Imperial College London

Epidemiology, healthcare resource utilisation, identification, and outcomes of different heart failure phenotypes in real world

PhD thesis

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Date: 1/18/2022

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Declaration of originality

I, Varun Sundaram declare that the material presented in this thesis is my own work. Where information has been derived from other sources, I confirm that this has been appropriately attributed.

Varun Sundaram

Acknowledgements

I am indebted to Prof Jennifer Quint, Prof Amitava Banerjee and Prof Jayakumar Sahadevan, who were my PhD supervisors for providing unstinting support throughout the duration of this project.

Foremost, I would like to thank my father, Dr Sundaram, who taught me by example that medicine is a way of life and inspired me to choose a life centred around patient care. Profound thanks to my mother, Rani Sundaram, whose life only revolved around her kids and their success.

My sincere gratitude to my sister-in-law, Dr Shilpa Gandhi, my perennial and greatest cheerleader whenever I chose to take a path less travelled, along with my brother, Dr Vivek Sundaram.

I would also like to thank my guru, Dr Subramanian Swamy whose life and teachings have truly been an inspiration for me and so many others.

Above all, I owe a debt of gratitude to my lovely wife, Pooja Kesavan, for her unconditional support during the last four and a half years, for all the late nights and early mornings, and sustaining me in ways I didn't know I needed. I can say with complete certainty that completing my PhD would have not been possible without her abundant moral support, patience, and love.

ABSTRACT (291 words)

While international guidelines for the management of heart failure (HF) largely overlap, important regional differences exist in patient characteristics, prescription patterns, healthcare resource utilisation and consequently, in clinical outcomes, between the Western and Asian countries. To date, comparative data on geographic differences in patient characteristics, management and outcomes has either been based on post-hoc analyses from clinical trials, aggregate patient data or from registries that lacked both quantum and generalisability. I therefore performed an individual patient-level analysis of more than one million non-consecutive heart failure hospitalisations across four countries – UK, US, Japan, and Taiwan – using nationally representative electronic health care records (EHR), which captured routine clinical encounters **(Specific Aims 1 and 2).**

Although, multiple studies have been undertaken to efficiently identify patients with HF in the real world using EHR, there is a paucity of evidence on identification and validation of algorithms for identifying patients with specific HF phenotypes, including heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). **As part of specific aim 3,** I have focussed on improving the ability to identify patients with different HF phenotypes within the EHR, by collecting additional data (including direct questionnaire to General Practitioner's), and by seeking to understand the impact of different algorithms for identification of HFrEF and HFpEF.

HFpEF patients are widely believed to be a heterogenous and can be broadly categorised into two further sub-phenotypes at the population level: 1) young obese patients and 2) older non-obese patients where hypertension, chronic kidney disease, coronary artery disease (CAD) and atrial fibrillation are the predominant drivers. **As part of specific aims 4 and 5**, I have evaluated the ***obese HFpEF sub-phenotype*** and the impact of coronary revascularisation in patients with HFpEF ***(CAD-HFpEF sub-phenotype)*** using nationwide EHR.

Contents

Chapter 1: **Introduction and overview**

BACKGROUND

Chronic heart failure (CHF) is one of the most pervasive cardiovascular diseases affecting approximately 23 million people worldwide.(1,2) As one of the preeminent causes for hospitalisation, heart failure's (HF) contribution to the global annual healthcare expenditure is estimated to be greater than $100 billion.(3) Research shows that the prevalence of CHF is on the rise due to an increase in the longevity of the population, alongside therapeutic innovations in the management of coronary artery disease (CAD) and CHF. HF is responsible for c.80,000 annual hospitalisations in the United Kingdom (UK), c.200,000 in Japan, c.30,000 in Taiwan, and over one million admissions in the United States of America (US).(4–8)

While international guidelines for the management of HF largely overlap,(9–11) important regional differences exist in patient characteristics, prescription patterns, healthcare resource utilisation (HRU) and consequently, in clinical outcomes, between the Western and Asian countries. (12) For instance, post-hoc analysis from contemporary clinical trials suggest that the length of hospital stay (LOHS) for HF is substantially longer in Japan than other countries. (13–15) It is important to note that many such analyses come from clinical trials comprising of select patients that are unrepresentative of the general population with HF. Patients excluded from clinical trials, by design or unintentionally, constitute the majority of patients in real-world clinical practice.

Access to de-identified, individual patient-level data in nationwide electronic healthcare records (EHR) and administrative databases enable the evaluation of differences in individual patient characteristics, LOHS, HRU and clinical outcomes of HF patients with similar attributes between the Western and Asian countries. Comparing the characteristics, outcomes and HRU of patients hospitalised with HF in these countries may also provide insights into healthcare effectiveness and efficiency. (13–23)**.** *This serves as the rationale for Aims 1 and 2 of this thesis*.

HF patients have differing aetiologies, prognosis, and therapeutic implications, based on ejection fraction measurements obtained from transthoracic echocardiograms. HF patients are usually classified into HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). An intermediate category of HF with moderately reduced ejection fraction (HFmrEF) has been defined in 2016 European Guidelines **(Figure 1.1)** (9). Nationally representative EHR provide an excellent resource to study HF at the population level, but a major limitation using the EHR is the unavailability of ejection fraction measurements. In the UK, *Read* codes, a clinical terminology system used in general practice, has been proposed for documenting diagnosis of HFrEF (e.g. left ventricular systolic dysfunction) and HFpEF (e.g., left ventricular diastolic dysfunction) (24,25). However, an important limitation of using *Read* codes, is that more than 70% of documentation of HF diagnosis in general

practice is done using non-specific HF codes (e.g., Heart Failure, congestive heart failure etc.) making it challenging to phenotype HF patients at the population level.(26) *This serves as the rationale for Aim 3 of this thesis*.

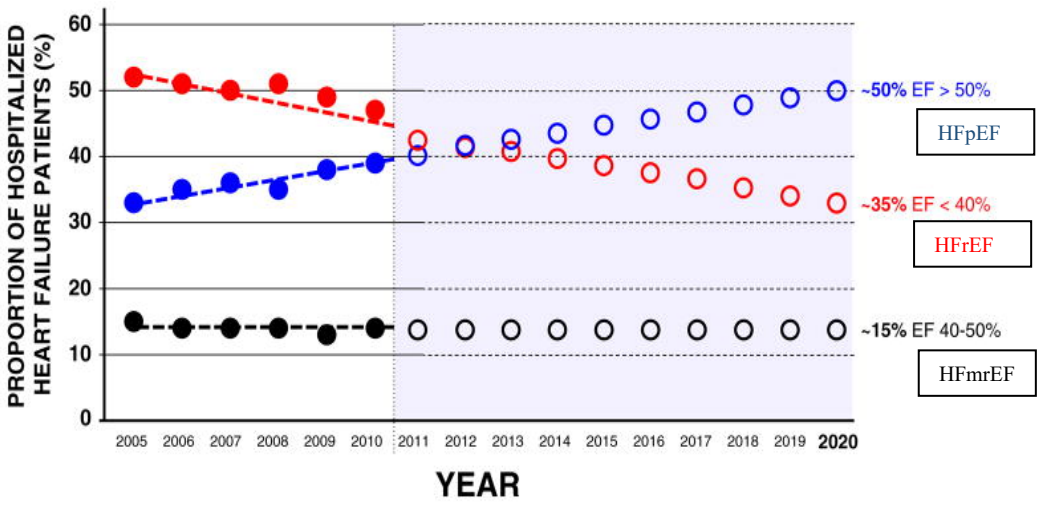
Figure 1.1: Definitions of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs *	Symptoms ± Signs *	Symptoms ± Signs *
	2	LVEF<40%	LVEF 40-49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. Relevant structural heart disease (LVH and/or LAE) b. Diastolic dysfunction (for details see Section 4.3.2)	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. Relevant structural heart disease (LVH and/or LAE) b. Diastolic dysfunction (for details see Section 4.3.2)

