0.001

Risk ratios or adjusted differences, and 95% confidence intervals (CI) compare 2014 to 2002, adjusting for year of diagnosis, age, sex, socioeconomic status and region. Primary care follow-up refers to the documentation of heart failure in primary care records during a follow-up consultation within 12 months of an incident diagnosis in hospital. Diagnostic investigations refer to investigations referred for within ± 6 months of incident heart failure. Treatment initiation refers to the issue of at least 1 prescription within 3 months of incident heart failure. Treatment dose presents the average daily dose prescribed in the first 12 months following incident heart failure, as % of guideline-recommended target dose. ***Abbreviations****: HF = heart failure, ACE-I = angiotensin-converting-enzyme inhibitor, ARB = angiotensin receptor blocker, MRA = mineralocorticoid receptor antagonists.*

Figure 6.2: Temporal trends in care delivery indicators following incident heart failure, by year of diagnosis, from 2002 to 2014



Results are presented as fitted local polynomial regression over yearly averages and 95% CIs (dashed lines). ***Abbreviations****: CPRD = Clinical Practice Research Datalink, NP = natriuretic peptides, ECG = electrocardiogram, ACE-I = angiotensin-converting-enzyme inhibitor, ARB = angiotensin receptor blocker.*

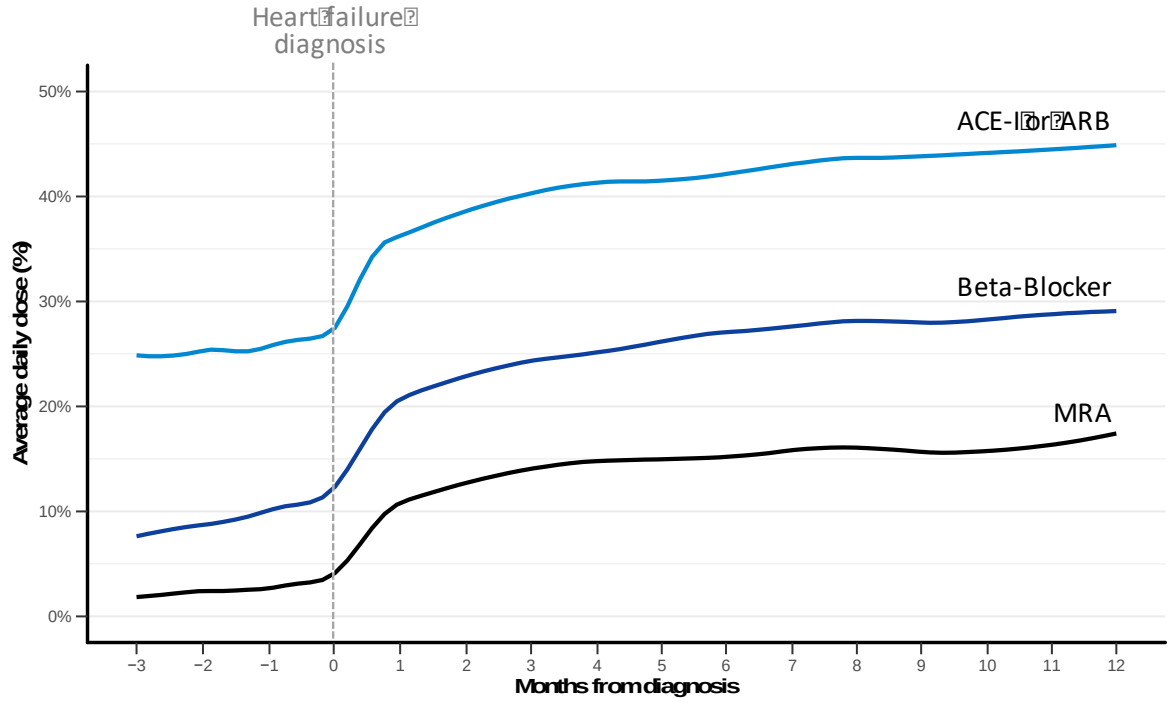
6.4.2 Treatment titration patterns before and after incident diagnosis

Prescription rates of the investigated drug classes in the three months preceding heart failure diagnosis were substantial (44% for ACE-I or ARB, 22% for beta-blocker and 3% for MRA) and were largely related to an existing diagnosis of hypertension (RR for the prescription of at least one treatment class in patients with hypertension vs. no hypertension: 2.07 [1.96, 2.18]).

Dose increments happened largely in the first 30 days following diagnosis, with no evidence of consistent increments thereafter (**figure 6.3**). Although overall doses changed over time, patterns of up-titration remained similar across time periods (**figure 6.4**). Because estimation of average doses across the whole population could potentially mask changes in dosing at the individual patient level, I further investigated changes to treatment dose by categories of 'no change', 'increase' or 'decrease' at fixed time intervals of 2 and 12 months after diagnosis. This showed that, even in more recent years (2012-2014), for about half of the patients (52%), there was no change in dosage of ACE-I or ARB between month 2 and month 12 after diagnosis. The treatment dose decreased in 19% and increased in 29% of patients. At the end of one year, 27% of patients received no ACE-I or ARB treatment and another 36% were on <50% of the guideline-recommended dose (**figure 6.5A**). The patterns of changes were similar for beta-blockers where a year after diagnosis 30% did not receive this treatment (**figure 6.5B**).

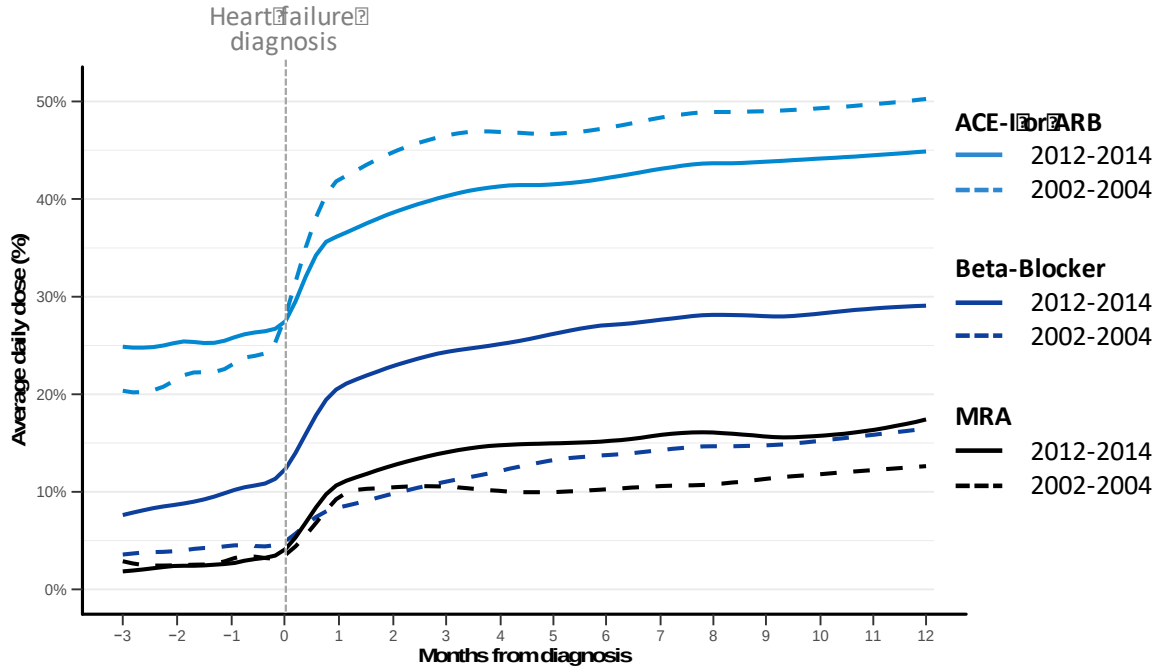
To allow comparison with clinical trials and cross-sectional observational studies, I further report maximal prescribed doses as well as dosages among patients initiated on therapy (**table 6.4**).

Figure 6.3: Average daily dose of guideline-recommended treatments prescribed around the time of incident heart failure, in patients diagnosed from 2012-2014.



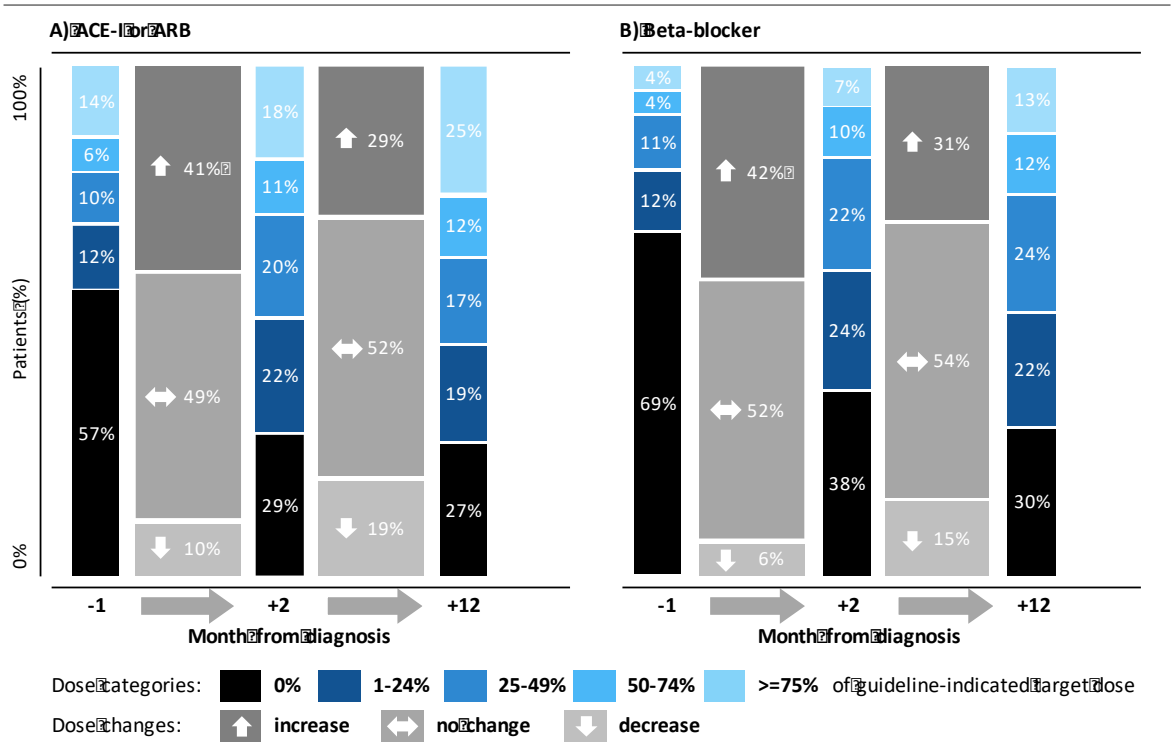
Average daily dose prescribed to patients with heart failure and reduced ejection fraction without drug-specific contraindications or intolerances, from 3 months prior up to 12 months following incident heart failure, in patients diagnosed between 2012 and 2014, smoothed with local polynomial regression. Average daily dose is expressed as a percentage of the guideline-recommended target dose. ***Abbreviations****: ACE-I = angiotensin-converting-enzyme inhibitor, ARB = angiotensin receptor blocker, MRA = mineralocorticoid receptor antagonists.*

Figure 6.4: Average daily dose of guideline-recommended treatments prescribed around the time of incident heart failure, by time period of diagnosis



Average daily dose prescribed to patients with heart failure and reduced ejection fraction without drug-specific contraindications or intolerances, from 3 months prior up to 12 months following incident heart failure, in patients diagnosed between 2012 and 2014 and in those diagnosed between 2002 and 2004. Average daily dose is expressed as a percentage of the guideline-recommended target dose. ***Abbreviations****: ACE-I = angiotensin-converting-enzyme inhibitor, ARB = angiotensin receptor blocker, MRA = mineralocorticoid receptor antagonists.*

Figure 6.5: Drug dose trajectory of A) angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker, and B) beta blocker, prescribed around the time of incident heart failure, in patients diagnosed from 2012-2014



Drug dose trajectory prescribed to patients with heart failure and reduced ejection fraction without contraindications or intolerances, in patients with incident heart failure between 2012 and 2014. 'Month -1' presents the average daily dose prescribed in the 30 days preceding incident heart failure. 'Month 2' presents the average daily dose prescribed in the second month (days 30 to 60) following incident heart failure. 'Month 12' presents the average daily dose prescribed in the twelfth month (days 335 to 365) following incident heart failure.

Table 6.4: Temporal trends in supplementary care indicators following incident heart failure, by year of diagnosis.

	Denominator cohort (n)	**2002-2014**	**2002**	**2014**	
Treatment dose, among patients initiated on therapy	Patients diagnosed or followed-up in primary care, reduced ejection fraction (11,042) and no drug-specific contra-indication, and initiated on therapy within 3 months.	**mean (SD)**	**mean (SD)**	**mean (SD)**	**Adjusted difference [95% CI]**
ACE-I / ARB	7,750	60% (43%)	64% (42%)	51% (40%)	-0.12 [-0.18, -0.06]
Beta-blocker	4,663	42% (30%)	39% (31%)	39% (32%)	0.03 [-0.05, 0.1]
MRA	1,999	83% (49%)	86% (45%)	66% (41%)	-0.17 [-0.31, -0.03]
Beta-blocker and ACE-I / ARB	3,759	52% (29%)	54% (26%)	46% (28%)	-0.07 [-0.15, 0.01]
Treatment uptitration, up to 50% of target dose	Patients diagnosed or followed-up in primary care, reduced ejection fraction (11,042) and no drug-specific contra-indication	**mean (SD)**	**mean (SD)**	**mean (SD)**	**Risk ratio [95% CI]**
ACE-I / ARB	9,922	5,716 (58%)	240 (63%)	367 (50%)	0.80 [0.72, 0.89]
Beta-blocker	8,432	2,490 (30%)	41 (13%)	224 (33%)	2.73 [2.06, 3.61]
MRA	10,898	2,784 (26%)	93 (23%)	278 (35%)	1.58 [1.25, 2.01]
Beta-blocker and ACE-I / ARB	7,770	1,671 (22%)	29 (10%)	143 (22%)	2.51 [1.68, 3.75]

Risk ratios or adjusted differences, and 95% confidence intervals (CI) compare 2014 to 2002, adjusting for year of diagnosis, age, sex, socioeconomic status and region. Treatment dose presents the average daily dose prescribed in the first 12 months following incident heart failure, as % of guideline-recommended target dose. Treatment uptitration refers to the issue of at least 1 prescription at 50% of the recommended target dose in the 12 months following diagnosis.
***Abbreviations**: HF = heart failure, ACE-I = angiotensin-converting-enzyme inhibitor, ARB = angiotensin receptor blocker, MRA = mineralocorticoid receptor antagonists.*

6.4.3 Stratified analyses by age, sex and socioeconomic status

Variations in care by age, sex and socioeconomic status were apparent (**figure 6.6**).

Women were less commonly diagnosed in outpatient settings and had lower rates of primary care follow-up, fewer diagnostic investigations, less treatment initiation, and lower treatment doses, than their male counterparts of similar age, socioeconomic status and region.

Older patients (aged ≥75 years) exhibited similar and significant differences, compared with their middle-aged counterparts (55 to 64 years old). The very young (<45 years), particularly young women, had lower rates of diagnostic investigations, across all four test types, compared with the 55 to 64 years age group (**table 6.5**).

Table 6.5: Diagnostic investigations following incident heart failure, stratified by age and sex.

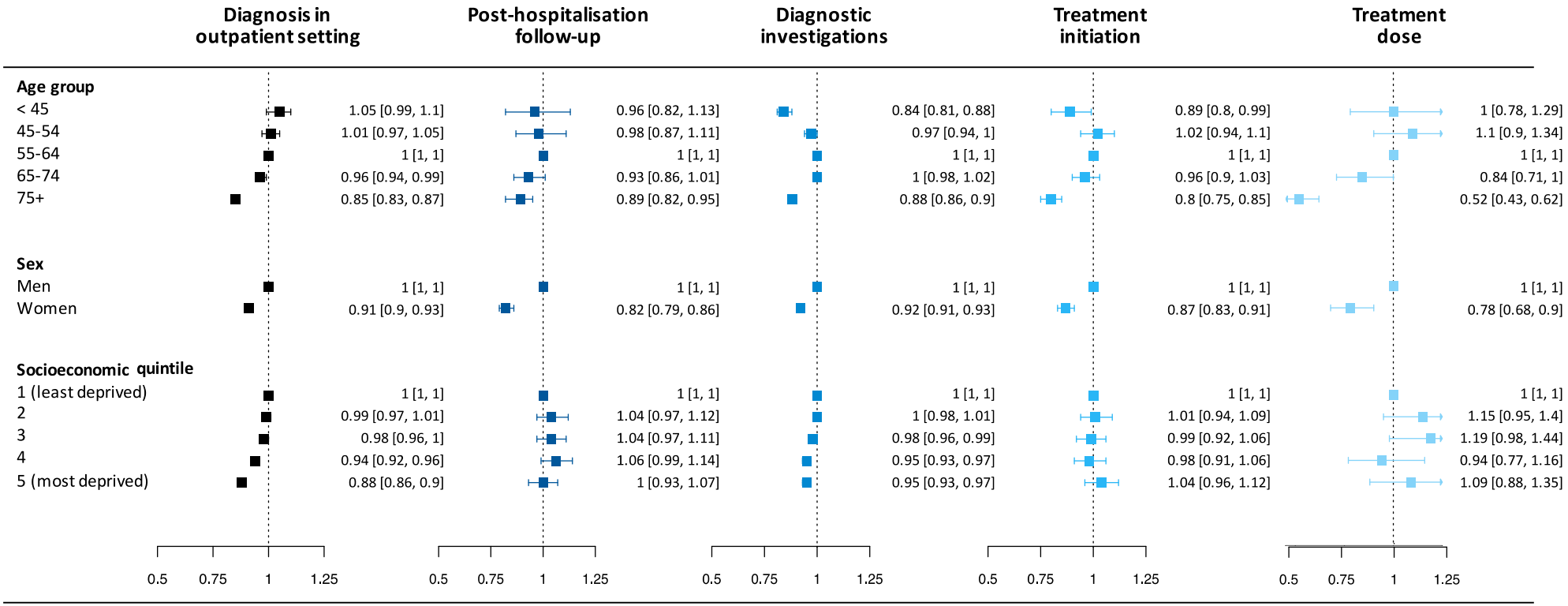
Age group (years)	**Full cohort (n = 47,925)**	**Men (n=25,848)**	**Women (n=22,077)**	**Risk ratio [95% CI]**
<45	750 (66%)	516 (70%)	234 (58%)	0.84 [0.76, 0.92]
45-54	1,684 (76%)	1,248 (78%)	436 (73%)	0.93 [0.88, 0.98]
55-64	4,092 (78%)	2,875 (79%)	1,217 (77%)	0.97 [0.94, 1.00]
65-74	7,890 (76%)	4,984 (77%)	2,906 (74%)	0.97 [0.95, 0.99]
75+	19,244 (66%)	9,504 (71%)	9,740 (63%)	0.90 [0.89, 0.92]

Risk ratios and 95% confidence intervals (CI) compare women to men, adjusting for year of diagnosis, sex, socioeconomic status and region. Diagnostic investigations refer to any of echocardiogram, electrocardiogram, natriuretic peptide test, or specialist assessment referred for within ± 6 months of incident heart failure.