BNP: B-type natriuretic peptide; LAE: left atrial enlargement; LVH: left ventricular hypertrophy; NT-pro BNP: N-terminal pro –B type natriuretic peptide (Based on the 2016 European Society of Cardiology Guidelines)

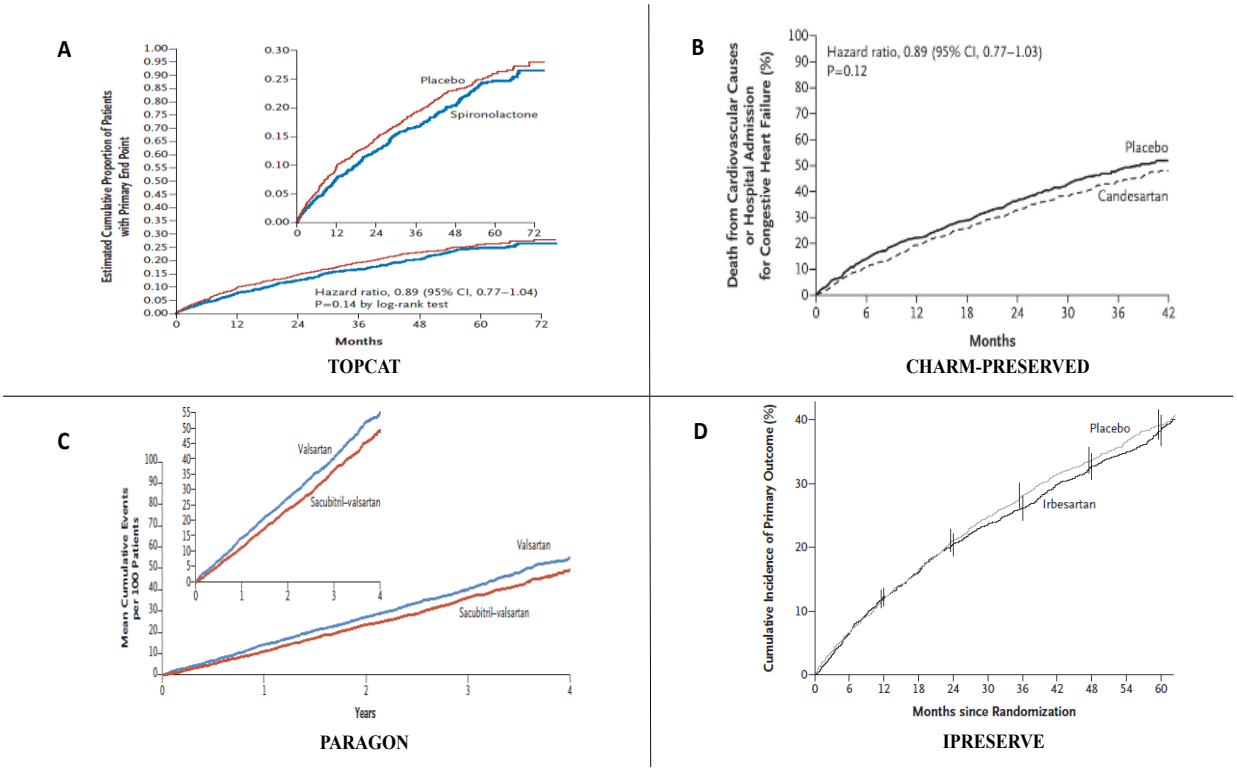
Historically, HFrEF patients' hospitalisations been more common, resulting in much of the HF research being dedicated to this phenotype. Although, there is now a clear increase in the proportion of patients with HFpEF being admitted with acute decompensation, such that the likelihood of acute HFpEF hospitalisations superseding HFrEF hospitalisations is imminent **(Figure 1.2)** (27) In fact, recent studies have revealed that HFpEF accounts for nearly half of HF cases in Europe and North America. (28,29)

Figure 1.2: Heart failure hospitalisations stratified by different phenotypes: Heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF) from 2005-2020. EF: left ventricular ejection fraction



While pharmacological treatment of HFrEF has been well-established, all phase 3 clinical trials in HFpEF patients have largely been neutral. (30–36) **(Figure 1.3)** This is widely believed to be related to the heterogeneous nature of HFpEF with no common unifying pathogenesis. Some of the risk factors implicated in the heterogeneity of HFpEF include older age, diabetes mellitus, chronic kidney disease, obesity, coronary artery disease, hypertension, and atrial fibrillation. Multiple sub-phenotypes have been described within HFpEF as a plausible explanation for the lack of response to homogenous treatment. Post-hoc analyses from clinical trials such as Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial (TOPCAT), Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction (I-PRESERVE) and Effects of Candesartan in Patients With Chronic Heart Failure and Preserved Left-Ventricular Ejection Fraction (The CHARM-Preserved Trial) revealed that HFpEF patients at the population level could be categorised further into two broad sub-phenotypes: 1) young obese patients and 2) older non-obese patients where hypertension, chronic kidney disease, coronary artery disease and atrial fibrillation are the predominant drivers. (32,34,36–38). This provides an additional layer of evidence for the heterogeneity hypothesis of HFpEF.

Figure 1.3 A-D: Landmark clinical trials of heart failure with preserved ejection fraction



TOPCAT: Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial; I-PRESERVE: Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction; CHARM-Preserved: Effects of Candesartan in Patients With Chronic Heart Failure and Preserved Left-Ventricular Ejection Fraction; P, PARAGON: Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

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Obesity is a major public health issue, and the global prevalence of obesity has increased substantially in the past three decades, across developed and developing economies (39). The risk of atherosclerotic vascular events with obesity has been the focus of research within the spectrum of cardiovascular disease. However, observational studies have demonstrated an association between obesity and heart failure, independent of the risk of vascular disease occurrence, with a differential risk identified for HFpEF over HFrEF (40,41). Multiple mechanisms have been postulated in the pathogenesis of obesity-related HFpEF, such as 1) leptin mediated secretion of aldosterone resulting in plasma volume expansion 2) increase in total body water attributed to total body weight 3) Obesity-diabetes twin epidemic (42,43). Obesity and diabetes frequently co-exist in the Western countries, for instance, over 80% of American patients with type 2 diabetes mellitus are obese. Conversely, the Asian countries have a low prevalence of obesity among diabetics (38,44,45). Diabetes has shown to increase the risk of incident heart failure, for both HFrEF and HFpEF, independent of concomitant CAD (46). Indeed, in diabetic patients, increased deposition of advanced glycated end-products is one of the posited mechanisms of impaired myocardial relaxation, resulting in HFpEF (47). It is possible that the high prevalence of diabetes among the obese population, as a consequence, could partly explain the risk of HFpEF among obese patients. The residual risk of HFpEF in obese patients after accounting for DM at the population level is unclear. In chapter 5, I have evaluated the complex interplay of DM and obesity at the population level among patients with HFpEF i.e., delineating the independent contribution of DM vs obesity to the rising prevalence of HFpEF. The characteristics and outcomes of obesity related HFpEF and the complex interplay with diabetes at the population level has not been systematically investigated. *This serves as the rationale for Aim 4 of this thesis.*

Figure 1.4: Possible mechanisms of heart failure with preserved ejection fraction in obesity

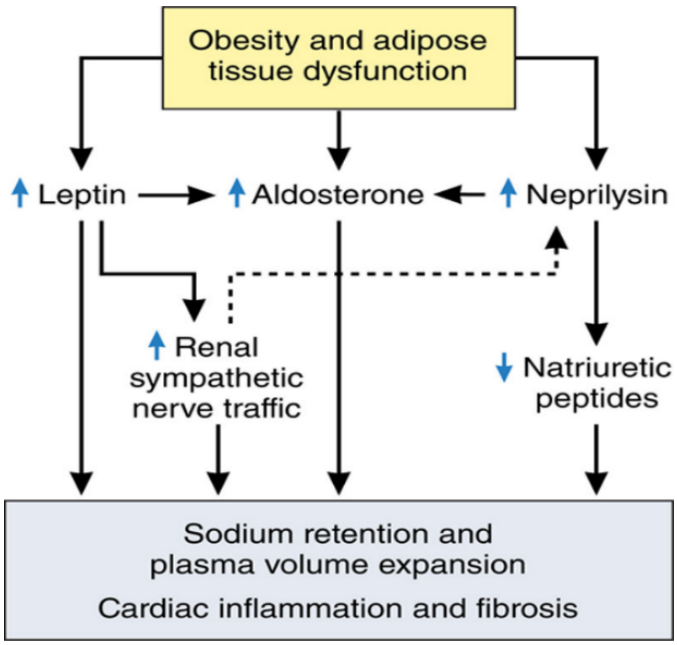
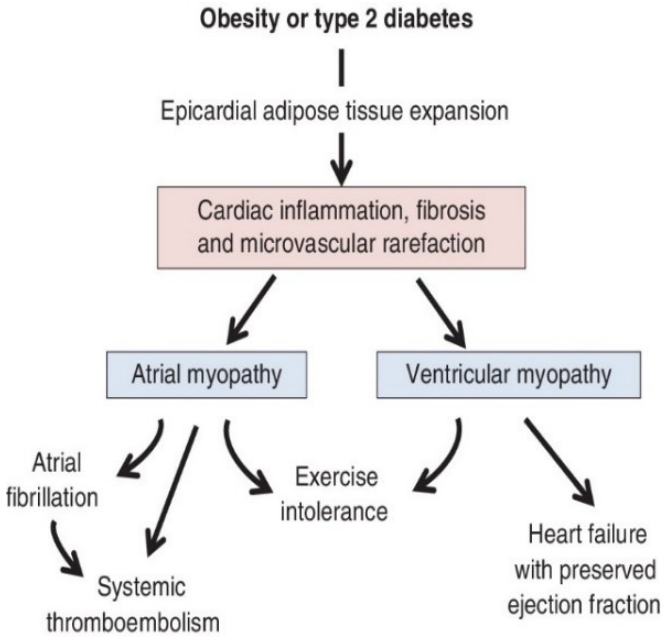
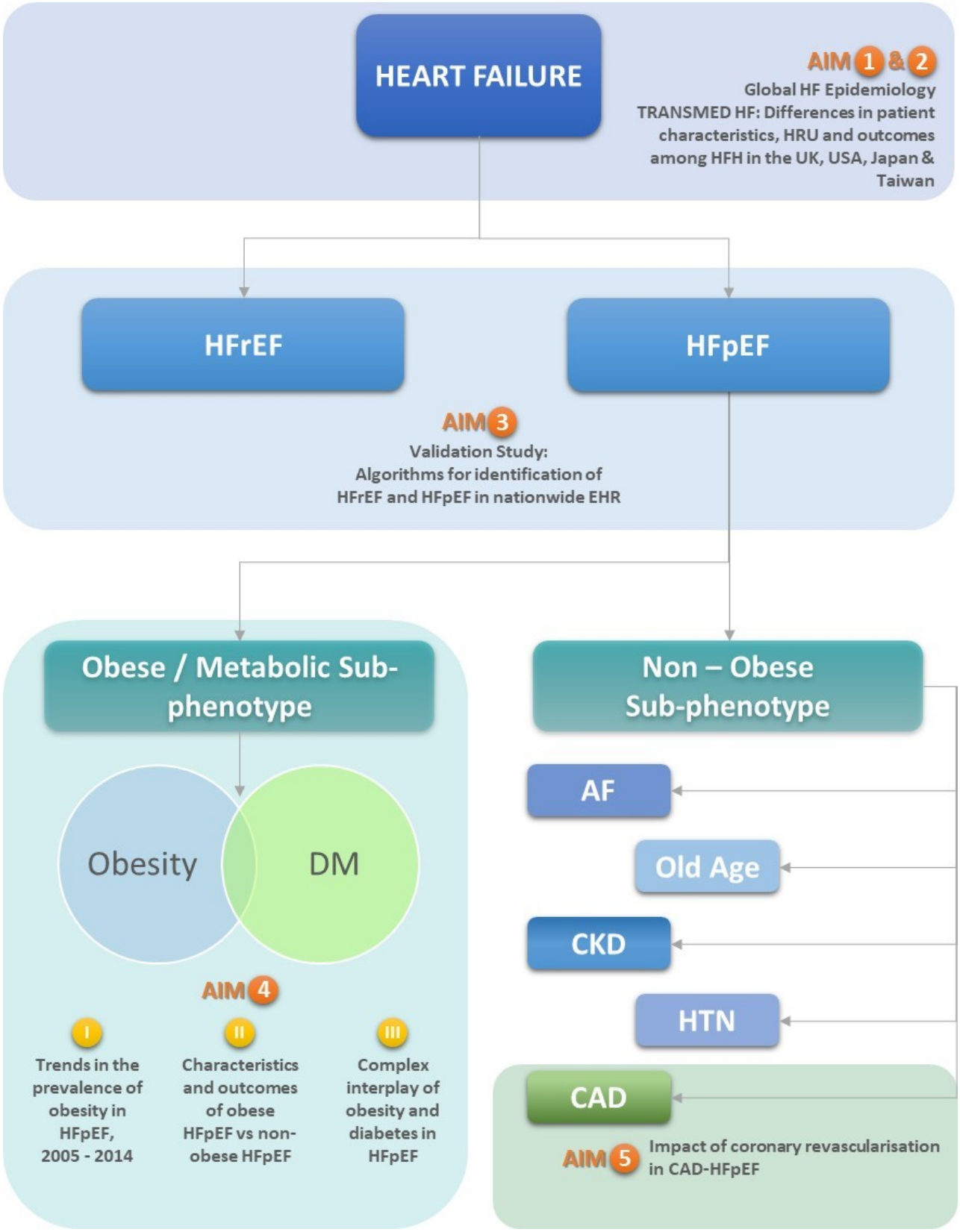