Among patients managed by their general practitioner, no socioeconomic disparities were apparent with regard to prescriptions of treatment or dose of treatment. However, deprived patients had lower rates of diagnosis in outpatient settings than their more affluent counterparts, and hence were overall less likely to receive primary care follow-up.

Disparities remained apparent, although attenuated after adjusting for differences in follow-up times, 30-day mortality and baseline comorbidities (see section **6.4.4 'Sensitivity analyses'**), with the exception of differences in primary care follow-up in patients aged ≥75 years.

Figure 6.6: Differences in care delivery indicators by age, sex and socioeconomic quintile, in patients with heart failure



Risk ratios and 95% confidence intervals from multivariable Poisson regression model adjusted for year of diagnosis, age group, sex, socioeconomic status and region. Diagnostic investigations refer to either one of echocardiogram, electrocardiogram, natriuretic peptides or specialist assessment, within ±6 months of incident heart failure diagnosis. Treatments refer to the prescription of both (i) angiotensin-converting-enzyme inhibitors (ACE-I) or an angiotensin receptor blockers (ARB) and (ii) beta-blocker (BB), in patients with heart failure and reduced ejection fraction without recorded contraindications or intolerances. Treatment initiation indicates at least 1 prescription within 3 months of incident heart failure diagnosis. Treatment dose indicates whether a patients' average daily dose, in the first 12 months following incident heart failure, was greater or equal to 50% of the guideline-recommended target dose.

6.4.4 Sensitivity analyses

To assess the robustness of my results, I have performed the following sensitivity analyses:

Accounting for patient-years of follow-up.

I computed rates as number of events per patient-years at risk, where time at risk was restricted to days alive, registered with a participating general practice, and to practice's 'up-to-standard' (UTS) periods. Rate ratios and 95% confidence intervals (CI) were computed using Poisson regression models with log offset of time-at-risk, adjusting for age, sex, socioeconomic status and region. These analyses led to higher rates of primary care follow-up, diagnostic investigations and treatment initiations, however temporal trends as well as disparities by age, sex, and socioeconomic status remained unchanged, with the exception of differences in primary care follow-up in patients aged ≥75 years, which were not significant.

Restricting analyses to those patients that were alive 30 days following their incident heart failure diagnosis.

When analyses where restricted to those patients that were alive 30 days following their incident heart failure diagnosis, results presented slightly higher rates of primary care follow-up, diagnostic investigations and treatment initiations, however temporal trends as well as disparities by age, sex, and socioeconomic status remained unchanged.

Adjusting regression models for 17 comorbid conditions.

When regression models were further adjusted for 17 chronic conditions, I found that disparities by age, sex, and socioeconomic status were attenuated, nevertheless all reported disparities remained significant.

Excluding those patients exempted from the national primary care audit 'quality and outcomes framework'.

Data from approximately 4% of patients with heart failure recorded in primary care, were exempted from the national primary care audit. Reasons for exemption included the labels 'patient unsuitable' and 'informed dissent'. Excluding those patients from my analyses led to no significant changes in the present results.

Restricting analyses to medicines recommended in the 2012 ESC guidelines.

When restricting medicines to those recommended in the 2012 ESC guidelines, I found that rates of treatment initiation and dosages were slightly reduced (in the range of 3 to 5%). However, temporal trends as well as disparities by age, sex, and socioeconomic status remained unchanged.

Documentation of diagnosis in primary care records as a prerequisite for subsequent disease monitoring and management

In main analyses, I assumed that the documentation of diagnosis in primary care records was a prerequisite for subsequent disease monitoring and management. The rationale for this was that physicians are unlikely to initiate medications for conditions that are not formally diagnosed. To verify this assumption, I investigated pharmacological treatment among patients with heart failure recorded during a hospital admission, discharged alive, and with no documentation of heart failure in primary care. This proved to be challenging, because hospital diagnoses are coded in the ICD-10 (International Classification of Diseases 10th edition) system which does not allow accurate identification of patients with reduced ejection fraction. Moreover, heart failure medicines are also used in the treatment of hypertension, which affects about two thirds of heart failure patients, and without a heart failure diagnosis one cannot reliably ascertain whether medications were given for heart failure or not. To best address the aforementioned circumstances, I investigated primary care rates of new prescriptions (initiation of therapy in patients who had not received these drugs in the 3 months prior to diagnosis) or dose increments (dose increase of 10% or more in patients who had received these drugs in the 3 months prior to diagnosis) for either ACE-I/ARB or beta-blocker within 3 months of diagnosis, and found these were present in 17% of patients. I considered extending the definition of follow-up in primary care with indications of pharmacological management and found that although this led to higher overall rates of follow-up in primary care (34% compared with 17% in my main analyses), temporal trends remained unchanged, i.e. declining by about 6% over the study period. In agreement with supervisors and co-authors, I concluded that although there is evidence that some patients receive primary care follow-up despite no formal documentation of

heart failure, these numbers were sufficiently low not to impact main conclusions; and that assumptions were suitable for the purpose of this study.

6.5 Discussion

6.5.1 Summary of main findings

This large-scale, population-based study provides important information on contemporary care of heart failure patients in routine clinical practice and insights into its variation over time, by age, sex, and socioeconomic status. This study confirms previous reports of high rates of guideline-indicated diagnostic investigations and treatment initiation in Western countries (**table 2.3**). However, further investigation of care across the continuum of primary and secondary services and from the pre-diagnosis stage to several months after incident diagnosis revealed important shortcomings in the management of patients. First, rates of outpatient diagnoses and follow-up in primary care after hospital discharge are low and have been declining over time. Second, doses of key medicines remain far below those recommended in guidelines in all groups of patients and for all three drug-classes investigated, even a year after diagnosis. Finally, deficiencies in care were more common in women, older people and, to some extent, in socioeconomically deprived individuals.

6.5.2 Comparison with existing literature

This study presents an important complement to the existing literature on heart failure management in high income countries (**table 2.2**). So far, most studies have mainly focused on pharmacological treatment initiation, typically investigating prescriptions at the time of registry enrolment; and only few studies have investigated other aspects of care such as diagnostic tests or treatment titration, although these are essential components of clinical care guidelines.

When comparing recent studies that report treatment initiation in American or European cohorts, I found that treatment rates were generally high for ACE-I or ARB and beta-blocker, ranging from 87% to 99% ACE-I or ARB, and from 87% to 93% for beta-blocker in studies investigating data from 2010 onwards.[2,44,47] For MRAs, which are indicated only in patients who remain symptomatic despite treatment with an ACE-I and beta-blocker, treatment initiation

rates were generally lower and ranged from 39% to 69%.[2,48] Selected studies have reported treatment doses as the proportion of patients achieving the guideline-recommended target dose and found that target doses are rarely achieved in practice. For example, the BIOSTAT-CHF survey found that only 22% of patients achieved the guideline-recommended target dose for ACE-I or ARB, and for beta-blocker that number dropped to 12%.[46] The Swedish Heart Failure Registry has shown that the proportion of patients achieving at least 50% of the guideline-recommended target dose is noticeably higher (e.g. 37% and 31% for ACE-I or ARB and beta-blocker, respectively), and yet still far from 100%.[50] Medication prescription rates across studies are difficult to compare due to differences in cohort characteristics and the different time points at which treatment plans are being evaluated at. Indeed, most registry studies report the treatment prescribed on registry enrolment (or even later) which often happens several months after initial diagnosis, whereas in this thesis, reports refer to prescription within 3 months of first heart failure diagnosis, and with less time to initiate treatment, rates will inevitably be lower. Specifically in the UK, the two national healthcare reporting programmes[43,7] - the primary source of quality of care data in heart failure so far - both report rates of diagnostic investigations (91-95%)[44,45] and treatment initiation (85-99% for ACE-I or ARB)[44,45] that, given the differences in variable definitions, are comparable to the findings reported in this thesis. My research extends these reports through a broader perspective and a patient- (rather than system-) centred assessment of care over time, and uncovers important shortcomings in the delivery of care, as well as disparities by age, sex, and socioeconomic status.

6.5.3 General discussion of findings

This study found that rates of outpatient diagnoses have been declining while more patients are being diagnosed acutely in hospital. Relatedly, findings show that only 17% of patients who were first diagnosed in hospital were subsequently followed up with a heart failure diagnosis in primary care and this rate has also been declining, in particular when heart failure was not the primary discharge diagnosis. The reasons for the declining trends in diagnosis and follow-up of heart failure patients outside the acute hospital setting are not entirely clear and seem rather surprising, when put in the context of the growing access to diagnostic services, such as blood

BNP, outside hospitals, and the reported shift in diagnosis from hospitals to outpatient settings elsewhere.[24] Findings from the present study suggest that out-of-hospital screening and follow-up are sub-optimal, and could, at least partly, be due to poor record-keeping in primary care and inadequate information exchange between hospitals and primary care. It might also be that the national primary care reporting and incentives scheme[101] itself paradoxically contributed to these trends, with general practitioners for instance using free text descriptions to record patients' problems rather than formally recording heart failure as a diagnosis. Such practices that avoid registering certain patients that will not achieve management recommendations to achieve higher overall adherence rates have been reported for other chronic conditions, such as depression.[102,153] Recent investments in specialist heart failure clinics and nurse-led services[154] might also have contributed to the observed patterns by creating artificially low primary care diagnosis and follow-up rates. Support for this comes from sensitivity analyses which indicate that some patients receive heart failure medicines in primary care despite no formal documentation of heart failure (refer to section **6.4.4 'Sensitivity analyses'**).

However, irrespective of the underlying reasons, the declining rates of heart failure recording in primary care are likely to have important consequences for patient care as well as research. The UK healthcare system relies on primary care as the cornerstone of chronic disease management. In such systems, general practitioners take a central role in screening, coordination and continuous management of common conditions such as heart failure. Even where specialist clinics and nurse-led community services exist, general practitioners remain responsible for medication prescriptions and the coordination of specialty care. Accurate disease recording in primary care is therefore particularly important for this patient population with a high number of both cardiovascular and non-cardiovascular comorbidities[152] and gaps in healthcare records are likely to have effects on subsequent monitoring and management of patients. This under-registration might also explain why some previous analyses concluded that the incidence of heart failure is declining in the UK[36] (which was refuted in subsequent studies that used linked records to capture cases across primary and secondary care).[152]

The increase in the proportion of patients initiated on evidence-based therapy for heart failure in recent years is important and encouraging, because prescription of treatment, even at low dose, is an essential component of heart failure management. Yet gaps remain, particularly for beta-blocker and mineralocorticoid receptor antagonists. While comparison across studies is difficult due to varying inclusion criteria and time-points at which treatment plans are evaluated, rates appear somewhat lower than those reported in other countries (**table 2.2**); and underuse of these therapies are likely to be associated with significant loss of life; both quantity and quality.[155] Moreover, the average dose received per patient remained far below the guideline-recommended doses, and despite increasing numbers of patients initiated on therapy the overall dose prescribed did not change substantially from 2002 to 2014. Titration was largely restricted to the 30-day period after incident diagnosis, yet landmark clinical trials have established the value of optimal drug dosages in conferring clinical benefits.[156–158] While it may not be possible for every patient to achieve guideline-recommended doses, the rates reported by the present study remain below rates achieved through community-based interventions or in clinical trials.[159] These findings hence question whether current efforts into community heart failure services sufficiently address the long-term needs of patients with heart failure. In addition, they show that the current UK focus on monitoring diagnostic tests and treatment initiation might distract attention away from medication maintenance and titration as a measure of quality of care.

Age, sex and socioeconomic differences

This study further shows that the management of women, older people and deprived individuals was even less satisfactory. For example, all were more likely to be first diagnosed during a hospital admission. This may suggest that, in these patients, early signs and symptoms have not been appropriately recognised in non-acute health-care settings. Alternatively, this may be related to patient preferences to seek care in hospital, or, for deprived populations, more difficult access to outpatient consultations.[160] Correcting such disparities is an important challenge for a system that intentions to offer equality of access to and quality of care.

The underlying reasons for the variations in medical practice in diagnosing and managing heart failure in the community has been subject to research, specifically in the UK.[161,162] These reasons fall into three broad categories: (i) uncertainty about clinical practice (including worries about using medications in frail and elderly patients), (ii) lack of awareness of relevant research evidence, and (iii) individual preferences and local organisational factors (including negative clinical experiences, availability of diagnostic services and cardiologists, or interactions between professionals in primary or secondary care).

Differences in treatment in the elderly may indeed, at least in part, reflect a more cautious approach of general practitioners among patients with multi-morbidity and associated polypharmacy. Nevertheless, age-disparities in the use of guideline-indicated therapy remained significant after adjusting for 17 major chronic conditions, sex, and socioeconomic status. The perception that the blood-pressure lowering effects of heart failure therapies may place patients at higher risk of falls, has also been reported as a barrier to effective management of heart failure patients in the community and may have further contributed to the observed trends.[161,162]

Sex differences reported in the present study are consistent with prior research showing an underutilisation of cardiovascular disease therapies among women compared with men.[163] Although this study was not designed to investigate the reasons underlying these differences, findings show that underutilisation of guideline-indicated therapy in women was not explained by differences in age, comorbidities, or socioeconomic status, and hence are due to other factors. Possible explanations relate to side-effects being higher in women, healthcare professionals seeing women as being at lower risk of heart failure consequences, or women being less likely to visit their general practitioners for their heart failure.

Socioeconomic disparities in the management of heart failure were essentially related to screening and post-hospitalisation follow-up, whereas diagnostic tests and treatments among those seen by their general practitioner did not present significant differences. These disparities were not explained by differences in patients' age, sex or comorbidities. The hypothesis that general practitioners would fail to offer regular follow up care to deprived individuals is argued

against by the comparable rates of prescribing across the social class spectrum. Individual preferences and local organisational factors appear more likely to contribute to the observed disparities. Indeed studies have reported the behaviour of deprived patients to differ substantially from other groups, by being more likely to seek healthcare advice from non-professionals or to seek care in hospital emergency rooms rather than attend their primary care physicians.[160] Finally although access to care in the UK is free for all residents, longer waiting times for general practice appointments and specialist services in deprived areas may, in part, explain a lower level of access for patients living in these areas.[164–166]

Healthcare reporting and incentives schemes

Healthcare reporting efforts play an important role in improving quality of care. This study presents changes in the delivery of care alongside the implementation of landmark quality improvement initiatives, in particular the 'Quality and Outcomes Framework'[101] and the 'National Heart Failure Audit'[7]. These schemes represent the primary source of quality of care data in the UK so far and report a very positive picture of heart failure management. However, the investigation of care across the continuum of primary and secondary services reveals important shortcomings in the management of patients, that analyses confined to individual clinical settings are unable to identify. When reflecting specifically on the financial incentives program, which applies to primary care, it appears that its design insufficiently addresses patients' long-term care needs. For heart failure, the scheme monitors referral for diagnostic investigations and yearly prescriptions of both beta-blocker and ACE-I or ARB, with financial rewards only for primary care practices that achieve set target rates. Findings from this thesis reveal that incentivised indicators have improved over time, but show no or negative changes in associated outcomes. Perhaps most importantly they reveal possible unintended consequences in the fact that following the introduction of the program, recording of diagnoses in primary care declined considerably, leading to a large and growing number of patients for whom continuous monitoring and management remains uncertain.

6.5.4 Strengths and limitations

A major strength of this study is the use of a large population-based cohort of patients, which allows a sufficient number of cases in each age, sex, and socioeconomic category for subpopulation analyses, and which increases the generalisability of findings compared with surveys enrolling more selected participants. Moreover, longitudinal data from electronic health records provide a unique opportunity to follow patients over time in different care settings, and hence address the limitations of selected single-setting and single-time-point indicators used in previous studies. One of the key limitations of this study was the incomplete clinical information contained in the available electronic health records. In particular, left ventricular ejection fraction values were not available. Hence, I could only characterise the type of heart failure in a subset of patients, for whom the diagnostic code made a clear reference to reduced ejection fraction. While this subset of patients is likely to underestimate the true prevalence of reduced ejection fraction in the community, its high specificity ensures the selection of patients is appropriate for my analyses. Moreover, secondary care records did not provide access to diagnostic investigations, procedures (such as device implantations), discharge prescriptions or referrals, or outpatient consultations, so that some analyses had to be restricted to primary care data. Finally, reliable information about patients' symptoms was not available and limited my ability to investigate precise indications for certain therapies, such as mineralocorticoid receptor antagonists.