Figure 1.5: Possible mechanisms of heart failure with preserved ejection fraction in diabetes. Complex interplay of diabetes and obesity



As mentioned above, complex heterogeneity of HFpEF necessitates that this group of patients be sub categorised into frequently occurring co-morbidities. CAD qualifies as an important co-morbidity for sub-phenotyping, as it is extremely common in HFpEF, with a prevalence of 40-60% (48,49) **(Figure 1.6).** CAD and HFpEF share common risk factors, including hypertension, chronic kidney disease, ageing etc, and it is plausible that CAD may be an innocent bystander in patients with HFpEF without any causal relationship (50,51). Investigating the role of coronary revascularisation in reducing HF burden and improving survival in HFpEF patients may provide insights into the causal relationship. *This serves as the rationale for Aim 5 of this thesis.*

Figure 1.6: Flow chart of Specific Aims 1-5



UK – United Kingdom; US: United States of America; HFrEF: Heart Failure with reduced ejection fraction; HFpEF: Heart Failure with preserved ejection fraction; AF: Atrial fibrillation; CKD: Chronic Kidney Disease; HTN: Hypertension; DM: Diabetes Mellitus; CAD: coronary artery disease

My study aims and thesis rationale are based on addressing the knowledge gaps and limitations identified in the background section. The five specific aims constructed for this purpose and the basis for conducting this research are: differences in HF patient characteristics, treatment, and outcomes across four different countries; algorithms for identification of HFrEF and HFpEF in EHR; looking at the epidemiology of important sub-phenotypes in HFpEF, obesity-related HFpEF and CAD-related HFpEF. I elaborate on each of the specific aims below:

Specific Aim 1: To provide detailed epidemiological differences in patient characteristics, length of hospital stays and healthcare resource utilisation (HRU) of patients with heart failure hospitalisation (HFH) across the Western and Asian countries using nationally representative electronic health records.

Previous reports evaluating international differences in patient characteristics among patients hospitalised for HF have primarily included convenience samples from clinical trials or patient registries (12–15,17,18). While the external validity of registries is superior to that of clinical trials population, it is not necessarily the gold standard for real world evidence (52,53). Patients in registries are likely recruited from tertiary medical centres, non-consecutively enrolled and treated differently than those in regular clinical practice. In contrast to registries, nationally representative EHR and administrative healthcare databases capture routine clinical encounters in clinical practice possibly mitigating the selection bias present in registries (54–56). The definitions employed for diagnoses, identification of comorbidities, diagnoses and procedure codes in these studies were either not reported or standardised across countries, making comparative research challenging. Finally, I found no comparative reports on healthcare resource utilisation based on individual patient-level data of routinely captured clinical encounters from nationally representative data sources. Based on these considerations, I performed an individual patient-level analysis of more than one million non-consecutive HFH across four countries – UK, US, Japan, and Taiwan – using nationally representative data. I provide detailed epidemiological differences in patient characteristics and HRU of patients with HFH across the Western (UK and US) and Asian countries (Japan and Taiwan). These nations were selected based on their diverse health system structures, demographic and cultural differences, and the availability of high-calibre nationally representative healthcare records.

Specific Aim 2: To investigate differences in clinical outcomes (mortality and 30-day readmissions) and patient characteristics that predict a high probability of in-hospital mortality and 30-day all-cause readmission among patients with HFH in the UK, US, Taiwan, and Japan

Previous studies have shown that short- and long-term mortality rates for patients with HFH were dissimilar across countries (12–15,17,18). However, comparative investigations on standardised or adjusted outcomes based on individual patient-level data from nationally representative data across

different countries were not available. To this end, I analysed the differences in crude, standardised and adjusted mortality and 30-day readmissions across developed countries from 3 different continents. Additionally, I evaluated the patient factors predicting in-hospital mortality and readmissions across these four countries.

Specific Aim 3: To test the accuracy of algorithms for identification of different HF phenotypes, HFrEF and HFpEF, in the primary care electronic health records by comparing the database records with additional information provided by the General Practitioner (GP)

The two most common phenotypes of HF are HFrEF and HFpEF(57). There is no single diagnostic test for HF (HFrEF and HFpEF). The diagnosis relies on the combination of history, physical examination, biomarkers, and confirmation with echocardiogram. HFrEF is defined by clinical signs and symptoms of HF with a left ventricular ejection fraction (LVEF) of < 40%. In contrast to HFrEF, where the diagnosis is quite straightforward, the diagnosis of HFpEF is cumbersome, especially in patients presenting with dyspnoea and multiple comorbidities in an out-patient clinic. For diagnosing HFpEF, dyspnoea and a normal left ventricular ejection fraction needs to be coupled with additional measures of left ventricular diastolic dysfunction (e.g. left ventricular hypertrophy, increased left atrial diameter, tissue Doppler studies etc.), or plasma levels of natriuretic peptides; making it rather complicated to diagnose in the outpatient setting (58,59). The difficulties in identification of HFpEF in the real world and the lack of effective treatment, represent a large and growing unmet need in cardiology today. Although, multiple studies have been undertaken to efficiently identify patients with HF in the real world using EHR, there is a paucity of evidence on identification and validation of algorithms for identifying patients with specific HF phenotypes, including HFrEF and HFpEF. Therefore, I have focussed on improving the ability to identify patients with different HF phenotypes within the EHR, by collecting additional data (hospital outpatient cardiology correspondence and a direct questionnaire to GPs), and by seeking to understand the impact (positive predictive value, negative predictive value, and specificity) of different algorithms for identification of HFrEF and HFpEF. I believe the results of this study will inform the definitions and patient selection for future observational studies and randomised controlled trials, especially in HFpEF, thereby increasing accuracy and reducing potential bias.

Specific Aim 4: To investigate the temporal trends in the prevalence of obesity among patients with HFpEF from 2005-2014. Additionally, I evaluated the epidemiological differences in patient characteristics and outcomes among obesity related HFpEF vs those with non-obese HFpEF

There are multiple sub-phenotypes within HFpEF and obesity related HFpEF is one such common sub-phenotype. I have evaluated the trends in the prevalence of obesity among patients with HFpEF in the last decade in the US, along with the distinctiveness and the specific factors influencing clinical

outcomes unique to this sub-phenotype. In addition, I have also evaluated the complex interplay between diabetes and obesity in HFpEF in this study.