6.5.5 Policy and practice implications

Results from this study present clinicians and policy makers with important elements to improve the management of heart failure in the UK, and may be applicable in many developed countries.

Health system design: These findings highlight the importance of continuity of care across various healthcare systems. Ensuring that patients are provided with a continuous follow-up after diagnosis is a crucial prerequisite for good management, and yet appears to be rarely investigated or monitored. Improvements are likely to require health services to consider patient trajectories as an integral part of health services design, and to support interactions between primary care, secondary care and community-based specialist services, such as heart

failure nurses. Such changes must also be reflected in healthcare reporting and incentives schemes. Evidence from this study shows that schemes that rely on a very restricted set of indicators and remain confined to individual clinical settings may fail to identify substantial gaps in the quality of care.

Research prioritisation: More research is needed to understand the reasons behind the low doses prescribed in routine clinical care, and to distinguish between drug tolerability issues from health system related matters.

Management of women, elderly and socioeconomically deprived individuals: Care gaps by age, sex, and socioeconomic status need to be addressed. For that purpose, optimal management of these patients may need to be redefined - in consideration of age, comorbidities, as well as physiological and behavioural factors - and implemented in routine clinical practice. Efforts may need to consider not only drug prescriptions but take a broader perspective to understand where and how these patients are diagnosed and treated.

6.5.6 Future research

The description of trajectories of care experienced by heart failure patients presented in this thesis also reveals several important results that deserve further investigation. The present work could be taken further by studies relying on richer datasets. Most importantly, stratifying analyses by type of ejection fraction (reduced or preserved) or by disease severity would provide valuable information to design more targeted health service policies. Investigating diagnostic tests and discharge prescriptions among patients diagnosed in hospital, as well as follow-up by specialist community services, such as heart failure nurses, would present as similarly beneficial.

Additionally, studies investigating healthcare systems in other countries could take these findings further and help health services in comparing performances of different healthcare settings and identifying best practices.

Finally, understanding how patterns of care relate to patients' health outcomes, such as mortality or hospitalisations, is crucial to support the design and implementation of more appropriate health services strategies and ultimately improve patient prognosis. The present

study was designed to be descriptive and not to investigate causality between indicators of care and patient outcomes. Although some studies have investigated this subject, associations between healthcare performance indicators and health outcomes are only partly understood and deserve further investigation.

6.6 Conclusion

Findings from this study have important implications for health services policies. The increased uptake of guideline-recommended diagnostic tests and treatment initiation among patients seen in primary care, suggests that early management of these patients has improved, probably due to a combination of physician awareness, clinical guidelines, and financial incentives. However, the limited changes to medication dosages, the disparities among sub-groups of patients, and the poor rates of primary care recording, indicate that more efforts are needed. Quality improvement efforts that remain confined within individual care settings have proven insufficient to identify important care gaps and to address challenges of this chronic condition with effective but complex treatment. Further improvements are likely to require a broader perspective to health services design to support appropriate care at every level of the patient journey.

6.7 Research in context

6.7.1 Evidence before this study

I searched Pubmed for reports published from 1 January 2005 to 30 October 2017 that included "heart failure", "guideline" and "adherence" in their title, reviewed references of clinical practice guidelines and consulted with experts for relevant studies. I found numerous registry and observational cohort studies that investigated care delivery in patients with heart failure. Most studies presented single-point-in-time measures, such as prescriptions at the time of registry enrolment, or were restricted to secondary care settings, which do not allow longitudinal assessment of chronic disease management in the whole health care system. To compare reports of physicians' adherence to guidelines for the diagnosis and management of chronic heart failure, I selected a subset of observational studies that (i) referred to European or north

American cohorts, (ii) considered outpatient settings, and (iii) included at least 1,000 patients. I found that reports frequently focused on a single aspect of guidelines (mostly pharmacological treatment initiation); few studies reviewed other aspects such as diagnostic tests or treatment titration, although these are essential components of clinical care guidelines. Moreover, studies generally assessed care indicators in prevalent heart failure cases, and hence were not able to assess whether the care was given timely following a first diagnosis of heart failure (**table 2.2**). I found no study that presented a longitudinal analysis of care delivery, covering diagnostic tests, treatment initiation and titration, following incident heart failure.

6.7.2 Added value of this study

This study provides important new information on contemporary care of heart failure patients in routine clinical practice and insights into its variation over time, by age, sex, and socioeconomic status.

This study assessed a broad set of care indicators that captured the journey of patients with heart failure from diagnosis up to one year later, describing management of this cohort across both primary and secondary care. Results highlight several shortcomings in the clinical care of heart failure patients in the UK. First, rates of outpatient diagnoses and follow-up in primary care after hospital discharge are low and have been declining over time. Second, doses of key medicines remain far below those recommended in guidelines in all groups of patients and for all three drug-classes investigated, even a year after diagnosis. Finally, deficiencies in care were more common in women, older people and, to some extent, in socioeconomically deprived individuals.

6.7.3 Implications of all the available evidence

The available evidence suggests that, in high-income countries, initiation of essential medications has improved, yet dosages remain far below targets recommended in guidelines. Further research is needed to understand the reasons behind the low doses prescribed in routine clinical care, so as to distinguish between drug tolerability issues from health system related matters.

Gaps in chronic care management have been shown to disproportionally affect women, older people and deprived individuals and suggest that optimal management of these patients may need to be better defined and implemented in routine clinical practice.

Experience from the UK Quality Outcome Framework (QOF) primary care scheme - one of the largest implementations of healthcare pay-for-performance in the world[102] - has shown that a small set of indicators measured in a single care setting can improve performance against those measures, but does not necessarily impact on associated outcomes. More importantly, when not ensuring a comprehensive registration of patients, such schemes may unintentionally disregard a large proportion of patients. This may depict a positive picture of care delivery without identifying its shortcomings. Other countries implementing pay-for-performance schemes may experience similar situations.

7. MORTALITY AND HOSPITALISATIONS

7.1 Introduction

The past 25 years have brought considerable improvements in heart failure care. New treatments, such as beta-blockers,[167] mineralocorticoid receptor antagonists[55], ivabradine[56], sacubitril/valsartan[126] and device therapies such as implantable cardioverter defibrillators[57] and cardiac resynchronisation therapy[58] have been introduced. Multidisciplinary management teams, including specialist nurses, have been developed to improve delivery of care.[60,61] Randomised trials have demonstrated the effectiveness of these treatments in reducing mortality and hospitalisations, and observational studies have shown that they are increasingly being used across the world.[2,47,168] Despite this evidence, several recent studies have reported that the decline in mortality rates amongst patients with heart failure has been stalling since the mid 2000s.[1,4,54] The reasons underlying this apparent paradox are unknown.

Most studies that have investigated outcomes following incident heart failure have restricted analyses to all-cause mortality, without investigating underlying patterns, such as changes by sub-group or cause-specific mortality (**table 2.3**). In addition, information about trends in cause-specific hospitalisation rates, which are of high importance to patients and service providers, remain poorly investigated. In-depth analyses investigating how specific causes of morbidity and mortality and changes in patient characteristics contribute to overall trends would complement these efforts and may provide valuable clues for the development of more targeted therapies or public health strategies.

To address these knowledge-gaps, I have used a database of electronic health records, that links information from primary care, secondary care, and the national death registry for a representative sample of the UK population. I performed a detailed assessment of health outcomes in patients newly diagnosed with heart failure, and analysed changes in cause-specific

mortality and morbidity over time and by important patient characteristics such as age, sex, and socioeconomic status.

Parts of this chapter have been published in *JAMA Cardiology* at:

https://jamanetwork.com/journals/jamacardiology/fullarticle/10.1001/jamacardio.2019.3593

The manuscript benefitted from the input of several co-authors as well as my thesis supervisors. My role consisted in designing the study, conducting the literature searches, the data extraction, all statistical analyses, and writing the first draft of the manuscript.

7.2 Aims

This study aims to analyse temporal trends and patterns in cause-specific mortality and hospitalisations after incident heart failure, and to examine variation by important patient features such as age, sex, and socioeconomic status.

7.3 Methods

7.3.1 Data source

The study was conducted using electronic health records from CPRD linked to secondary care admission records from HES Admitted Patient Care data. Primary care data was available from 1 January 1985 to 31 December 2015, and linkage was available from 1 January 1998 to 30 September 2015 (for a detailed description of the dataset refer to **Chapter 3**).

7.3.2 Eligible participants

Patients eligible for inclusion in the study were men and women aged 16 and over, contributing data during the period 1 January 2002 to 31 December 2013, registered with their general practice for at least 12 months, and whose record was labelled as 'acceptable' by CPRD quality control[5] and approved for CPRD and HES linkage. Compared with the previous two chapters, the patient cohort was restricted to those diagnosed before 2013, to allow for up to one year of follow-up after diagnosis.

7.3.3 Case identification

Heart failure diagnosis was defined as the first record of heart failure in primary care or hospital admission records from any diagnostic position, using a total of 147 diagnostic codes. (refer to section **4.5 'Study population'** for further description).

7.3.4 Study population

A total of 86,833 patients newly diagnosed with heart failure between 2002 and 2013 were identified following the methods described in **Chapter 5**.

7.3.5 Study design

The study was designed as a retrospective, population-based patient cohort study.

7.3.6 Study outcomes

This study investigated mortality rates at one year following incident diagnosis, as well as the number of hospital admissions with overnight stay within one year of incident diagnosis (not counting index admission for those diagnosed in hospital).

The cause of death was defined as the first reported cause in each patient's death certificate. The cause of hospitalisation was defined as the primary discharge diagnosis. Causes of death and hospitalisation were mapped to nine and eleven disease categories, respectively (see section **7.3.7 'Approach used to define disease categories for causes of deaths and hospitalisations'**). In sub-group analyses, disease categories were further grouped into cardiovascular and non-cardiovascular causes.

7.3.7 Approach used to define disease categories for causes of deaths and hospitalisations

The CPRD data used in this study provided causes of death and hospitalisations in the form of clinical codes from the ICD-10 (International Classification of Diseases, 10th edition) system. To allow for the identification of key patterns and trends, I sought to cluster causes of death and hospitalisations into a set of unique and clinically meaningful disease categories.

For that purpose, I used the following approach, which I applied to deaths and hospitalisations separately:

(i) As a starting point, categories were defined as each code's overarching ICD chapter (n = 22);

(ii) Chapters that presented similarities for the purpose of this study were grouped together (e.g. ICD chapters "Injury, poisoning and certain other consequences of external causes" and "External causes of morbidity and mortality" were grouped together and categorised as "Injuries");

(iii) Groups of conditions that, in 2013, represented at least 2% of deaths (for the categorisation of causes of deaths) or either 2% of deaths or hospitalisations (for the categorisation of causes of hospitalisations), e.g. kidney diseases or infections, were defined as independent categories;

(iv) Any remaining category that represented less than 2% of deaths/hospitalisations in itself was classified as "other".

Heart failure was defined as an individual disease category for hospitalisations, yet not for deaths, due to the difficulty of ascertaining heart failure as a cause of death. The resulting categorisation of causes of death and hospitalisations used for the purpose of this study is presented in **table 7.1**.

Table 7.1: Definition of disease categories for causes of deaths and hospitalisations

Causes of death	Causes of hospitalisation
Cardiovascular disorders: ICD chapter 'Diseases of the circulatory system' (code range: I00–I99), excluding codes relating to infections.	**Heart failure:** ICD codes: I50 'Heart failure' (incl. I50.0, I50.1, I50.9), I42.0 'Dilated cardiomyopathy', I42.9 'Cardiomyopathy, unspecified', I11.0 'Hypertensive heart disease with (congestive) heart failure', I25.5 'Ischaemic cardiomyopathy', I13.0 'Hypertensive heart and renal disease with (congestive) heart failure', I13.2 'Hypertensive heart and renal disease with both (congestive) heart failure and renal failure'.
	Other cardiovascular disorders: ICD chapter 'Diseases of the circulatory system' (code range: I00–I99), excluding codes relating to heart failure or infections.
Neoplasms: ICD chapter 'Neoplasms' (C00–D48).	
Infections: infectious and parasitic diseases, respiratory infections, urinary tract infections, and cellulitis, as defined by individual codes listed in **S Table 3**.	
Chronic respiratory diseases: individual codes listed in **S Table 4**.	
Digestive diseases: ICD chapter: 'Diseases of the digestive system' (K00–K93), excepting selected codes categorised as infections.	
Mental and neurological disorders: ICD chapter 'Mental and behavioural disorders' (F00–F99) and ICD chapter 'Diseases of the nervous system' (G00–G99)	
---	**Musculoskeletal disorders**: ICD chapter 'Diseases of the musculoskeletal system and connective tissue' (M00-M99).
Injuries: ICD chapters 'Injury, poisoning and certain other consequences of external causes' (S00–T98) and 'External causes of morbidity and mortality' (V01–Y98)	
Kidney disease ICD sub-chapters 'Renal failure' (N17-N19), 'Glomerular diseases' (N00-N08), 'Renal tubulo-interstitial diseases' (N10-N16), 'Other disorders of kidney and ureter' (N25-N29).	
Other: any code not falling into any of the above categories.	**Other**: ICD chapter 'Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified' (R00-R99) as well as any code not falling into any of the above categories.
In sub-group analyses, categories were grouped into cardiovascular (heart failure and other cardiovascular) causes and non-cardiovascular causes (all other categories).	

7.3.8 Validity of causes of death records

The present research is reliant on the accuracy of recorded causes of death on death certificates and their validity has therefore been carefully assessed.

The registration of deaths occurring in England and Wales is carried out by the Local Registration Service in partnership with the General Register Office (GRO). Information collected at death registration is normally supplied by the informant (usually a close relative of the deceased), underdoes automatic validation checks and is verified by the registrar. The cause of death is usually obtained from the Medical Certificate of Cause of Death (MCCD), completed by a medical practitioner when the death is certified. The final underlying cause of death takes account of additional information received from medical practitioners or coroners after the death has been registered; around 40% of deaths are referred to the coroner.[169]

The Office for National Statistics (ONS) collects information on all deaths that occur in England and Wales as well as deaths of all ordinary residents.[169] The dataset used in this study was restricted to patients whose record was linked to death information from ONS death certificates. Mortality data from the ONS is used by academics, demographers and health researchers, as well as major national and international health organisations (including Public Health England, Eurostat, and the United Nations) for disease surveillance and epidemiological research. A recent study performed by the ONS has examined causes of death recorded on death certificates in five pilot areas in the UK. The study found that, on scrutiny of an independent medical examiner, the broad underlying cause of death (as defined by International Classification of Diseases chapter (ICD)) remained unchanged in 88 per cent of cases.[170] In the present study, the 22 ICD chapters were grouped into higher-level disease categories (respectively 9 and 11 disease categories for death and hospitalisations), so that consistency is likely to be even higher than in the aforementioned ONS study. Moreover, no national coding reform has been introduced over the study period and there is no evidence to suggest recording practices have changed considerably over time or by age, sex, and socioeconomic sub-groups.[169]

In light of this information, I conclude that studies investigating UK death certificates data may present some level of inaccuracy and that their interpretation must consider the impact of

disease-specific changes in coding practices; yet that the information is appropriate for the study of long-term temporal trends of cause-specific mortality in large populations.

7.3.9 Accuracy of hospital episodes data

Accuracy of diagnostic coding in routinely collected hospital records in the United Kingdom has been widely studied and findings show that data are sufficiently robust to be used in healthcare research and decision-making. Specifically, a recent systematic review identified 32 studies were that compared routinely collected data with case or operation notes. Although accuracy presented significant variation between studies, their findings show that since the 2002 introduction of the 'Payment by Results' programme, accuracy has improved, and for primary discharge diagnoses accuracy was 96.0%.[171]

7.3.10 Patient characteristics

For those with incident heart failure, baseline characteristics (systolic and diastolic blood pressure, smoking status, and body mass index (BMI)) were abstracted from electronic health records as the most recent measurement within 2 years prior to heart failure diagnosis, alongside information on comorbidities, socioeconomic status, ethnicity, and region (for a detailed description of covariates refer to **Chapter 4**).

7.3.11 Statistical analyses

Baseline characteristics are presented as frequencies (%) for categorical data, medians and interquartile range (IQR) for non-normally distributed continuous data, or means and standard deviation (SD) for normally distributed continuous data, over the whole heart failure patient cohort and stratified by time period of diagnosis. Number and percentage of records with missing data are displayed for variables with missing entries. For categorical variables, frequencies refer to complete cases.

Findings report crude mortality and hospitalisation rates, as well as adjusted rate ratios by calendar year and sub-groups (age, sex, socioeconomic status, place of diagnosis). Crude mortality rates were computed as the cumulative incidence of mortality at one year accounting for observation time. Cause-specific mortality rates were computed accounting for competing

risk of death from other causes.[172] Hospitalisations were assessed as the number of hospital admissions with overnight stay per patient-years of follow-up within one year of heart failure diagnosis. To examine trends over time and by sub-group, I used Poisson regression models offset for observation time, and present resulting rate ratios and 95% confidence intervals (CI). All models account for year of diagnosis, age at diagnosis (as a continuous variable), sex, region, socioeconomic status, and baseline comorbidities (17 conditions as defined in **Chapter 4**). To test whether temporal trends significantly differed between sub-groups, I calculated interaction p-values, by including an interaction term combining the sub-group category and year of diagnosis in the model. Follow-up time was considered from the date of incident heart failure diagnosis up to the earliest of the following dates: patient died, patient de-registered from practice, or the practice ceased contributing data, and for a maximum of one year.

I performed several sensitivity analyses to assess the robustness of observed temporal trends. Specifically, I grouped the first three and the last three years of the study together, and assessed whether direction and statistical significance of trends were similar to those reported in the main analyses. I further investigated rates of inpatient mortality among patients diagnosed in hospital and how these changed over time.