Specific Aim 5: To investigate the impact of coronary revascularisation (coronary artery bypass grafting) in reducing heart failure burden and improving long term survival among patients with CAD-HFpEF.

CAD is a commonly occurring co-morbidity in patients with HFpEF. Multiple pre-clinical studies have demonstrated a mechanistic link between CAD and HFpEF. However, the impact of treating CAD in the pathophysiologic progression of HFpEF remains unclear (50,60). In this aim, I have investigated the impact of coronary artery bypass surgery in reducing HF hospitalisations and mortality among patients with HFpEF.

STRUCTURE AND ORGANISATION OF THESIS

The thesis is organised as follows.

Chapter 1 provides the background, rationale, and an overview of the existing evidence of the transnational differences in HF management, complexities in the identification of different HF phenotypes in EHRs and the important sub-phenotypes within HFpEF.

Chapter 2 provides a detailed summary of the electronic and administrative healthcare datasets from the UK, US, Japan, and Taiwan used for this data analyses.

Chapters 3 & 4 describes the methodology, results, and discussion of the transcultural differences in the management of HF. Here, I provide a detailed account of differences in patient characteristics, healthcare resource utilisation and outcomes of patients with heart failure hospitalisation from UK, US, Japan, and Taiwan.

Chapter 5 details the validation study for algorithms for identification of HFrEF and HFpEF and ***Chapter 6*** describes the results of epidemiological analyses of obesity related HFpEF.

Chapter 7 explains the results of the study on the impact of coronary revascularisation in HFpEF. ***Each of these chapters (Chapter 3-7) contains a detailed discussion section, which examines the results in the context of other work.***

Chapter 8 outlines the clinical and research implications of the entire findings with a specific focus on directions for future HFpEF research.

Chapter 2: **Data sources**

PREAMBLE

This chapter provides a detailed overview of the data sources for my studies, and elaborates on the methods of data extraction, generalisability, strengths, and limitations of the individual datasets. The patient-level data for the UK was sourced from the UK's primary care datasets - the Clinical Practice Research Datalink (CPRD-GOLD) and The Healthcare Improvement Network (THIN). The comparative electronic and administrative healthcare records for the US, Japan and Taiwan was derived from The Healthcare Utilisation Project (HCUP), Nationwide Claims Database (JROAD-DPC) and the National Health Insurance Research Database (NHIRD) respectively. I used the National Veteran Affairs Electronic Health Records for the final specific aim. The EHR and administrative healthcare records represent an excellent resource for outcomes research as these provide large volumes of real-world data, albeit with shortcomings as the databases were constructed for clinical and reimbursement functions rather than research.

Table 2.1 Data sources used for specific aims

Country	Data sets	Pros	Cons (general and related to the study)
USA (Specific Aims 1,2 & 4)	NIS/NRD	• NIS: 20% of all hospitalisations in the US (randomly sampled) • NRD: 50 % of all hospitalisations in the US (randomly sampled) • Largest nationally representative administrate healthcare records in the US • Reliable data on procedural use and healthcare resource utilisation • Ability to identify different heart failure phenotypes, especially heart failure with preserved ejection fraction	• Readmissions cannot be tracked across different states or across calendar years • No data on out of hospital mortality • No linkage to outpatient health records • No data on pharmacy • No laboratory data
USA (Specific Aim 5)	VA-VINCI	• Largest integrated health system in the US with EHR available for > 16 million patients • Natural Language Processing algorithm for extraction of left ventricular ejection fraction • Validated algorithms for identification of different heart failure phenotypes • Reliable data on mortality • Outpatient data linked to hospitalisation records • Reliable data on prescriptions	• Population not generalizable • < 3% women • No reliable data on the cause of death
UK (Specific Aims 1 & 2)	CPRD	• Primary care data linked hospitalisation data (Hospital Episode Statistics-HES) • Linkage enables longitudinal follow of patients over a long period of time • Reliable data on mortality • Cause of death available via linkage with Office of National Statistics (ONS) • Reliable data on prescriptions	• Includes only ~ 8-9% of the overall population • Linkage to HES in only 40-60% of the patients • Inability to phenotype heart failure patients • Laboratory data available: missingness is an issue
UK (Specific Aim 3)	THIN	• Primary care data linked hospitalisation data (Hospital Episode Statistics-HES) which enables potential tracking of patient journeys between primary and secondary care • Reliable data on prescriptions • The THIN database's innate structure coupled with the nature of its contract with the GPs, makes it more suitable than CPRD to perform prospective validation studies	• Includes only ~ 6% of the overall population • Inability to phenotype heart failure patients • Laboratory data: missingness is an issue
Taiwan (Specific Aims 1 & 2)	NHIRD	• Most comprehensive EHR covering more than 99.6% of the Taiwanese population • Primary care data linked to hospitalisation data • Reliable data on prescriptions • Reliable data on mortality	• Inability to phenotype heart failure patients
Japan (Specific Aims 1 & 2)	JROAD-DPC	• Data from ~ 600 health systems across Japan • Most comprehensive nationally representative administrative healthcare records from Japan regularly audited by the Japanese circulation society • Minimal missingness on laboratory data	• Inability to phenotype heart failure patients • No linkage to outpatient records • No reliable data on out of hospital mortality

CPRD/HES: Clinical Practice Research Datalink linked to Hospital Episode Statistics (United Kingdom)

NHIRD: National Health Insurance Research Database (Taiwan)

JROAD: Japanese Registry of All Cardiac and Vascular Diseases – Diagnoses Procedure Combination

THIN: The Health Care Improvement Network (United Kingdom)

VA-VINCI: Veteran Affairs Informatics and Computing Infrastructure (United States of America)

STRUCTURE AND ORGANISATION OF UK DATA: CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

Specific Aims 1 and 2

In the UK, the National Health Service (NHS) is an all-inclusive nation-wide free healthcare system for its residents. Within the NHS system, the General Practitioners (GP) function as the doorway to the outpatient care. Over 98% of the British population are registered with a GP, who refer patients to the speciality services as required (61). The GPs or healthcare staff record the outpatient encounters electronically through coded diagnosis and free text. Similarly, reports from secondary care (e.g., specialist consultations, hospitalisations etc) are entered into the system retrospectively by healthcare workers. The pharmacy prescriptions and some laboratory test results are automatically recorded in the system (61,62).

2.1.1 Structure and organisation of CPRD

CPRD was initially established in London in 1987 as the Value-Added Medical Products (VAMP) dataset. The VAMP was later modified and called the General Practice Research Database (GPRD) in 1993, which was then expanded to be called the CPRD in 2012. The CPRD data are sourced from c.700 general practices that include 50 million patients of which 15 million are currently registered active patients (63). The inactive patients have either died or are no longer registered at a participating practice. All patients registered with CPRD participating GP practices are included in the dataset by default unless patients actively request to opt out of data sharing. The CPRD uses the VISION software system to collect routine clinical encounters (as anonymised data) from participating general practices and provides this data on a monthly basis (63,64).