Study findings are reported in accordance with the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) recommendations.[117] Analyses were prospectively specified in the study protocol and all statistical analyses were performed in R, version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

7.4 Results

A total of 86,833 patients who developed incident heart failure from 2002 to 2013 were identified. At the time of diagnosis, 48% of patients were aged 80 years or more, 49.0% were women, and 79% had three or more comorbidities. Over the study period, patient characteristics presented a modest increase in age at diagnosis, a marked increase in multimorbidity, and a greater proportion of patients diagnosed in secondary care settings as opposed to primary care (**table 7.2**).

Table 7.2: Baseline characteristics of patients with incident heart failure from 2002 to 2013

Characteristic	All cases (n=86,833)	Time period	
		2002-2004 (n=21,943, 25%)	2011-2013 (n=22,065, 25%)
Age [years], mean (SD)	76.6 (12.6)	76.5 (12.1)	76.9 (12.9)
Age >= 80 years, no. (%)	41,888 (48%)	10,129 (46%)	11,079 (50%)
Women, no. (%)	42,581 (49%)	10,889 (50%)	10,718 (49%)
Ethnicity, no. (%)			
White	51,215 (88%)	12,038 (92%)	16,219 (87%)
Missing	28,316 (33%)	8,912 (41%)	3,431 (16%)
Socioeconomic quintile, no. (%)			
1 (least deprived)	17,024 (20%)	4,177 (19%)	4,514 (20%)
2	18,680 (22%)	4,680 (21%)	4,808 (22%)
3	18,709 (22%)	4,769 (22%)	4,734 (21%)
4	17,149 (20%)	4,387 (20%)	4,230 (19%)
5 (most deprived)	15,271 (18%)	3,930 (18%)	3,779 (17%)
Systolic blood pressure			
Mean (SD) [mmHg]	133 (21)	137 (24)	130 (19)
Missing, no. (%)	5,080 (6%)	2,601 (12%)	682 (3%)
Diastolic blood pressure			
Mean (SD) [mmHg]	75 (11)	77 (12)	73 (11)
Missing, no. (%)	5,192 (6%)	2,601 (12%)	705 (3%)
BMI category, no. (%)			
Underweight	2,022 (4%)	329 (3%)	611 (4%)
Normal	16,090 (31%)	3,000 (31%)	4,632 (31%)
Overweight	17,397 (34%)	3,434 (35%)	4,889 (32%)
Obese	9,742 (19%)	1,824 (19%)	2,872 (19%)
Severely obese	6,440 (12%)	1,086 (11%)	2,080 (14%)
Missing	35,142 (40%)	12,270 (56%)	6,981 (32%)
Smoking, no. (%)			
No	27,405 (41%)	5,081 (41%)	7,377 (41%)
Ex	30,191 (45%)	5,192 (42%)	8,416 (46%)
Yes	9,002 (14%)	2,031 (17%)	2,320 (13%)
Missing	20,235 (23%)	9,639 (44%)	3,952 (18%)
Three or more comorbidities, no. (%)	68,451 (79%)	14,876 (68%)	19,018 (86%)
Diagnosis setting			
Primary care	38,448 (44%)	11,952 (54%)	8,266 (37%)
Hospital admission, HF primary cause	10,838 (12%)	2,650 (12%)	2,588 (12%)
Hospital admission, HF secondary cause	37,547 (43%)	7,341 (33%)	11,211 (51%)

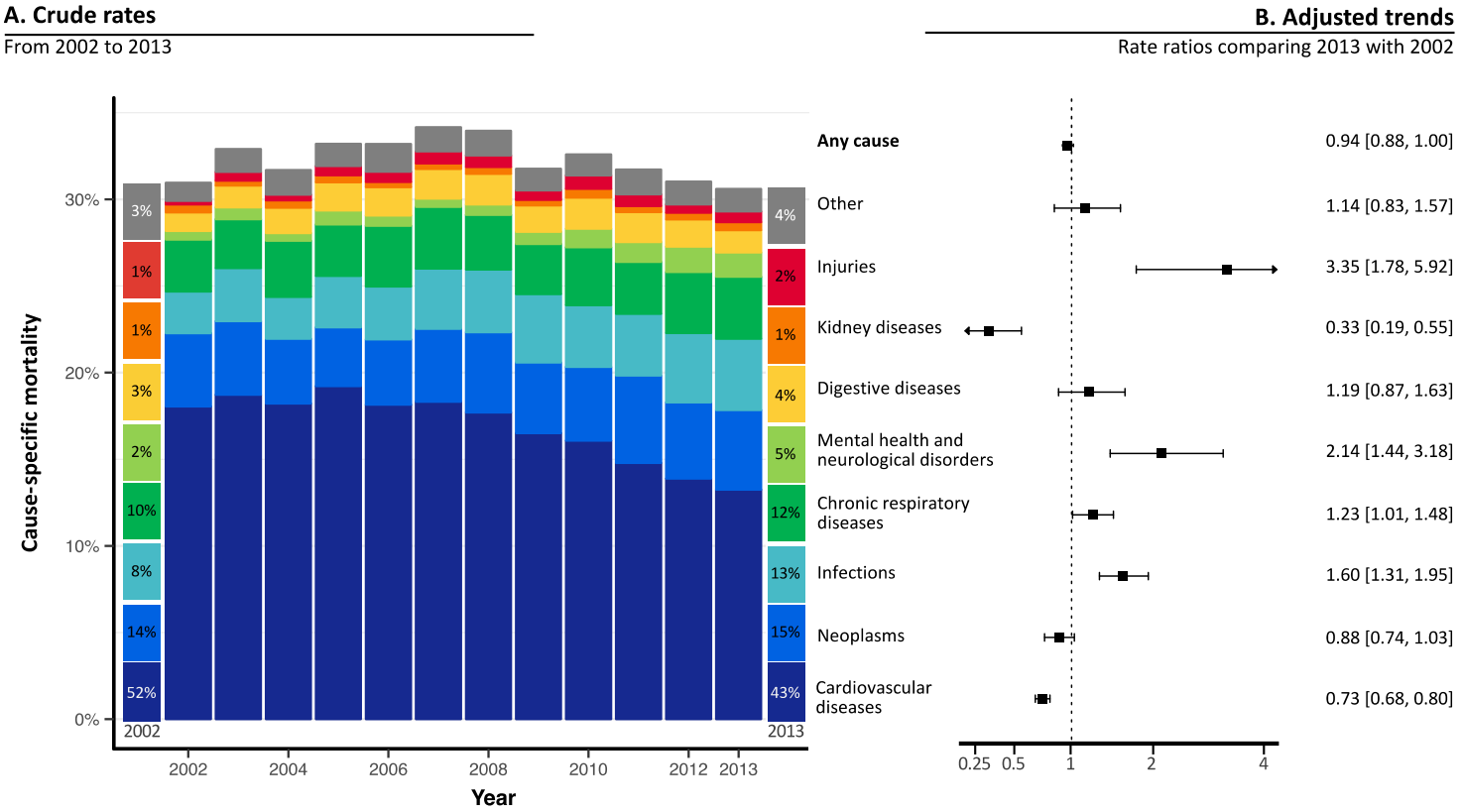
Number and percentage of records with missing data are displayed for variables with missing entries. Category percentages refer to complete cases. Socioeconomic status refers to Index of Multiple Deprivation (IMD) 2015 quintile, with 1 referring to the most affluent and 5 to the most deprived quintile. Number of comorbidities refers to any of the 17 conditions investigated (see Methods).

7.4.1 Mortality

One-year mortality rates following incident heart failure were high (32%), and declined only modestly over the period of study (adjusted rate ratio (RR) and 95% CI comparing 2013 with 2002: 0.94 [0.88, 1.00]).

When overall mortality rates were stratified by specific causes, diverging trends between death from cardiovascular and non-cardiovascular causes became apparent. One-year mortality from cardiovascular causes declined from 18% in 2002 to 13% in 2013 (RR 2013 vs. 2002: 0.73 [0.67, 0.80]), while non-cardiovascular mortality increased over the same period from 13% to 17% (RR 2013 vs. 2002: 1.22 [1.11, 1.33]). Among patients who died in 2013, the most frequent causes of death after cardiovascular diseases (43% of all deaths), were neoplasms (15%), infections (13%), and chronic respiratory conditions (12%). Deaths related to infections, chronic respiratory diseases, injuries, and mental health or neurological disorders, increased during the period of study (**figure 7.1**). Mortality due to infections accounted for the largest absolute increase over time, representing 8% and 13% of deaths in 2002 and 2013, respectively (RR 2013 vs. 2002: 1.60 [1.31, 1.95]). Further analyses of individual causes of death revealed influenza and pneumonia as important and increasing causes of death (6% of deaths at one year, RR 2013 vs. 2002: 1.59 [1.26, 1.99]), now accounting for about as many deaths as myocardial infarction and more deaths than cerebrovascular disease. Although mortality from chronic respiratory diseases was largely due to chronic obstructive pulmonary disease, the increase over time in this category was essentially attributable to interstitial lung diseases, which represented 1% and 2% of deaths in 2002 and 2013 respectively, RR 2013 vs. 2002: 3.37 [1.77, 6.42]). Finally, deaths from injuries were most commonly related to falls or unspecified accidental causes, and deaths attributed to mental health and neurological disorders were largely due to dementia, including Alzheimer's disease (**table 7.3**).

Figure 7.1: Temporal trends in all-cause and cause-specific mortality rates at 1-year following incident heart failure



A. Crude rates of all-cause and cause-specific mortality at 1 year following incident heart failure diagnosis. Labels for years 2002 and 2013 present individual causes of death as a share of the total number of deaths at 1-year. B. Rate ratios from multivariable Poisson regression models comparing 1-year mortality rates in 2013 with 2002, by first reported cause, adjusting for patients' age, sex, socioeconomic status, region, and 17 baseline comorbidities.

Table 7.3: Number of deaths due to cardiovascular diseases, neoplasms, infections, chronic respiratory diseases, mental health and neurological disorders, and injuries, by disease sub-group

	All years (n = 27,398)	2002-2004 (n=6,884)	2011-2013 (n=6,616)
Cardiovascular diseases			
Chronic ischaemic heart disease	4,881 (34%)	1,501 (38%)	848 (29%)
Acute myocardial infarction	3,010 (21%)	868 (22%)	583 (20%)
Heart failure	1,794 (13%)	509 (13%)	295 (10%)
Cerebrovascular diseases	1,619 (11%)	396 (10%)	386 (13%)
Other forms of heart disease	3,027 (21%)	687 (17%)	862 (29%)
Neoplasms			
Malignant neoplasms of digestive organs	819 (22%)	219 (25%)	211 (21%)
Malignant neoplasms of respiratory and intrathoracic organs	708 (19%)	184 (21%)	190 (19%)
Malignant neoplasms of lymphoid, haematopoietic and related tissue	533 (14%)	102 (12%)	155 (16%)
Malignant neoplasms of male genital organs	374 (10%)	90 (10%)	107 (11%)
Malignant neoplasms of urinary tract	237 (6%)	53 (6%)	66 (7%)
Malignant neoplasm of breast	227 (6%)	50 (6%)	62 (6%)
Other	830 (22%)	183 (21%)	204 (21%)
Infections			
Influenza and pneumonia	1,915 (64%)	411 (72%)	566 (69%)
Other forms of respiratory infections	137 (5%)	13 (2%)	28 (3%)
Urinary tract infections	351 (12%)	50 (9%)	74 (9%)
Sepsis	192 (6%)	23 (4%)	59 (7%)
Intestinal infectious diseases	146 (5%)	20 (4%)	30 (4%)
Cellulitis	88 (3%)	11 (2%)	34 (4%)
Infections affecting the heart	61 (2%)	15 (3%)	14 (2%)
Tuberculosis	17 (1%)	6 (1%)	3 (0%)
Other infectious or parasitic diseases	62 (2%)	20 (4%)	18 (2%)
Chronic respiratory diseases			
Chronic obstructive pulmonary disease	1,907 (67%)	477 (73%)	460 (64%)
Interstitial lung disease and pulmonary Sarcoidosis	493 (17%)	74 (11%)	170 (24%)
Asthma	62 (2%)	13 (2%)	15 (2%)
Pneumoconiosis	24 (1%)	4 (1%)	12 (2%)
Other chronic respiratory diseases	341 (12%)	84 (13%)	58 (8%)

	All years (n = 27,398)	2002-2004 (n=6,884)	2011-2013 (n=6,616)
Mental health and neurological disorders			
Dementia	386 (55%)	46 (39%)	199 (70%)
Alzheimer	85 (12%)	18 (15%)	23 (8%)
Other diseases of the nervous system	207 (30%)	47 (40%)	58 (20%)
Other mental and behavioural disorders	22 (3%)	6 (5%)	4 (1%)
Injuries			
Accidental exposure to unspecified factor	202 (43%)	37 (49%)	48 (38%)
Falls	152 (33%)	18 (24%)	44 (35%)
Complications of medical and surgical care	39 (8%)	14 (19%)	17 (14%)
Other external causes of morbidity and mortality	74 (16%)	6 (8%)	16 (13%)

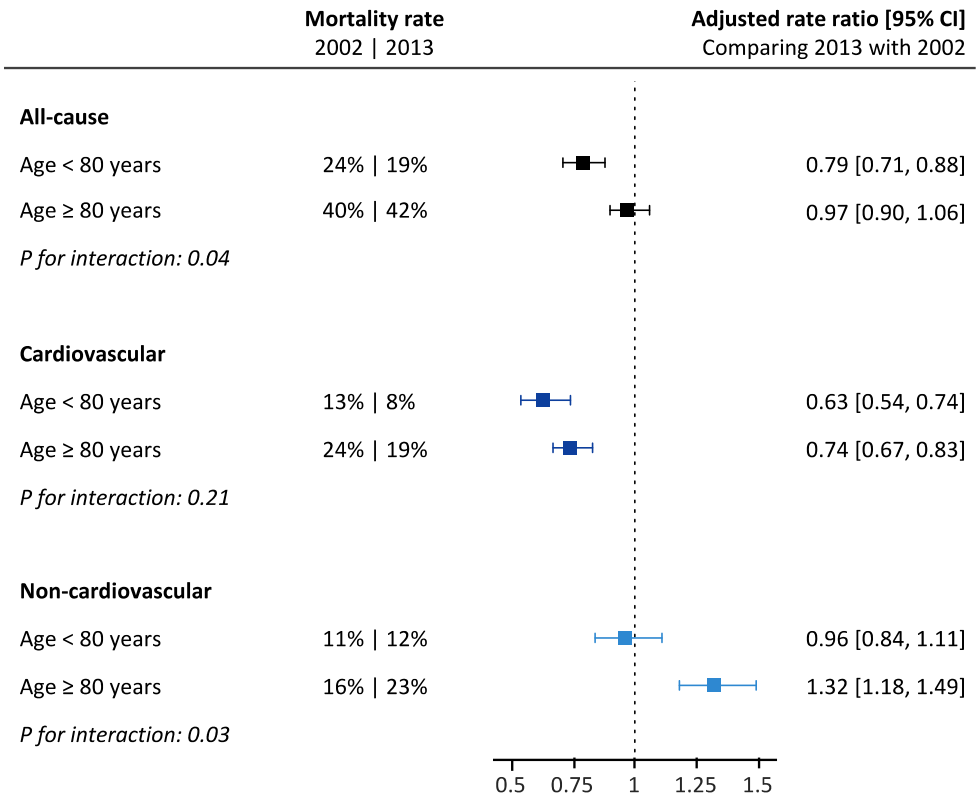
N refers to the number of deaths at 1 year attributed to individual causes. Percentages refer to the total number of deaths within each disease category. Clinical codes used to identify each disease group are available upon request.

Mortality increased with age and one-year rates of death from any cause ranged from 12% in patients under 55 years of age to 64% in those above 95 years. Age-stratified analyses further revealed diverging trends over time: all-cause mortality declined among patients under 80 years of age (RR 2013 vs 2002: 0.79 [0.71, 0.88]), but not in older individuals (RR 2013 vs 2002: 0.97 [0.9, 1.06], p for interaction = 0.04) (**figure 7.2**, **figure 7.3**). Cause-specific analyses showed that cardiovascular mortality declined across all age groups, although less steeply in older age groups, and that the increase in non-cardiovascular mortality was largely attributable to older age groups (**figure 7.2**). Individual causes of death also differed by age. Specifically, digestive diseases (in particular liver cirrhosis) and neoplasms were more common in younger patients, while infections and mental health or neurological disorders were more common in older age groups (**figure 7.4**).

While overall mortality was similar in men and women (**figure 7.5**), there were sex-specific patterns in particular causes of death. Cardiovascular causes accounted for half of deaths in men, independently of age, whereas in women the proportion of deaths due to a cardiovascular cause increased with age. Among women under 65 years of age, cancer and infections accounted for a higher share of deaths than in men of the same age (**figure 7.4**).