The data in CPRD are categorised into several files **(Table 2.2).** Each file has a unique patient identification number which is used to link all patient-level files **(Table 2.2)** (65)**.**

Figure 2.1 Data structure in CPRD; Source: based on Herrett et al., 2015 [63].

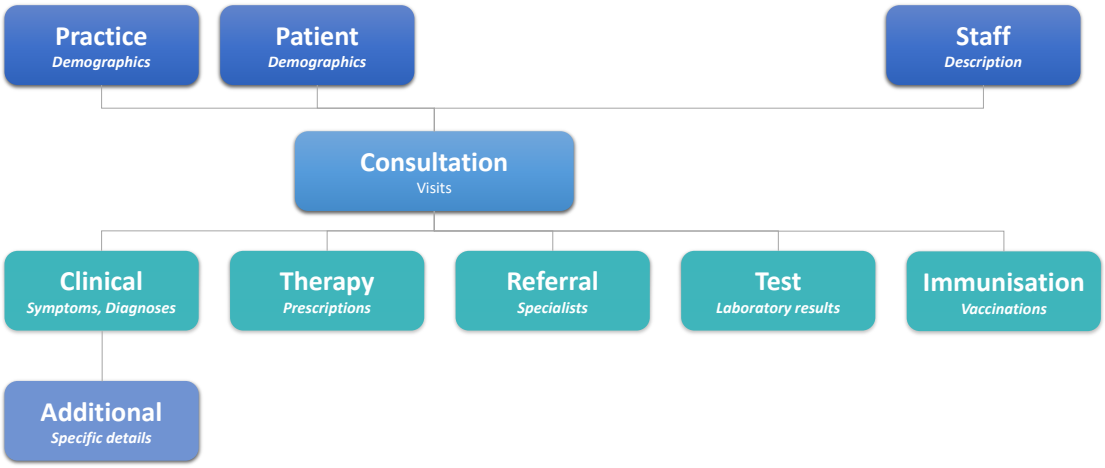


Table 2.2: Individual patient-level files in CPRD

File type	What it holds	Example of contents (variables)
Patient	Demographic data and details relating to registration status of patients One row per patient	Patient identifier (patid) Month and year of birth Date of registration, first or current (frd, crd), Date of death (death date) Transfer out date, and reason for leaving practice (tod; toreason)
Practice	Practice administrative data One row of data per practice	Practice identifier Geographical region Date practice achieved "up to standard" status (uts) Last data collection date (lcd)
Staff	Information about practice staff members One row of data per staff member	Staff identifier Staff gender and role
Consultation	Administrative information about the consultation One row of data per consultation	Date of consultation (event date) Date of data entry (sysdate), Type of consultation (constype) Consultation identifier (consid) Additional (clinical) data identifier (adid)
Clinical	Clinical and diagnostic data about a patient recorded during the course of a consultation Multiple rows per patient	Patient/consultation identidfiers Date of clinical event/date of data entry CPRD medical code corresponding to selected *Read* code (medcode) Additional details identifier (adid) Entity type (enttype)
Additional Clinical Details (ACD)	Specific/more detailed data about a clinical event, including results of routine tests or lifestyle factor measurements Multiple rows per patient	Patient/consultation identifiers Date of clinical event/date of data entry Additional details identifier (adid) Entity type (enttype)
Referral	Details on referrals to secondary care or specialists Multiple rows per patient	Method of referral, referral specialty, urgency of referral
Immunisation	Data associated with immunisations given Multiple rows per patient	Reason for immunisation, type, stage, status, and the compound used
Test	Test results Multiple rows per patient	Type of test, result, normal range of result, unit of measure
Therapy	Information about prescribed therapies, including medications and appliances Multiple rows per patient	The CPRD product code for the medication (prodcode) British National Formulary code, quantity of product, dose, pack size, number of days prescribed

Source: based on Herrett et al., 2015 [63].

2.1.2 Diagnosis coding system in CPRD

CPRD uses *Read* coding system for recording diagnosis and comorbidities of patients in the primary care setting. The *Read* coding system was first developed in early 1980s, by a British GP – Dr James *Read* (66–68). It is a hierarchical clinical classification system and is structurally similar to the International classification of diseases (ICD) coding system **(Table 2.3).** All *Read* codes are cross-referenced to ICD9 and ICD10 coding systems. This clinical terminology system was used widely in

the general practice setting in the UK until 2018 (69–71). For my thesis, I used the *Read* version 2, which has over 96,000 codes.

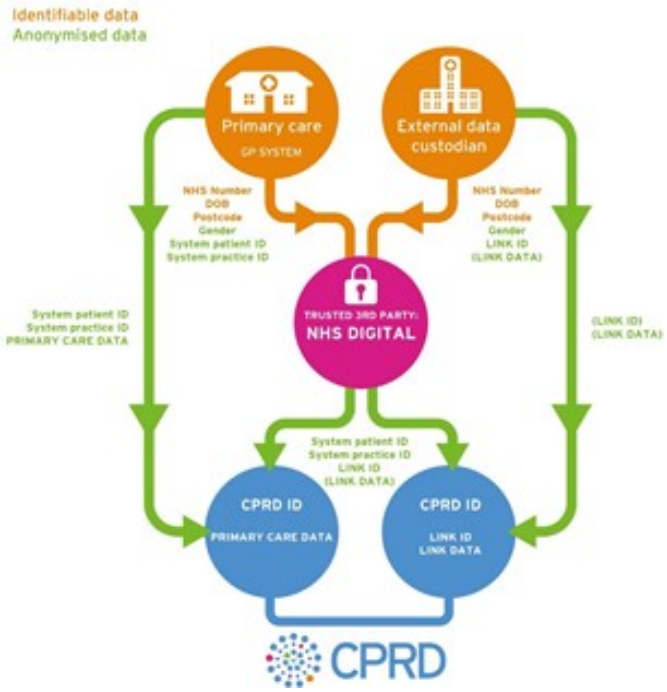
Table 2.3 Structure of Hierarchies, Adapted from Nick Booth. What are *Read* codes? Health Libr Rev. 1994 Sep;11(3):177-82.

Level	Read Code	Term
1	A	Infectious disease
2	A1	Tuberculosis
3	A14	TB GIT/peritoneum/mesenteric gland
4	A14y	Other GI tuberculosis
5	A14y2	Tuberculosis small intestine

2.1.3 Linkage of CPRD to other data sets: (i) Hospital Episode Statistics

c.60% of all CPRD records are linked with Hospital Episode Statistics (HES) data using a unique patient ID **(Fig 2.2).** The HES data has been well-validated and used extensively for observational research (72–75). The HES contains details of all hospitalisations (HES – Admitted Patient Care: HES–APC), critical care utilisation (HES – Adult Critical Care), hospital outpatient appointments (HES–OP) and accident and emergency attendances (HES–A&E) at the NHS hospitals in England.