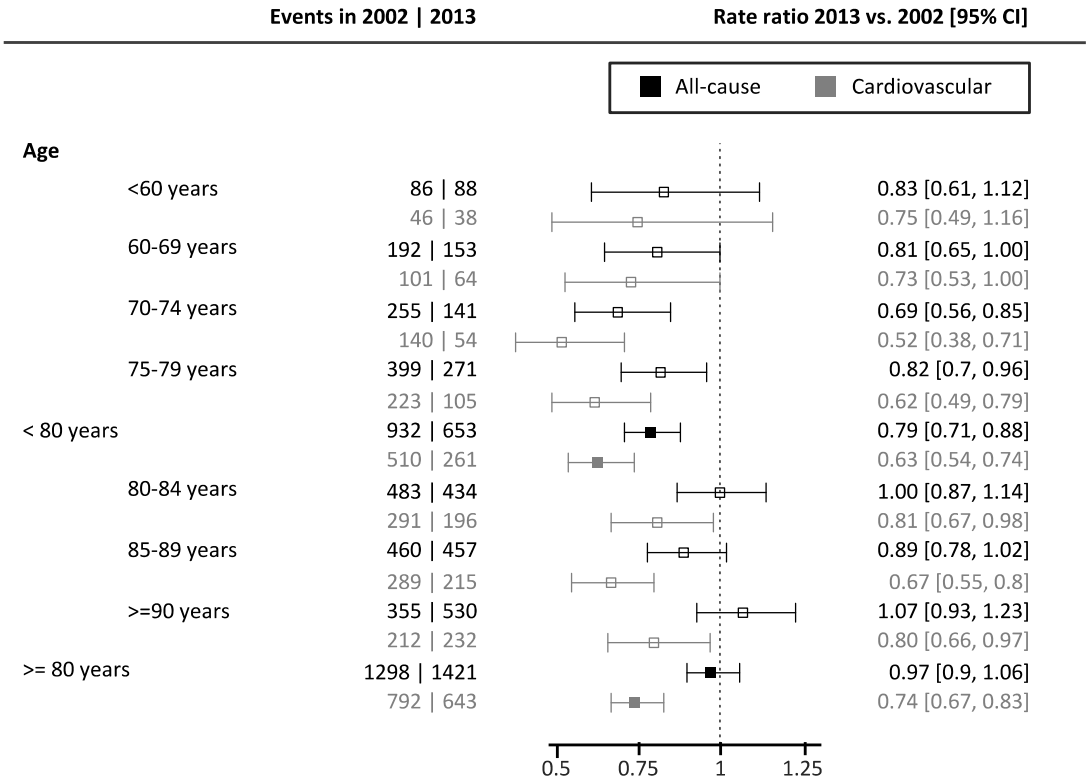
Finally, patients' socioeconomic background and the care setting in which patients were first diagnosed were important predictors of health outcomes. For the same age and sex, patients from more deprived socioeconomic backgrounds had 19% higher mortality rates than their more affluent counterparts (RR for one-year mortality, most deprived vs least deprived quintile: 1.19 [1.15, 1.24]) (**figure 7.5**). One-year mortality was also higher in patients diagnosed with heart failure in hospital (41%) compared with those diagnosed in primary care (22%) (RR from hospital vs primary care diagnoses: 2.29 [2.23, 2.35]) (**figure 7.5**). Among those diagnosed in hospital, 21% died before discharge, and rates did not change significantly over the period of study (21% and 19% in 2002 and 2013 respectively, RR 2013 vs. 2002: 0.91 [0.82, 1.01]).

Figure 7.2: Temporal trends in all-cause and cause-specific mortality rates at 1-year following incident heart failure, by age group categorised in <80 and ≥ 80 years.



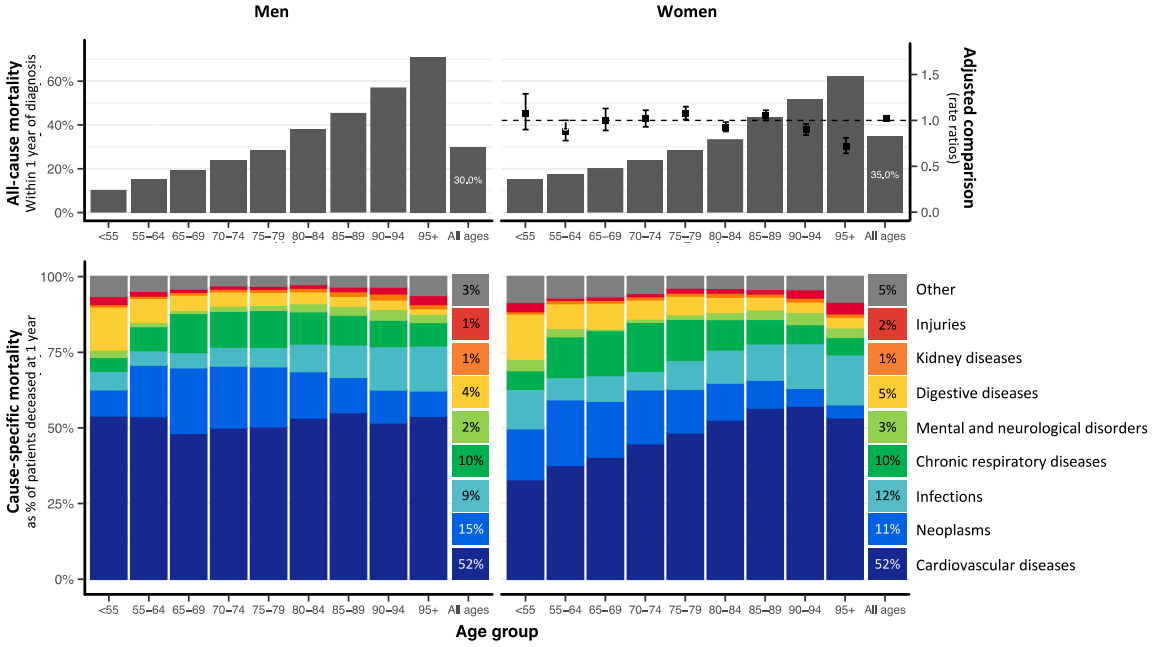
Crude mortality rates by age-groups alongside rate ratios, 95% confidence intervals (CI), and interaction p-values from multivariable Poisson regression models accounting for year of diagnosis, age (as a continuous variable), sex, socioeconomic status, region, and 17 baseline comorbidities. Interaction p-values refer to the interaction between age-group (categorised as age <80 years or age ≥ 80 years) and year of diagnosis.

Figure 7.3: Temporal trends in one-year mortality rates following incident heart failure, by age group categorised in <60, 60-69, 70-74, 75-79, 80-84, 85-89, ≥ 90 years.



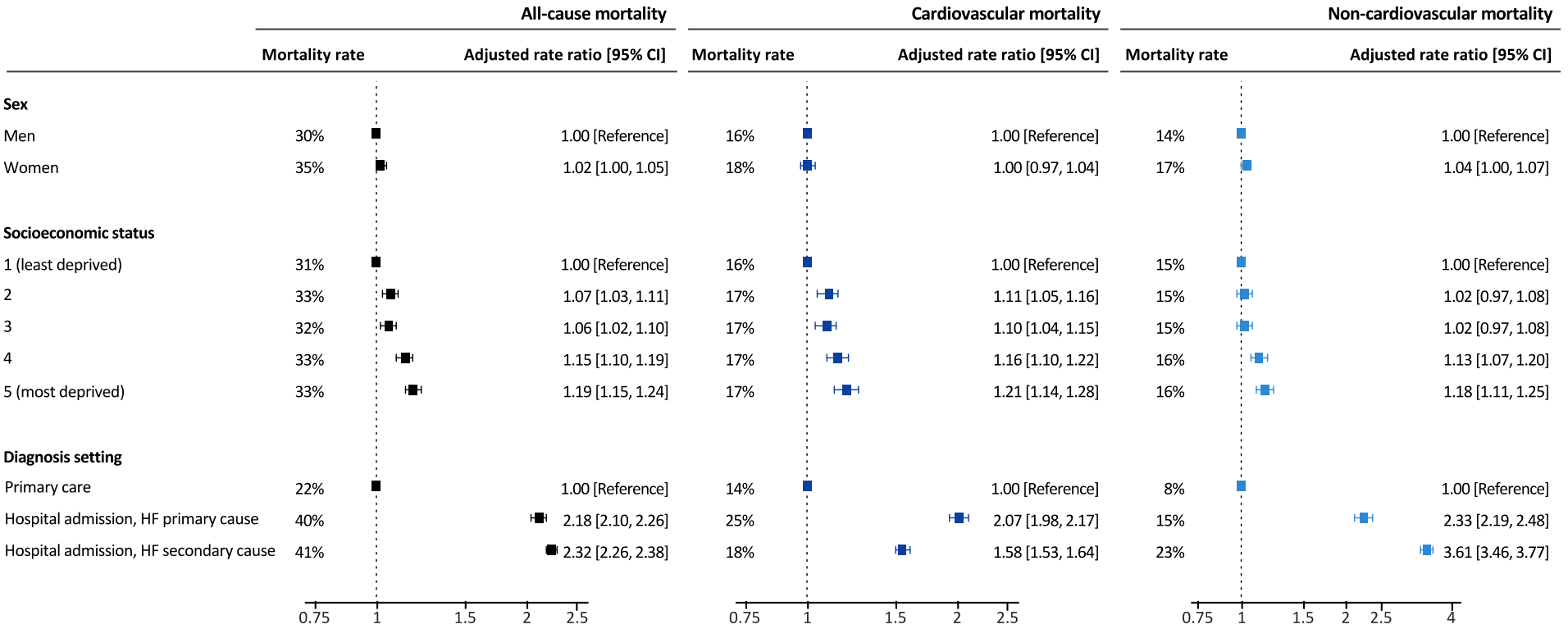
Rate ratios and 95% confidence intervals (CI) comparing 2013 and 2002, from multivariable Poisson regression models accounting for year of diagnosis, age (as a continuous variable), sex, socioeconomic status, region, and 17 baseline comorbidities.

Figure 7.4: All-cause and cause-specific mortality rates at 1-year following incident heart failure, by age and sex



Crude rates of all-cause mortality rates at 1 year following incident heart failure diagnosis, as well as cause-specific mortality presented as a proportion of patients deceased at 1-year. Adjusted comparison present rate ratios for all-cause mortality at 1 year in women versus men from multivariable Poisson regression models adjusting for year of diagnosis, socioeconomic status, region, and 17 baseline comorbidities.

Figure 7.5: Differences in mortality rates one year after incident heart failure, by sex, socioeconomic status and diagnosis care setting



Crude mortality rates by sub-groups alongside rate ratios and 95% confidence intervals (CI) from multivariable Poisson regression models accounting for year of diagnosis, age (as a continuous variable), sex, socioeconomic status, region, and 17 baseline comorbidities. Socioeconomic status refers to Index of Multiple Deprivation 2015 quintile, with 1 referring to the most affluent and 5 to the most deprived socioeconomic quintile.

7.4.2 Hospitalisations

The number of hospital admissions in the year following incident heart failure was high (1.15 hospitalisations per patient-year at risk). Although crude rates increased by 20% over time, adjusted rates accounting for patient characteristics and comorbidities at baseline declined by 6% over the study period (RR 2013 vs 2002: 0.94 [0.90, 0.98]) (**figure 7.6**).

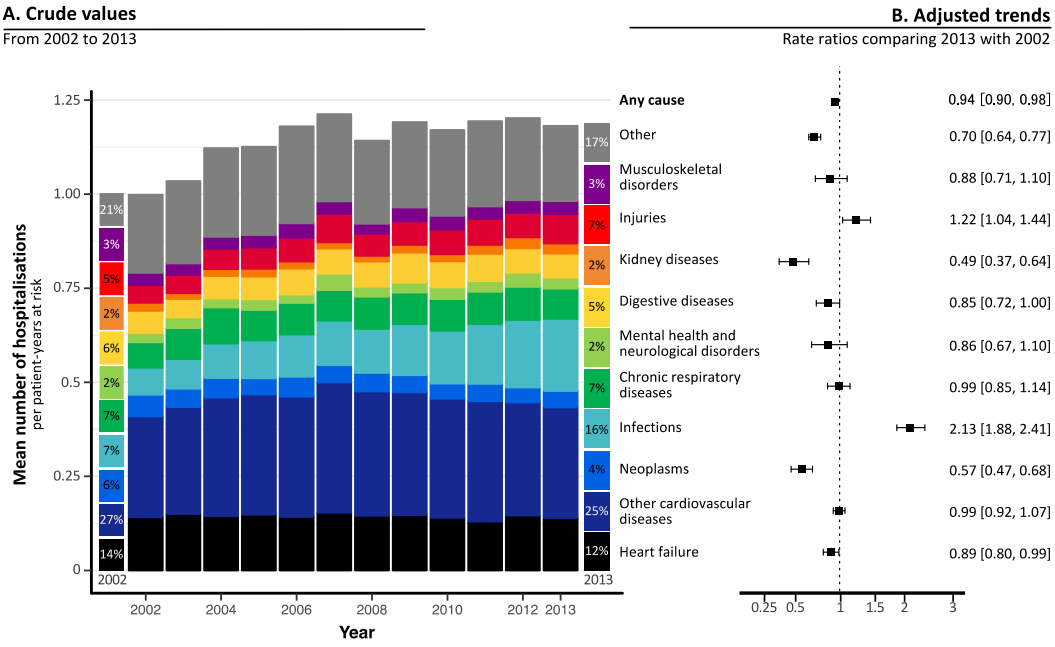
Admissions for heart failure represented 13% of hospitalisations from any cause within a year of diagnosis (0.14 hospitalisations per patient-year at risk) and showed a relative decline of 11% over the study period (RR 2013 vs 2002: 0.89 [0.80, 0.99]). Overall, hospitalisations relating to any cardiovascular reason (heart failure or another cardiovascular disorder) represented less than half of all admissions and did not change significantly over time (0.46 hospitalisations per patient-year at risk, RR 2013 vs 2002: 0.96 [0.91, 1.03]). In parallel, admissions for some non-cardiovascular causes, in particular infections and injuries, increased (**figure 7.6**). By one year, 44% of patients had experienced at least one hospitalisation for any cause and 9% had experienced at least one heart failure-related admission. Another 23% died without hospitalisation, 31% survived for over one year without hospitalisation, and 2% stopped contributing data with no record of hospitalisation or death.

Age-stratified patterns of hospital admissions were similar to those reported for mortality. The number of admissions declined among patients under 80 years of age (RR 2013 vs 2002: 0.82 [0.77, 0.88]), but not in older individuals (RR 2013 vs 2002: 1.12 [1.04, 1.21]). Differences by sex, socioeconomic status and place of diagnosis were also consistent, although less pronounced than those reported for mortality (**figure 7.7**).

7.4.3 Sensitivity analyses

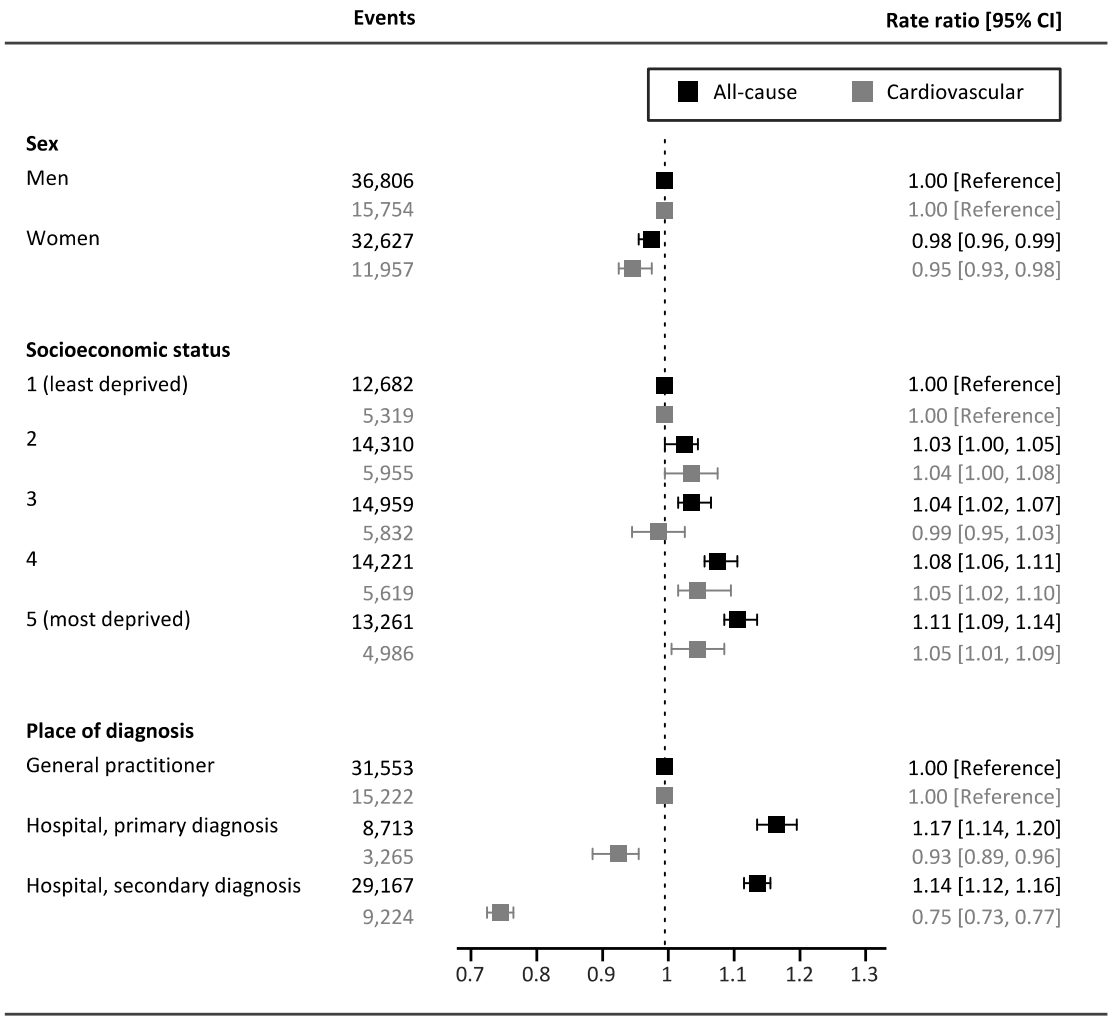
To assess the robustness of observed temporal trends, I grouped the first three and the last three years of the study together, and assessed whether direction and statistical significance of trends were similar to those reported in the main analyses. I found that although small differences in significance levels became apparent, sensitivity analyses confirmed the robustness of my main findings and messages presented here.

Figure 7.6: Temporal trends in all-cause and cause-specific mean number of hospitalisations, at 1-year following incident heart failure



A. Crude mean number of hospitalisations within 1 year of incident heart failure per patient-years at risk, by primary discharge diagnosis. Labels displayed for 2002 and 2013 present individual discharge diagnoses as a share of the total number of hospitalisations in the given year. B. Rate ratios from multivariable Poisson regression models comparing mean number of hospitalisations at 1 year in 2013 with 2002 offset for patient-years at risk, by primary discharge diagnosis, adjusting for age, sex, socioeconomic status, region, and 17 baseline comorbidities.

Figure 7.7: Differences in hospital admissions within a year of incident heart failure, by sex, socioeconomic status and diagnosis care setting



Hospital admissions refer to the number of admissions per patient-years at risk within a year of incident heart failure diagnosis. Rate ratios and 95% confidence intervals (CI) from multivariable Poisson regression models accounting for year of diagnosis, age (as a continuous variable), sex, socioeconomic status, region, and 17 baseline comorbidities. Socioeconomic status refers to Index of Multiple Deprivation 2015 quintile, with 1 referring to the most affluent and 5 to the most deprived socioeconomic quintile.

7.5 Discussion

7.5.1 Summary of main findings

This study reveals possible explanations for the plateauing of mortality rates observed among patients with heart failure in many high-income countries. Important improvements in cardiovascular mortality appear to have been offset by a large and increasing number of deaths due to non-cardiovascular disorders, such as infections and respiratory problems, especially in older individuals. Overall survival rates improved in younger and middle-aged patients as a result of fewer cardiovascular deaths, yet mortality changed little in patients aged 80 years or more who comprised almost half of all heart failure cases. Broadly similar findings were seen for hospital admissions.

7.5.2 Comparison with existing literature

The overall temporal trends in all-cause mortality rates observed in this study are in line with earlier reports from high-income countries that have also shown little change since the early 2000s (**table 2.3**). Previous studies have rarely investigated the underlying causes of death or hospitalisations and had limited ability to adjust for other concomitant changes such as the rise in comorbidities over time. To the best of my knowledge, the only study that has reported cardiovascular and non-cardiovascular mortality and morbidity trends separately was the Olmsted county study, which was limited by sample size and statistical power to make robust conclusions about changing patterns.[1] Complementing these earlier studies, this research shows that within the last 15 years, the relative risk of death from cardiovascular causes after incident diagnosis of heart failure has declined by 27%. However, this important improvement in outcomes was offset by a 22% increase in non-cardiovascular death rates.

7.5.3 General discussion of findings

Age-stratified analyses provide additional insights into underlying mechanisms and offer opportunities to improve patient care. On the one hand, the observation that death rates from cardiovascular disease improved across all age groups attests to important achievements in cardiovascular care. On the other hand, the rise in deaths due to non-cardiovascular causes, in

particular among older patients, highlights the importance of multimorbidity, frailty, and senescence, rather than cardiac dysfunction, as important determinant of prognosis. With about 80% of heart failure patients being multimorbid and almost 50% aged 80 years or more at the time of diagnosis, it appears crucial to investigate challenges and treatment opportunities in usual practice. To be relevant, future clinical trials will have to include different patient populations than in the past, and consider comorbidities alongside heart failure.

Current management of heart failure is intrinsically disease-centred and essentially focused on cardiac dysfunction and its consequences (e.g. neurohumoral activation). Cardiovascular mortality and admissions for heart failure are used as key indicators of the effectiveness of heart failure-specific treatments. Thus, the decline in cardiovascular events is encouraging, and is likely to be, at least partly, attributable to the introduction and increased use of evidence-based therapies observed during the study period.[168] However, this study also revealed that non-cardiovascular outcomes account for the majority of deaths and hospitalisations - a much higher share compared with reports from clinical trials.[173] This finding is consistent with other studies investigating heart failure mortality in unselected patient populations,[1,54] and has implications for future research into the development of life-saving therapies.

These non-cardiovascular comorbidities, hospitalisations and deaths, are in themselves, an important potential therapeutic target in patients with heart failure. For example, infections appeared to represent the single largest driver behind the recent increase in non-cardiovascular mortality and hospitalisations observed in the present study. The vast majority of infection-related deaths were due to influenza and pneumonia and some of those may have been preventable through better care. For instance, the coverage of influenza vaccination among heart failure patients in the UK, although high compared to many other countries,[174] has been declining,[175] which could have contributed to the observed trend. Hospital-acquired bacterial infections are another possible source of infections in elderly patients, and increasing rates of hospital admissions, haemodialysis, and device implantations, may have further contributed to the observed increase, despite important reductions in hospital-acquired bacterial infections per bed-days achieved during the study period.[176]

Chronic respiratory conditions, injuries and dementia further contributed to the increasing rates of non-cardiovascular mortality, yet with a more modest impact on overall burden. The observed increase in mortality from chronic respiratory conditions was largely attributable to interstitial lung diseases. While this finding is consistent with reports of increasing rates of detection, incidence and mortality related to interstitial lung diseases in the general population, in the UK and worldwide[177–179] and may, therefore, not be specific to heart failure; Patients with heart failure often receive treatments known to cause pulmonary fibrosis, including antibiotics, amiodarone and repeated exposure to therapeutic oxygen.[180,181] Further studies are needed to fully understand the reasons for increasing rates of interstitial lung diseases among patients with heart failure, and to guide clinical decision making in patients at high risk of pulmonary complications.

Falls are common in elderly populations,[182] and the perception that the blood-pressure lowering effects of heart failure therapies may place patients at even higher risk sometimes creates a barrier to effective management of heart failure patients in the community.[161,162] This study quantifies the long-term impact of injuries on patients with heart failure over a period of time that has witnessed a gradual increase in the use of blood pressure lowering therapies,[168] and shows that while rates of injuries in this cohort have increased over time, their contribution to overall mortality and morbidity in patients with heart failure remains relatively modest (2% of deaths and 7% of hospitalisations relate to injuries). Hence these findings do not support the perception that falls present a major health burden among patients with heart failure. Nevertheless, strategies to avoid falls and prevent injuries are an appropriate focus in these patients, in particular in the context of high rates of osteoporosis in this patient group.[183]

Dementia is known as a major cause of death in elderly people and the prevalence of dementia in patients with heart failure is high.[1,184] Although deaths related to dementia in the present study increased over time, they were comparatively few in number, even in the most recent years of follow-up. Efforts to increasingly recognise dementia as a cause of death are likely to have contributed to the observed trend.[185] Nevertheless, dementia prevention is a key goal in older patients with heart failure, and pathogenic pathways in cognitive impairment are yet to be

further explored and exploited, for example as pertains to thromboembolism and its prevention in patients with atrial fibrillation and heart failure.[186,187]

7.5.4 Strengths and limitations

A major strength of this study is the very large patient cohort studied, providing sufficient cases for cause-specific analyses, and the long period of study, which allowed study of long-term trends. This population-based cohort also reflects patients as encountered in routine care, compared with surveys and, particularly clinical trials, which enrol selected participants. One of the key limitations of this study was the relatively limited clinical information contained in electronic health records. In particular, left ventricular ejection fraction measurements were not available and hence I was unable to stratify analyses by type of heart failure. While this limitation is important, particularly as heart failure treatments have only been demonstrated to be effective in patients with heart failure and reduced ejection fraction, evidence from several large-scale observational studies shows that mortality rates and trends over time do not differ significantly between patients with preserved or reduced ejection fraction.[1,188] Moreover, the current evidence base does not suggest that the case-mix of newly diagnosed heart failure patients would have shifted significantly towards one or the other type of ejection fraction over period of study.[1]

7.5.5 Policy and practice implications

Results from this study present clinicians and policy makers with several actionable insights to improve patient prognosis.

Management of non-cardiovascular outcomes: Most importantly, this study shows that the current approach to heart failure management that is intrinsically focussed on cardiovascular outcomes is insufficient since, among unselected heart failure populations, mortality and morbidity is largely due non-cardiovascular causes. To develop more effective therapies and management strategies, both cardiovascular and non-cardiovascular outcomes need to be addressed - this approach represents a paradigm shift in heart failure management and for the design of heart failure trials. Moreover, several therapies exist to manage common

comorbidities associated with heart failure, but their prevalence and importance is insufficiently recognised in clinical guidelines and practice. For example, secondary prevention is currently essentially focussed on myocardial infarction and stroke; but infections are equally important (in fact these findings show that influenza and pneumonia now represent about as many deaths as myocardial infarction and more deaths than cerebrovascular disease), are largely preventable and present a major opportunity to improve patient prognosis. Other conditions, including chronic respiratory conditions, dementia, and injuries, also deserve more systematic prevention strategies among heart failure patients.

Management of elderly populations: With almost 50% aged 80 years or more at the time of diagnosis, it appears crucial to investigate challenges and treatment opportunities in consideration of the special needs of elderly populations where heart failure is often complicated by multimorbidity, polypharmacy and senescence.

Management of women: Women also present about half of all heart failure patients yet still remain largely underrepresented in clinical trials data. Findings from this study show that women present with different patterns of mortality and morbidity than men and suggest that further research is needed to fully understand the extent of sex-differences in heart failure.

Management of socioeconomically deprived individuals: The present study shows that mortality, one-year following a new heart failure diagnosis, is about 20% higher in socioeconomically deprived individuals than in their affluent counterparts. This disparity affects both cardiovascular and non-cardiovascular outcomes, and call for further research to understand underlying reasons and develop more targeted health policies.

7.5.6 Future research

Analyses of cause-specific health outcomes among heart failure patients presented in this study also reveal several important results that deserve further investigation. The present work could be taken further by studies relying on richer datasets. Most importantly, stratifying analyses by type of ejection fraction (reduced or preserved), by disease aetiology (e.g. hypertensive, ischaemic, etc.), or by disease severity would provide valuable information to design more

targeted management strategies. Investigating health outcomes over longer periods of follow-up (e.g. up to five or ten years after diagnosis) would present as similarly beneficial.

Additionally, understanding how mortality or hospitalisations patterns have changed in more recent years, particularly after the introduction of new treatments, such as sacubitril/valsartan,[126] would further improve our understanding of heart failure and further support the development of life-saving therapies.

Finally, studies investigating mortality and hospitalisations among heart failure patients in other countries could help in validating the present findings in different settings of care.

7.6 Conclusion

These findings have important implications for public health policies. Significant reductions in cardiovascular events and improvements in the prognosis of heart failure patients under the age of 80 years attest to the progress in patient care and encourage continued efforts to increase the use of evidence-based therapy. More efforts are needed to understand optimal treatment in older patients and non-cardiovascular disorders associated with heart failure. Prevention of infections appears as a major priority and opportunity. Further improvements are likely to require a broader perspective to heart failure management, one that considers not only patients' cardiovascular health but also the wide range of associated comorbidities and special needs of elderly patients.

7.7 Research in context

7.7.1 Evidence before this study

I searched Pubmed for reports published from 1 January 2012 to 15 February 2019 that included "heart failure" and "mortality" in their title, reviewed references from clinical practice guidelines and consulted with experts for relevant studies. I found numerous studies that investigated mortality following a hospital admission for heart failure, though few studies reported survival rates after incident diagnosis. In an attempt to compare various reports, I selected studies that reported 1-year mortality rates following a new diagnosis of heart failure and (i) referred to

European or North American cohorts, (ii) included at least 1,000 patients, (iii) were not restricted to clinical trials, special care management programmes, certain age-groups or associated conditions, and (iv) reported trends over time. A few relevant studies were identified (**table 1.3**). Overall these reported improvements in mortality up to around 2005 but stable rates thereafter, despite increasing uptake of new treatments, in particular beta-blockers. Most studies confined investigations to all-cause mortality, with only one study distinguishing between cardiovascular and non-cardiovascular mortality. No study investigated underlying patterns and cause-specific mortality.

7.7.2 Added value of this study

In-depth analysis of temporal trends in hospitalisations and mortality by sub-groups and specific causes reveals that the observed standstill in mortality rates among patients with new-onset heart failure masks a complex pattern of changes and diverging trends in cause-specific outcomes and age groups.

Hospitalisations for heart failure and mortality from cardiovascular causes declined over time, likely due to more effective treatment of heart failure. However, improvements in patients' cardiovascular health have been offset by an increase in non-cardiovascular events, particularly among older patients, mostly related to infections and chronic respiratory conditions. Consequently, overall prognosis improved amongst patients aged less than 80 years, but not amongst older patients, attesting of complex barriers to progress in elderly individuals, where heart failure is often complicated by multimorbidity, conflicting treatment priorities and senescence

7.7.3 Implications of all the available evidence

Significant improvements have been achieved in preventing cardiovascular events in patients with heart failure, and that across all age groups. It is important to highlight these advances, and should encourage continued efforts to implement evidence-based care. However, with growing proportion of non-cardiovascular events, additional efforts are needed to extend management strategies to non-cardiovascular health outcomes. With almost half of the patients aged 80 years

or more at the time of heart failure diagnosis, it also appears crucial to better understand the special needs of elderly patients, and to reassess research objectives and therapeutic options accordingly.

8. DISCUSSION

8.1 Summary of main findings

This thesis consisted of one literature search, two methods, and three results chapters investigating the epidemiology of heart failure. This discussion chapter will discuss the overall results of this thesis; specific discussion points for each chapter are provided in the respective discussion sections.

Chapter 2 described the results of in-depth literature searches on heart failure and its epidemiology. Prior evidence on incidence, delivery of care and mortality was synthesised, and summary tables were created to facilitate comparison of relevant studies. Results from these searches were essential to fully appreciate the current level of evidence, identify knowledge gaps and refine research objectives.

Chapter 3 outlined foundational work in determining the most appropriate dataset to investigate the research questions this thesis set out to address. Strengths and limitations of electronic health records (EHRs) and, specifically, the CPRD, were assessed in detail and compared with traditional epidemiological studies. Particular attention was given to representativeness and validity of the dataset, which I have studied thoroughly and led me to conclude that the CPRD dataset is appropriate for the purpose of this study. Finally, the chapter also described the structure of the dataset, alongside important data protection and ethical considerations.

Chapter 4, as the second methods chapter, described the data extraction and processing, variable definitions and study design in sufficient detail for readers to replicate the study in subsequent analyses. Data extraction and processing represented a major part of the work undergone for the completion of this thesis, particularly in light of the large number of variables extracted and analysed. The development of an original phenotype algorithm to extract heart

failure diagnoses from the CPRD involved the review of medical dictionaries, synthesis of previous work, and consultations with clinical and technical experts to assess its appropriateness for use in the CPRD; and represents an important research output that is likely to be valuable to a broad range of future studies investigating heart failure in similar settings.

Chapter 5, the first of three results chapters, investigated the incidence of heart failure in a very large general population cohort and examined changes over time, and by age, sex and socioeconomic status subgroups. Most importantly, the study found that the burden of heart failure in the UK is increasing over time, and is now similar to the four most common causes of cancer combined. Results further showed major socioeconomic disparities in disease incidence and age at onset, which highlight the potentially preventable nature of heart failure that still needs to be tackled. One of the key strengths of this work relies on the calculation of age and sex standardised values on a publicly available standard population, which will allow comparison of disease incidence rates across studies, time periods and geographical regions. Country-wide estimates for the total number of patients affected are also presented and allow public health bodies to evaluate the impact heart failure has on the UK population and health services. Finally, the fact that the study relied on a very large, unselected general population cohort further contributes to generalisability of findings and its importance for epidemiological research and public health services.

Chapter 6 examined trends and patterns in the clinical care received by heart failure patients in the UK. The analysis revealed that the management of heart failure patients in the UK presents important shortcomings that affect screening, continuity of care and medication titration, and disproportionally impacts women and older people. National reporting and incentives schemes that have been introduced in the UK over the past decade have been insufficient to identify these gaps, essentially because they remained confined to individual clinical settings. A major strength of this study relies on the longitudinal data analyses, through which patients were followed from the date of incident diagnosis up to a year later, and the richness of the studied dataset which allowed the investigation of follow-up consultations, diagnostic tests, and drug prescriptions.

Chapter 7 investigated mortality and hospitalisation patterns among patients newly diagnosed with heart failure, stratified by specific cause, as well as age, sex, and socioeconomic status sub-groups. Findings present compelling evidence explaining the apparent standstill in mortality among patients with heart failure observed in many high-income countries. Indeed, although all-cause mortality rates declined only modestly over time, and underlying patterns presented explicit trends: considerable progress has been achieved in reducing cardiovascular mortality and premature deaths, and improvements to overall mortality are hindered by high and increasing rates of non-cardiovascular events. These findings highlight the need for a greater emphasis on associated comorbidities and provide valuable clues to improve patient prognosis, which will have implications for the design of future trials, service planning and health policy. A major strength of this study is the very large patient cohort studied, providing sufficient cases for cause-specific analyses, and the long period of study, which allowed study of long-term trends. This population-based cohort also reflects patients as encountered in routine care, so that findings are likely to be more broadly generalisable compared with surveys or clinical trials, which enrol selected participants.

Table 8.1 presents a brief overview of studies undertaken in thesis. The next section will discuss overall strengths and limitations in more detail.