Figure 2.2: Primary care and linked data flow Source: Padmanabhan et al., 2018 [65].



The HES–APC data dates back to 1989 and contains information on all admissions to NHS hospitals in England. Each line within the HES–APC database specifies a 'Finished Consultant Episode' (FCE)

(Table 2.4), representing a continuous period of care under one consultant, with a start and an end date (76).The HES–APC records contains clinical information about diagnoses and operations/procedures, demographic information (such as age group, gender and ethnicity), administrative information, and dates and methods of admission and discharge. Each FCE can have up to 20 clinical diagnoses, which are coded using the internationally recognised ICD-10 system of coding. The first diagnosis listed in the FCE is the primary cause for hospitalisation. Diagnoses listed in the second and successive positions are likely to be pre-existing chronic conditions or comorbidities that could contribute to the patient's current hospitalisation (76,77).

Table 2.4 Selection of key data fields available for each finished consultant episode (FCE) in HES–APC (Adapted from Herbert et al, 2017 (76)

Patient	Admission/FCE	Clinical	Geography	Provider/Organisational
HESID	Episode start date	Diagnoses (up to 20) Operations (up to 24)	Government office region	Care provider (hospital)
Age at admission	Episode end date	Operation dates (up to 24)	Local authority	General practice of patient
Age at discharge	Date of admission	Consultant specialty (admitting and treating consultant)	Clinical commissioning group	
Sex	Date of discharge	Diagnoses (up to 20) Operations (up to 24)		
Ethnic group	Admission method (e.g. - planned, emergency, birth)	Operation dates (up to 24)	Index of multiple deprivation (IMD) 2004 rank, deciles and domains	
Patient	**Admission/FCE**	**Clinical**	**Geography**	**Provider/Organisational**
	Discharge method	Consultant specialty (admitting and treating consultant)	Government office region	
	Admission source	Diagnoses (up to 20) Operations (up to 24)	Local authority	
	Discharge destination	Operation dates (up to 24)		
	Waiting time (from date of decision to admit to date of admission)			

2.1.4 Linkage of CPRD to other data sets: (ii) Office of National Statistics (death registration data)

Similar to HES, c.60% of CPRD records are also linked to the death registration data from the Office for National Statistics (ONS), UK. The ONS death registration data records the date, place, and cause of death, and is considered the gold standard for mortality data in the UK. The cause of death from January 1998, is coded (ICD) using the death certificate for the population of England and Wales (78,79). Linking the CPRD, HES and ONS is done using a deterministic linkage algorithm that uses the patients' exact NHS identification number, sex, date of birth, and residential postcode. *The CPRD-HES-ONS linked individual patient-level data was used for Specific Aims 1 and 2 of this thesis.*

STRUCTURE AND ORGANISATION OF UK DATA: THE HEALTHCARE IMPROVEMENT NETWORK-(THIN)

Validation study (Specific Aim 3)

The Healthcare Improvement Network (THIN) is an electronic medical data collection scheme that sources anonymised patient data from more than 3.7 million active patients across 587 general practices in the UK (80). THIN's longitudinal patient records began prospective data collection in September 2002, with approximately 55 million patient-years of follow-up, or nearly 10 years per patient. The THIN database accounts for c.6% of the British population and these patients have been shown to be representative of the population in terms of age, gender, medical conditions and death rates **(Figure 2.3 and Table 2.5)** (81)**.**

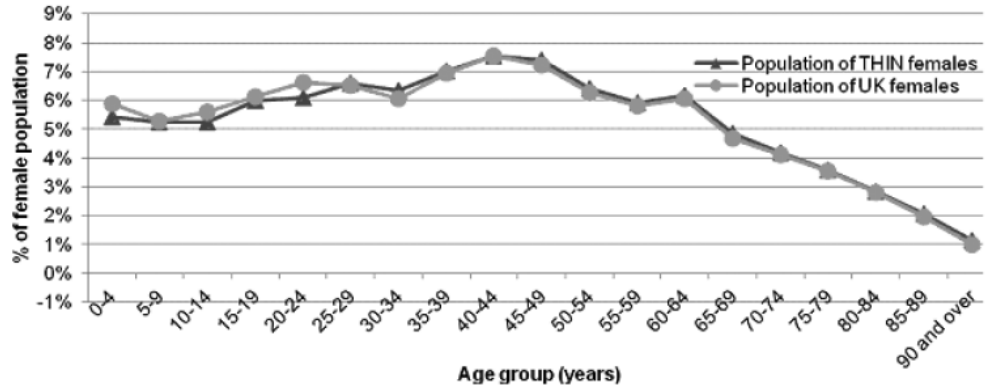
THIN-contributing general practices electronically record all conditions and symptoms during patient consultations with the healthcare staff. In addition to medical diagnoses, information on prescriptions, tests requested, laboratory results and referrals to secondary care are also available in this database. Analogous to the CPRD, the THIN database uses the *Read* coding system and a similar individual clinical filing system including recording of patient diagnoses and comorbidities. The THIN database's innate structure coupled with the nature of its contract with the GPs, makes it more suitable than CPRD to perform prospective validation studies, which involve sending questionnaires to GPs. The THIN database is also linked to HES-APC and the linkage methodology is similar to those employed by the CPRD(82). However, the research questions related to this thesis did not require linkage of THIN to HES and the validation was only based on primary care EHR data. Multiple validation studies have been performed using the THIN databases, particularly while conducting pharmacoepidemiology research (83–85).

Table 2.5: Quality and Outcomes Framework (QOF) condition crude prevalence's in THIN compared with UK national QOF data; ***Table adapted from Blak et al Inform Prim Care. 2011;19(4):251-5.***
Data from the QOF year 2006/2007 were used and data from THIN were derived for this 2006/2007 cross-section in time