Table 8.1: Summary of studies undertaken in thesis

Aim	Participants	Main outcomes and measures	Conclusions
Investigate incidence and prevalence of heart failure in the general population (Chapter 5)	4,048,213 individuals, free of heart failure on study entry	Crude and standardised rates of incidence and prevalence Poisson regression models to examine changes over time and by sub-group	The burden of heart failure in the UK is increasing, essentially due to population growth and aging. Major socioeconomic disparities in disease incidence and age at onset persist and highlight the need for more targeted prevention measures.
Investigate the clinical care received by heart failure patients from diagnosis up to one year later (Chapter 6)	93,074 patients newly diagnosed with heart failure between 2002 and 2014*	Five indicators of care: (i) diagnosis care setting (inpatient or outpatient) (ii) post-hospitalisation follow-up (iii) diagnostic investigations (iv) prescription of essential drugs (v) drug treatment dose Poisson and linear regression models to examine changes over time and by sub-group	Management of heart failure patients in the UK presents important shortcomings that affect screening, continuity of care, and medication titration. Gaps in care disproportionally affect women, older people and, to some extent, socioeconomically deprived individuals. National reporting and incentives schemes confined to individual clinical settings have been insufficient to identify these gaps and address patients' long-term care needs.
Examine cause-specific mortality and hospitalisations after incident heart failure (Chapter 7)	86,833 patients newly diagnosed with heart failure between 2002 and 2013**	Mortality rates and number of hospitalisations, one year after incident heart failure, stratified by specific cause Poisson regression models to examine changes over time and by sub-group	Over time, considerable progress has been achieved in reducing cardiovascular mortality across all age groups and all-cause deaths among those aged less than 80 years. Further improvements are hindered by high and increasing rates of non-cardiovascular events, which now represent the majority of deaths and hospitalisations at one year. Infections emerged as an important preventable cause of death, and presents as an opportunity to improve prognosis.

**Follow-up in primary care records was available until December 2015. ** Follow-up for deaths and hospitalisations was available until December 2014.*

8.2 Strengths and limitations

8.2.1 Validity and generalisability

The CPRD is a unique and powerful dataset, and has been used for epidemiological research for a broad range of conditions and study designs. Although the dataset relies on data from the UK, given the similarity of trends in cardiovascular disease and population ageing from the UK with other European countries, North America and Australasia,[139,140] results from the analyses performed in this thesis are likely to be broadly applicable to much of the rest of the developed world.

General considerations on the reliability and validity of CPRD data are discussed in **Chapter 3**. Studies using CPRD data must also use appropriate data extraction and processing techniques to ensure consistent results. In this thesis, particular attention was given to ensure a meticulous and systematic approach and a range of data quality checks were performed throughout the data extraction process. These checks included the restriction to patients and practices with data that passed the CPRD quality control, exclusion of values outside a reasonable range (refer to **Chapter 4**), as well as consistent and thorough checks following data operations, such as table merges or transformations.

8.2.2 Large population size

Analyses in this thesis have benefited from the large population size available in the CPRD. With a general population cohort of over 4 million individuals and 25 million patient-years at risk, investigations of heart failure incidence refer to one of the largest datasets ever used to investigate this research question (**table 2.1**). Similarly, investigations of clinical care and mortality among patients newly diagnosed with heart failure each refer to over 85,000 patients, a considerably larger sample size than most traditional cohorts or registries (**table 2.2** and **2.3**). The large sample size of the CPRD data provides a unique opportunity by allowing small margins of error and sufficient power to detect statistically significant associations, even when effect sizes are small. Sample sizes were particularly relevant to identify significant differences over

time, by age, sex or socioeconomic sub-groups, when previous studies have not had the adequate power to detect such effects.

8.2.3 Longitudinal data

The availability of longitudinal data is another major advantage of the CPRD data and has been beneficial for all analyses in this thesis. Most importantly, longitudinal data has allowed the identification of incident heart failure diagnoses, by enabling accurate identification of patients' first heart failure diagnosis, when most of the literature refer to prevalent cases. Beyond its importance for the calculation of heart failure incidence rates in Chapter 5, accurate identification of incident diagnoses also allowed investigation of trajectories of care and mortality following a first heart failure diagnosis. This feature is particularly important for the study of heart failure, as patterns of clinical care, mortality and hospitalisations are highly dependent on the time elapsed since diagnosis. For example, risk of death has been shown to be very high in the weeks following heart failure diagnosis and to gradually reduce thereafter.[189] Another key aspect of the longitudinal nature of the data, was the ability to follow patients over time and explore trajectories of care across different care settings. Particularly calculations and visualisations of drug dose titration patterns with daily granularity represents perhaps the most original aspect of the research performed in this thesis.

8.2.4 Breadth of variables

The CPRD has a wide range of variables available that provide information on patients' demographic, clinical and social characteristics. This has made it possible to establish a comprehensive patient profile, including clinical blood pressure measurements, smoking status, and prevalent comorbidities. Particularly the combination of clinical and socioeconomic data is a distinctive feature of the CPRD that is rarely available in other research cohorts, and the reported socioeconomic disparities in the incidence, age at onset, delivery of care and mortality constitute a unique addition to the existing literature. Similarly, the availability of cause-specific data on mortality and hospitalisation was especially useful in the study of health outcomes affecting patients with heart failure (**Chapter 7**).

On the other hand, several important variables were not available or frequently missing in the CPRD. In this thesis on the epidemiology of heart failure, values of or categorisation by ejection fraction would have been particularly valuable and their absence presented a major limitation. Nevertheless, meticulous research on disease phenotyping and diagnostic coding practices have made it possible to characterise the type of heart failure in a small subset of patients, for whom the diagnostic code made a clear reference to reduced ejection fraction. Other important information that was not available relate to over-the-counter medications, patients' adherence to medication, or signs and symptoms. Moreover, secondary care records did not provide access to diagnostic investigations, procedures, discharge prescriptions or referrals, or outpatient consultations. Finally, even though the issue of diagnostic tests was generally recorded, the results of these tests were most often missing. This meant that important blood tests results, such as natriuretic peptides or creatinine, could not be studied.

8.2.5 Routinely-collected data

By collecting healthcare information from routine clinical practice, the population included in the CPRD dataset has been shown to be representative of the general UK population in terms of age, sex and ethnicity.[5] This is a major advantage when compared to other epidemiological cohorts, where issues like selection bias and the healthy-cohort effect may lead to over or under-estimation of results. Furthermore, as the CPRD reflects real health care utilisation, results from this thesis have high relevance to health service planning and policy implementation.

Using EHR data further reduces the likelihood of some forms of bias. Most importantly, the risk of recall bias, which is often associated with self-reported data is low, as EHR provides specific timing for variables such as doctor-diagnosed conditions, blood test results and clinical measurements. Risk of observer bias is also low, as neither patient nor practitioner are aware of the future research questions that will be applied to the routinely-collected data. Finally, the Hawthorne effect, which refers to a change in a subject's behaviour due to knowledge of being observed, is less likely to be an issue in electronic health record data.[65] On the other hand, the CPRD exclusively records data on patients who use primary healthcare services. Although in the UK, over 98% of individuals are registered with a primary care practice and consultations are

free of charge for all residents,[5] some level of selection bias towards people with higher health literacy and interest is inevitable. Moreover, certain sub-populations, such as homeless people, prisoners, and private patients, are missing from the CPRD.[5] Nevertheless, this bias is likely to be lower than in other epidemiological studies, where participants must actively opt in.[65]

8.2.6 Missing data

In this thesis, analyses have relied on variables with complete data (such as age, sex, socioeconomic status, and region). Variables with missing data, such as blood pressure, smoking status or body mass index were presented as descriptive information alongside rates of missingness. For the study of diagnoses, the absence of a diagnostic code was treated as absence of a disease, as is usual practice in studies using electronic health record data.[5] Finally, information on mortality and hospitalisations studied in this thesis were also complete, since studies were restricted to records that were approved for linkage to ONS and HES datasets.

8.2.7 Index of Multiple Deprivation

Analyses in this thesis have relied on the Index of Multiple Deprivation (IMD), one of the most commonly used measure of socioeconomic levels in healthcare research.[92,136,190,191] The overall index covers seven dimensions of deprivation including income, employment, education, health, crime, housing, living environment.[36,92] The health and disability domain encompasses four measures: years of potential life lost, comparative illness and disability ratio, rate of emergency admissions to hospital, and proportion of adults younger than 60 years who have mood or anxiety disorders.[92,136] Although inevitably partially correlated with health, exclusion of the health component from an earlier version of the IMD has been shown to make little difference to either the deprivation quintiles[191], their association with census markers of health[191], or the risk of overall cardiovascular disease incidence[190]. Several limitations of IMD quintiles must also be acknowledged. First, IMD quintiles relate to small neighbourhoods, in which social heterogeneity is inevitably present, rather than individual measures of deprivation. Nevertheless, the small area boundaries remain fixed over time allowing consistent comparisons of temporal trends. Moreover, the small mean population (typically 1500) improves the

population homogeneity compared with other measures of neighbourhood deprivation.[36,92] Another limitation of the, IMD score is that, as a composite measure of several socioeconomic indicators, it is not possible to identify individual components (e.g. education or living environment), nor to disentangle definite social and economic factors from other geographical environmental factors (such as urbanisation levels).

8.3 Implications for clinical practice

The importance of this analysis can be broadly divided into its relevance to clinical care, public health and future research. With regard to clinical care, results from this thesis bear important implications for the prevention, screening, and management of heart failure.

Prevention: Independently of population changes, incidence and prevalence of heart failure have not declined as much as other cardiovascular disorders over the past decade, and appears to have declined less so in the UK than in recent US-based studies. Moreover, incidence and prevalence were substantially higher in deprived groups than in more affluent ones. These findings suggest that better prevention of heart failure is possible with currently available means and that more efforts are needed to prevent and delay the onset of heart failure, particularly among socioeconomically deprived sub-groups.

Screening: Analyses from this thesis suggest that screening for heart failure in the UK primary care setting is insufficient, particularly as pertains to the youngest and oldest age-groups as well as women, and especially so among young women. My analyses further show that an equal number of men and women are affected, and although heart failure is rare at a young age, it cannot be completely dismissed. Heart failure being a severe condition, early diagnosis is crucial for timely initiation of life-saving medications, and findings from this thesis highlight the need for adequate screening across all groups of patients.

Management: This thesis presents several important findings that relate to the management of heart failure. Perhaps most importantly, findings highlight the need for improved coordination of care among healthcare settings and services. Better communications among services are likely to support the continuous management of patients who visit different services over the course

of their illness as well as support the management of the many comorbidities associated with heart failure. Second, sub-optimal management of heart failure has been shown to disproportionally affect women and older people, and suggests that special efforts are needed to ensure equal access to evidence-based care across all groups of patients. Third, dose maintenance and titration of life-saving medicines have been shown to be low in routine clinical practice and suggests the need for a stronger emphasis on attaining, if possible, the target doses proven to be of benefit in clinical trials.

8.4 Implication for healthcare systems and policy

These results further present with a number of implications for the design of healthcare systems and public health strategies.

8.4.1 Integrated care

The large burden of comorbid conditions among heart failure patients and their consequences on mortality highlight the need for an integrated approach to care. This includes greater coordination and communication between primary care, secondary care, and specialist services to adequately monitor patients and their various other medical conditions. An integrated approach is particularly important to address non-cardiovascular outcomes, a traditionally neglected aspect of care in heart failure patients, yet which now represent the majority of deaths and hospitalisations. Such an approach would move away from the established 'single-disease' care and consider the interactions of multiple conditions and therapies within each patient.

Integrated care is also essential in ensuring that every heart failure patient has their diagnosis recorded by their GP or attending physician. Analyses in **Chapter 6** have revealed that only 17% of patients diagnosed with heart failure in hospital and discharged alive had their diagnosis subsequently recorded by their GP in the next 12 months. Yet accurate recording of diagnosis is a crucial prerequisite for good management and also relies on good information exchange between health services. Improvements are likely to require health services to consider patient trajectories as an integral part of health services design.

8.4.2 Healthcare reporting and incentives schemes

Healthcare reporting and incentives schemes play an important role in improving quality of care. Analyses investigating trajectories of care (**Chapter 6**) have shown that a small set of indicators measured in a single care setting (such as measures from the Quality Outcome Framework (QOF) or the National Heart Failure Audit (NHFA)) can improve performance against those measures (e.g. improvements have been observed in those two indicators monitored by QOF, which relate to diagnostic investigations and treatment initiation), but does not necessarily impact on associated outcomes (such as post-hospitalisation follow-up or treatment dose which are not monitored). Analyses also show that these two schemes have failed to identify substantial gaps in care relating to screening and continuous management, essentially because they have remained confined to individual settings of care, rather than considering clinical management across the continuum of primary care, secondary care and specialist services. These findings suggest that the design of such schemes may need to be revised and are likely to be relevant to other countries implementing pay-for-performance schemes.

8.4.3 Clinical guidelines

Another important implication of the substantial burden of comorbidities on the prognosis of heart failure patients observed in this thesis, is the need for specific clinical guidelines on their prevention and management among heart failure patients. Currently, heart failure guidelines' recommendations on secondary prevention are essentially focussed on cardiovascular outcomes, such as myocardial infarction and stroke. Research from this thesis has shown that several other conditions, such as infections or respiratory disorders represent a similar burden to heart failure patients, and may need to be recognised in clinical guidelines.

8.4.4 Electronic health records

Electronic health records data, such as the one used in this thesis, has great utility in providing valuable population health information for heart failure as well as a broad range of other conditions. Improving data integration across health services is likely to help communications across specialties and settings, and ultimately benefit patient care. Integration of electronic

health records with other types of data, such as ambulatory blood pressure monitoring devices, may help further support collaborative approaches to disease monitoring between patients and clinicians. Finally, it is likely that the ongoing advancement and standardisation of electronic health records systems will improve the accessibility and utility of such data for research purposes.[65]

8.5 Implications for the design of future research

8.5.1 Replication of findings

An important step towards designing effective heart failure interventions is understanding the development, progression and consequences of heart failure over time. This thesis provides a valuable evidence-base to address these gaps, and replication of findings using other data sources will increase the strength of evidence. Studies investigating cohorts from other countries would also be useful in providing a comparison to analyse differences by region and health system setting. So far, evidence on the epidemiology of heart failure in low- and middle-income countries is scarce and such perspectives would be particularly useful in establishing a more global picture of heart failure and its consequences.[3]

Methodological aspects from this thesis could also be applied to a range of other conditions. The structure and analytical methods used in this thesis are likely to be especially useful for chronic conditions or those where diagnosis and management relies on the care of different specialties, such as diabetes or chronic obstructive pulmonary disease.

8.5.2 Extension of findings

The results presented in this thesis have highlighted some important questions that deserve further exploration:

(i) **Socioeconomic disparities in the incidence and age at onset of heart failure**: Socioeconomic disparities in the incidence and age at onset of heart failure remain poorly understood. Previous research has shown that known risk factors, such as smoking, obesity or blood pressure, only explain about half of the observed disparities.[130,131] Therefore, future studies investigating risk factors that contribute to the development of heart failure and how these differ by socioeconomic gradient would

provide crucial support for the development of more effective and targeted prevention measures.

(ii) **Medical conditions and the risk of developing heart failure**: The association between certain medical conditions and the risk of developing heart failure has not been studied comprehensively. This thesis has identified several conditions which presented a surprisingly high prevalence among heart failure patients. Although, this finding may in part be explained by the concomitant presence of conditions linked to old age, further studies are warranted to investigate whether some of these conditions or associated therapies, for example as pertains to osteoarthritis or other inflammatory conditions, actively contribute to the development of heart failure.

(iii) **Reasons for the low drug dosages observed in routine clinical practice**: So far, evidence on the reasons for the low drug dosages in routine clinical practice is limited. The low doses prescribed in routine clinical care could be due to health system related matters, yet could also relate to drug tolerability issues, or a combination of both. This thesis was not designed to investigate the reasons behind the observed low dosages and, if we are to improve medication titration in routine practice, new studies are needed to investigate this question.

(iv) **Socioeconomic disparities in mortality following incident heart failure**: Evidence that would help explain and address the observed disparities in mortality by socioeconomic gradient is scarce. Reducing such inequalities will evidently lead to overall improvement in prognosis, but is also a duty for healthcare systems that aim to provide equity in treatment. Further studies are needed to understand the reasons underlying the observed disparities and provide the necessary support for the development of adequate management strategies.

(v) **Disease-disease interactions or disease-treatment interactions and their impact on mortality in heart failure patients**: The relationship between heart failure and key medicines used for the management of this syndrome, and the incidence of certain conditions is not fully understood. This thesis has revealed surprisingly high and increasing rates of mortality from certain non-cardiovascular causes, such as interstitial lung disease and dementia. More studies are needed to understand whether the observed associations are causal and adjust clinical management accordingly.

8.5.3 Therapies development

Finally, this thesis also provides valuable evidence to inform the design of future trials and the development of life-saving management strategies. A major finding from this research relates to the profile of heart failure patients seen in routine clinical practice of which about half are women, almost half are over 80 years old and about 80% had three or more comorbidities at the

time of diagnosis. These findings suggest that, to be relevant, future trials will need to include different populations that in the past (often mostly young male patients with few comorbidities).[110] Another key finding relates to the fact that, among heart failure patients seen in routine clinical practice, non-cardiovascular causes account for the majority of deaths and hospitalisations, and suggests that the development of effective life-saving therapies will need to consider the management of associated comorbidities alongside traditional cardiovascular targets.

8.6 Conclusions

Research from this thesis extends the current knowledge base on the epidemiology of heart failure through in-depth analyses of disease incidence, delivery of care, and patient outcomes in a large general population-based cohort. First, the burden of heart failure in the UK is increasing with major socioeconomic disparities in disease incidence and age at onset. Second, the management of heart failure patients in the UK presents important shortcomings that affect screening, continuity of care, and medication titration, and disproportionally affect women, older people. Finally, considerable gains in reducing cardiovascular mortality and premature death rates over the past decade have been tempered by the substantially high, and increasing, rates of non-cardiovascular events, which now represent the majority of deaths and hospitalisations. These findings have important implications for clinical practice, health policy design and future research that are likely to be generalisable to many high-income countries. Most importantly, results highlight the need to address socioeconomic disparities that affect disease incidence and health status of affected patients; and call for increased efforts to improve the coordination of care among health settings and specialities so as to ensure continuity of care and more effective management of associated comorbidities.

APPENDIX

Online supplement

An online repository was set-up to share the clinical code lists for each of the 17 comorbidities investigated and can be accessed under: www.researchgate.net/profile/Nathalie_Conrad3. These files are not included in the printed format of this thesis due to their large size, as well as to allow other researchers to download and re-use documents in a computer-ready format.

Supplementary tables

Table S1: Clinical codes used to identify diagnostic tests from general practice records

A. Echocardiogram

Code Type	Code	Description
Entity	342	Echocardiogram
Read	5853.11	Echocardiogram
Read	7935200	Transoesophageal echocardiography
Read	5853100	Echocardiogram abnormal
Read	R132000	[D]Echocardiogram abnormal
Read	585f.00	Echocardiogram shows left ventricular systolic dysfunction
Read	585g.00	Echocardiogram shows left ventricular diastolic dysfunction
Read	5853	U-S heart scan
Read	5853z00	U-S heart scan NOS
Read	5C20.00	Echocardiogram equivocal
Read	33BB.00	Left ventricular ejection fraction
Read	7P0H100	Transoesophageal echocardiography
Read	7P0H000	Transthoracic echocardiography
Read	7P0H400	Stress echocardiography
Read	7935500	Transluminal intracardiac echocardiography
Read	7P0Hz00	Diagnostic echocardiography NOS
Read	7P0H300	Epicardial echocardiography
Read	7P0Hy00	Other specified diagnostic echocardiography
Read	9Ee0800	Adult echocardiography procedure report
Read	R132200	[D]Ultrasound cardiogram abnormal
Read	7P0H600	Contrast echocardiography
Read	8A54400	Monitoring of cardiac output using echocardiography
Read	7P0H.00	Diagnostic echocardiography

B. Specialist assessment

Code Type	Code	Description
nhsspec	28	Cardiology (for extraction from 'referral' table)
Read	8H4R.00	Referral to cardiology special interest general practitioner
Read	8HVJ.00	Private referral to cardiologist
Read	8H44000	Referral to cardiology multidisciplinary team
Read	8H44.00	Cardiological referral
Read	8HTL000	Referral to rapid access heart failure clinic
Read	8HTL.00	Referral to heart failure clinic
Read	ZL5A100	Referral to cardiologist
Read	8Hkt.00	Referral to community cardiology service

C. Electrocardiogram

Code Type	Code	Description
Entity	217	Electrocardiogram
Entity	304	ECG exercise
Entity	379	ECG ambulatory
Read	R143100	[D]Electrocardiogram (ECG) abnormal
Read	32...00	Electrocardiography
Read	32Z..00	Electrocardiography NOS
Read	7P0G.00	Diagnostic electrocardiography

Code Type	Code	Description
Read	7P0Gz00	Diagnostic electrocardiography NOS
Read	3297.11	Electrocardiogram: Mobitz type 1 second degree AV block
Read	329H.00	Electrocardiogram: Mobitz type 2 second degree AV block
Read	7P0P.00	Other diagnostic electrocardiography
Read	3216	ECG normal
Read	32...12	ECG
Read	3299	ECG: right bundle branch block
Read	3214000	Ambulatory ECG normal
Read	3217	ECG abnormal
Read	3213000	Exercise ECG normal
Read	3213100	Exercise ECG abnormal
Read	3272	ECG: atrial fibrillation
Read	3212	Standard ECG
Read	329A.00	ECG: left bundle branch block
Read	3282	ECG: ventricular tachycardia
Read	326..00	ECG: ectopic beats
Read	324..00	ECG:left ventricle hypertrophy
Read	3273	ECG: atrial flutter
Read	323..00	ECG: myocardial infarction
Read	322..00	ECG: myocardial ischaemia
Read	32L..00	ECG: left ventricular strain
Read	329..00	ECG: heart block
Read	321B.00	12 lead ECG
Read	3242	ECG: shows LVH
Read	3262	ECG: extrasystole
Read	327..00	ECG: supraventricular arrhythmia
Read	3221	ECG: no myocardial ischaemia
Read	3274	ECG: paroxysmal atrial tachy.
Read	3297	ECG: Wenckebach phenomenon
Read	328..00	ECG: ventricular arrhythmia
Read	321..00	ECG - general
Read	3263	ECG: ventricular ectopics
Read	324Z.00	ECG: LVH NOS
Read	32F2.00	ECG: T wave abnormal
Read	32E3.00	ECG: S-T elevation
Read	32F4.00	ECG: T wave inverted
Read	32FZ.00	ECG: T wave NOS
Read	32J2.00	ECG: QRS complex abnormal
Read	3294	ECG:partial A-V block-long P-R
Read	3234	ECG:posterior/inferior infarct
Read	3222	ECG:shows myocardial ischaemia
Read	3231	ECG: no myocardial infarction
Read	3233	ECG: antero-septal infarct.
Read	329Z.00	ECG: heart block NOS
Read	3241	ECG: no LVH
Read	328Z.00	ECG: ventricular arrhythmia NOS
Read	3283	ECG: ventricular fibrillation
Read	3291	ECG: no heart block
Read	32B..00	ECG: Q wave
Read	322Z.00	ECG: myocardial ischaemia NOS
Read	3293	ECG:complete sinu-atrial block
Read	325..00	ECG:right ventricle hypertrop.
Read	3232	ECG: old myocardial infarction
Read	3295	ECG: partial A-V block - 2:1
Read	3298	ECG: complete A-V block
Read	32E4.00	ECG: S-T depression
Read	32A3.00	ECG: P mitrale
Read	32C2.00	ECG: R wave abnormal
Read	326Z.00	ECG: ectopic beats NOS

Code Type	Code	Description
Read	32K3.00	ECG: Q-T interval prolonged
Read	32E2.00	ECG: S-T interval abnormal
Read	32B2.00	ECG: Q wave abnormal
Read	32EZ.00	ECG: S-T interval NOS
Read	32D2.00	ECG: S wave abnormal
Read	32F3.00	ECG: T wave flattened
Read	32I3.00	ECG: P-R interval prolonged
Read	32E1.00	ECG: S-T interval normal
Read	327Z.00	ECG: supraventric. arryth. NOS
Read	3236	ECG: lateral infarction
Read	3292	ECG: partial sinu-atrial block
Read	321C.00	ECG sinus rhythm
Read	32A2.00	ECG: P wave abnormal
Read	3235	ECG: subendocardial infarct
Read	32F..00	ECG: T wave
Read	3271	ECG: no supraventric. arryth.
Read	32E..00	ECG: S-T interval
Read	32I2.00	ECG: P-R interval abnormal
Read	32A..00	ECG: P wave
Read	323Z.00	ECG: myocardial infarct NOS
Read	32J1.00	ECG: QRS complex normal
Read	3252	ECG: shows RVH
Read	3251	ECG: no RVH
Read	32C..00	ECG: R wave
Read	325Z.00	ECG: RVH NOS
Read	32A4.00	ECG: P pulmonale
Read	32B3.00	ECG: Q wave pathological
Read	32AZ.00	ECG: P wave NOS
Read	32B1.00	ECG: Q wave normal
Read	32K..00	ECG: Q-T interval
Read	32CZ.00	ECG: R wave NOS
Read	32J3.00	ECG: QRS complex prolonged
Read	32I4.00	ECG: P-R interval shortened
Read	32C1.00	ECG: R wave normal
Read	32I..00	ECG: P-R interval
Read	32BZ.00	ECG: Q wave NOS
Read	32G..00	ECG: U wave
Read	32K1.00	ECG: Q-T interval normal
Read	32C3.00	ECG: R wave tall
Read	32IZ.00	ECG: P-R interval NOS
Read	32K2.00	ECG: Q-T interval abnormal
Read	32G1.00	ECG: U wave normal
Read	32G2.00	ECG: U wave abnormal
Read	32K4.00	ECG: Q-T interval shortened
Read	32D3.00	ECG: S wave deep
Read	32F1.00	ECG: T wave normal
Read	32KZ.00	ECG: Q-T interval NOS
Read	3261	ECG: no ectopic beats
Read	32A1.00	ECG: P wave normal
Read	32JZ.00	ECG: QRS complex NOS
Read	3281	ECG: no ventricular arrhythmia
Read	32I1.00	ECG: P-R interval normal
Read	32D1.00	ECG: S wave normal
Read	3296	ECG: partial A-V block - 3:1
Read	32J..00	ECG: QRS complex
Read	329B.00	ECG: trifascicular block
Read	329D.00	ECG: left anterior fascicular block
Read	329C.00	ECG: bifascicular block
Read	329F.00	ECG: right bundle branch and left anterior fascicular block

Code Type	Code	Description
Read	32DZ.00	ECG: S wave NOS
Read	329G.00	ECG: right bundle branch and left posterior fascicular block
Read	329E.00	ECG: left posterior fascicular block

D. Natriuretic peptides

Code Type	Code	Description
Read	44AR.0	Plasma B natriuretic peptide level
Read	44AF.0	Brain natriuretic peptide level
Read	44AN.0	Plasma pro-brain natriuretic peptide level
Read	44AP.0	Serum pro-brain natriuretic peptide level

Table S2: Clinical codes used to identify drug-class-specific contraindications or intolerances from general practice records

Drug Class	Medcode	Read code	Description
ACE inhibitors	13043	14LM.00	H/O: angiotensin converting enzyme inhibitor allergy
ACE inhibitors	11130	U60C400	[X]Angiotensin-convert-enz inhib caus advers eff therap use
ACE inhibitors	26495	U60C414	[X]Adverse reaction to lisinopril
ACE inhibitors	45023	U60C412	[X] Adverse reaction to enalapril
ACE inhibitors	47141	U60C413	[X] Adverse reaction to ramipril
ACE inhibitors	68465	U60C411	[X] Adverse reaction to captopril
ACE inhibitors	48350	TJC7700	Adverse reaction to captopril
ACE inhibitors	20747	TJC7900	Adverse reaction to ramipril
ACE inhibitors	21039	TJC7800	Adverse reaction to enalapril
ACE inhibitors	25369	ZV14D00	[V]PH angiotensin-converting-enzyme inhibitor allergy
ACE inhibitors	104857	K043000	Acute renal failure due to ACE inhibitor
ACE inhibitors	25369	ZV14D00	[V]PH angiotensin-converting-enzyme inhibitor allergy
ACE inhibitors	10568	8I28.00	Angiotensin converting enzyme inhibitors contraindicated
ACE inhibitors	12135	8I3D.00	Angiotensin converting enzyme inhibitor declined
ACE inhibitors	10883	8I64.00	Angiotensin converting enzyme inhibitor not indicated
ACE inhibitors	11350	8I74.00	Angiotensin converting enzyme inhibitor not tolerated
ARB	13040	14LN.00	H/O: angiotensin II receptor antagonist allergy
ARB	11601	U60CB00	[X]Angiotensin II receptor antagon adverse effect therap use
ARB	34469	ZV14E00	[V]PH of angiotensin II receptor antagonist allergy
ARB	11510	8I2H.00	Angiotensin II receptor antagonists contraindicated
ARB	22335	8I3P.00	Angiotensin II receptor antagonist declined
ARB	18721	8I6C.00	Angiotensin II receptor antagonist not indicated
ARB	12571	8I75.00	Angiotensin II receptor antagonist not tolerated
Beta Blocker	13033	14LL.00	H/O: betablocker allergy
Beta Blocker	11667	TJC6.00	Adverse reaction to betablockers
Beta Blocker	98477	U60B900	[X]Adverse reaction to bisoprolol
Beta Blocker	98766	U60BB00	[X]Adverse reaction to nebivolol
Beta Blocker	100019	ZVu6i00	[X]Personal history of allergy to bisoprolol
Beta Blocker	47554	ZV14C00	[V]Personal history of betablocker allergy
Beta Blocker	68505	TJC0000	Adverse reaction to practolol
Beta Blocker	46411	TJC0200	Adverse reaction to propranolol
Beta Blocker	10567	8I26.00	Beta blocker contraindicated
Beta Blocker	98220	8I2g.00	Bisoprolol contraindicated
Beta Blocker	98752	8I2h.00	Carvedilol contraindicated
Beta Blocker	100018	8I2i.00	Nebivolol contraindicated
Beta Blocker	10767	8I36.00	Beta blocker therapy refused
Beta Blocker	98478	8IAS.00	Bisoprolol therapy refused
Beta Blocker	100020	8IAT.00	Carvedilol therapy refused
Beta Blocker	100021	8IAV.00	Nebivolol therapy refused
Beta Blocker	10566	8I62.00	Beta blocker not indicated
Beta Blocker	98360	8I6i.00	Bisoprolol not indicated
Beta Blocker	99741	8I6j.00	Carvedilol not indicated
Beta Blocker	99742	8I6k.00	Nebivolol not indicated
Beta Blocker	11231	8I73.00	Beta blocker not tolerated
Beta Blocker	98301	8I7K.00	Bisoprolol not tolerated
Beta Blocker	100199	8I7L.00	Carvedilol not tolerated
Beta Blocker	100200	8I7M.00	Nebivolol not tolerated
Beta Blocker	13026	TJC6200	Adverse reaction to atenolol
Beta Blocker	39564	TJC6700	Adverse reaction to sotalol
Beta Blocker	42993	TJC6z00	Adverse reaction to betablockers NOS
Beta Blocker	43499	TJC6100	Adverse reaction to acebutolol
Beta Blocker	46076	TJC6400	Adverse reaction to metoprolol
Beta Blocker	52662	TJC6800	Adverse reaction to timolol
Beta Blocker	57521	TJC6300	Adverse reaction to labetalol
Beta Blocker	61975	TJC6500	Adverse reaction to nadolol
Beta Blocker	94109	TJC6600	Adverse reaction to oxprenolol

Drug Class	Medcode	Read code	Description
Beta Blocker	20916	U60B711	[X] Adverse reaction to betablockers
Beta Blocker	30300	U60B700	[X]Beta-adrenorecep antag caus advers eff in ther use, NEC
Beta Blocker	41412	U60B712	[X] Adverse reaction to propranolol
Beta Blocker	46541	U60B71C	[X] Adverse reaction to betablockers NOS
Beta Blocker	48351	U60B715	[X] Adverse reaction to atenolol
Beta Blocker	49679	U60B71A	[X] Adverse reaction to sotalol
Beta Blocker	65814	U60B716	[X] Adverse reaction to labetolol
Beta Blocker	73878	U60B717	[X] Adverse reaction to metoprolol
Beta Blocker	96531	U60B714	[X] Adverse reaction to acebutolol
Beta Blocker	109335	U60B71B	[X] Adverse reaction to timolol
Beta Blocker	98765	U60BA00	[X]Adverse reaction to carvedilol
MR Antagonist	48902	8I2L.00	Spironolactone contraindicated
MR Antagonist	50174	TJE4400	Adverse reaction to spironolactone
MR Antagonist	55032	U60E51C	[X] Adverse reaction to spironolactone
MR Antagonist	100950	8I3K000	Spironolactone declined
MR Antagonist	110297	8I6A000	Spironolactone not indicated
MR Antagonist	110011	8I2D000	Eplerenone contraindicated
MR Antagonist	110032	8I3K100	Eplerenone therapy declined

***Abbreviations**: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; MRA = mineralocorticoid receptor antagonist; NICE = National Institute for Health and Clinical Excellence.*

Table S3: Recommended maintenance dosages of pharmacological treatments indicated in patients with heart failure and reduced ejection fraction, as per ESC and NICE guidelines during the study period

Drug Class	Drug Name	Daily Target Dose					
		Unique value defined for the purpose of this study	European Society of Cardiology guidelines				NICE guidelines
			2001	2005	2008	2012	2003
ACE inhibitors	Captopril	150 mg	75-150 mg	75-150 mg	150-300 mg	150 mg	150-300 mg
ACE inhibitors	Cilazapril	1 mg	1-2.5 mg	-	-	-	1-2.5 mg
ACE inhibitors	Enalapril	20 mg	20 mg	20 mg	20-40 mg	20-40 mg	20-40 mg
ACE inhibitors	Fosinopril	20 mg	20 mg	-	-	-	40 mg
ACE inhibitors	Lisinopril	20 mg	5-20 mg	5-20 mg	20-35 mg	20-35 mg	30-35 mg
ACE inhibitors	Perindopril	4 mg	4 mg	-	-	-	4 mg
ACE inhibitors	Quinapril	5 mg	5-10mg	-	-	-	10-20 mg
ACE inhibitors	Ramipril	10 mg	5-10 mg	5-10 mg	10 mg	10 mg	10 mg
ACE inhibitors	Trandolapril	4 mg	4 mg	4 mg	4 mg	4 mg	-
ARB	Candesartan	32 mg	4-16 mg	4-32 mg	32 mg	32 mg	4-16 mg
ARB	Losartan	150 mg	50-100 mg	50-100 mg	-	150 mg	50-100 mg
ARB	Valsartan	320 mg	80-320 mg	80-320 mg	320 mg	320 mg	80-320 mg
Beta Blocker	Bisoprolol	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Beta Blocker	Carvedilol	50 mg	50 mg	50 mg	50-100 mg	50-100 mg	50-100 mg
Beta Blocker	Metoprolol succinate	200 mg	200 mg	200 mg	200 mg	200 mg	-
Beta Blocker	Metoprolol tartrate	150 mg	150 mg	-	-	-	-
Beta Blocker	Nebivolol	10 mg	-	10 mg	10 mg	10 mg	-
MRA	Eplerenone	50 mg	-	25 mg	50 mg	50 mg	-
MRA	Spironolactone	25 mg	25 mg	12.5-25 mg	25-50 mg	25-50 mg	12.5-25 mg

***Notes**: The evidence-base underlying heart failure treatment recommendations has changed over the study period (2002-2014). So as to compare changes in drug doses over the time, I included all drugs referred to in the guidelines applicable during the study period, and defined a unique target dose for the purpose of this study as the minimal recommended target dose in the latest guideline available during the study period. I further highlight in blue those drugs that are considered evidence-based treatments as per 2016 ESC guidelines. The 2010 NICE guidelines do not contain target dosages for the treatment of heart failure. **Abbreviations**: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; MRA = mineralocorticoid receptor antagonist; NICE = National Institute for Health and Clinical Excellence.*

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