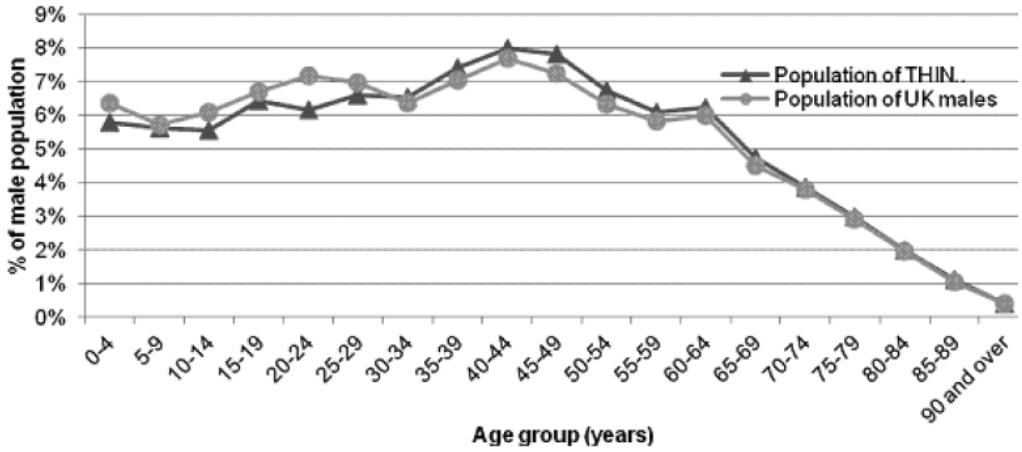
QOF conditions	THIN (%), Confidence interval	UK National QOF (%)
Atrial fibrillation	1.4 (1.4–1.4)	1.3
Asthma	6.0 (5.9–6.0)	5.8
Cancer	0.9 (0.9–0.9)	0.9
Coronary heart disease	3.9 (3.9–3.9)	3.7
Chronic kidney disease	2.5 (2.5–2.5)	2.3
COPD	1.6 (1.6–1.6)	1.5
Dementia	0.5 (0.5–0.5)	0.4
Diabetes	3.5 (3.5–3.5)	3.7
Heart failure	0.9 (0.9–0.9)	0.8
Hypertension	12.7 (12.6–12.7)	12.7
Learning disability	0.3 (0.3–0.3)	0.3
Obesity	8.3 (8.3–8.3)	7.5
Palliative care	0.1 (0.1–0.1)	0.1
Stroke/TIA	1.9 (1.9–1.9)	1.7
Hypothyroidism	2.7 (2.7–2.8)	2.6

Figure 2.3 Comparison of The Health Improvement Network (THIN) population and UK population in 2009 according to age and gender

Female



Male



** Figure adapted from Blak et al Inform Prim Care. 2011;19(4):251-5*

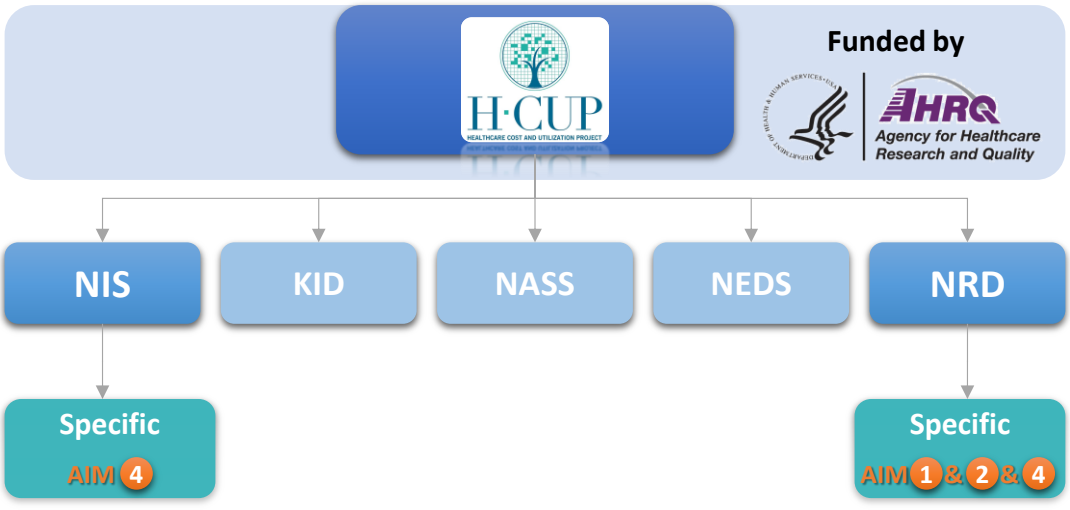
STRUCTURE AND ORGANISATION OF US DATA: HEALTHCARE UTILISATION PROJECT (HCUP)

The American health system, in contrast to the NHS, is a combination of public and private, for-profit and non-profit insurers and healthcare providers (86). However, private insurance is the predominant form of coverage and is primarily provided by employers. Adults over the age of 65 years, people with certain chronic diseases (such as end-stage renal disease among others), and a particular group of paediatric patient population (determined by need / income level) receive funding from the federal government under the National Medicare and Medicaid program (87). In 2018, nearly 92% of the population was estimated to have medical coverage, leaving around 27.5 million people uninsured (88).

The Healthcare Cost and Utilisation Project (HCUP) is an agglomeration of healthcare databases created by a Federal-State-Industry partnership sponsored by the Agency for Healthcare Research and Quality (AHRQ) and the U.S. Department of Health and Human Services (HHS) **(Figure 2.4**) (88). As a consequence, the HCUP databases serve to be the most expansive hospital care data available in the United States, containing several nationwide databases available for research. The HCUP databases document patient-level demographic and clinical information including all-listed diagnoses and procedures, in-patient stays, ambulatory surgery and services visits, emergency department encounters, discharge status, and charges for all patients, regardless of payer (e.g., Medicare, Medicaid, private insurance, uninsured).[87]

The databases offered in the HCUP are National Inpatient Sample (NIS), Kid's Inpatient Database (KID), Nationwide Ambulatory Surgery Sample (NASS), Nationwide Emergency Department Sample (NEDS) and Nationwide Readmissions Database (NRD) (88).I have used the NIS and NRD for the studies related to my thesis **(Figure 2.4).**

Figure 2.4: Structure of the Healthcare and Utilisation Project (HCUP) family of databases



NIS: Nationwide Inpatient Sampling database; Kid's Inpatient Database (KID), Nationwide Ambulatory Surgery Sample (NASS), Nationwide Emergency Department Sample (NEDS) and Nationwide Readmissions Database (NRD)

2.1.5 Nationwide Inpatient Sampling (NIS) database

The NIS is the largest HCUP database with information on more than 8 million hospital stays (all-payer in-patient care), collected from c.1,000 hospitals to approximate a 20% stratified sample of the community hospitals in the US (88,89). The NIS is constructed annually, with data from 1988 to 2017 available for research. Each in-patient encounter can have up to 15 clinical diagnoses, coded using the ICD system. Similar to the HES database, the first diagnosis listed is the primary cause for hospitalisation, with subsequent positions likely containing comorbidities contributing to the patient's hospitalisation. Additionally, each in-patient encounter can have information on up to 15 procedures per hospital stay (89). The NIS includes detailed information on patient demographics, pre-existing comorbidities, survival to discharge, disposition, hospital charges, and length of stay. Therefore, the NIS is an optimal administrative healthcare database to investigate national trends in hospitalisations, procedural use, in-hospital survival and complications (90).

The NIS has several strengths but some important limitations. While the NIS has detailed information on in-hospital course and healthcare resource utilisation, it does not capture outpatient encounters. The database does not identify individual patients, and recurrent hospitalisations appear as distinct observations i.e., captured encounters represent hospitalisation records, and not distinct patients. Consequently, the NIS data cannot be combined across years to create a multi-year database (89). For my thesis, I used the NIS data for part of the specific aim 4 **(Table 2.1).**

2.1.6 Nationwide Readmissions Database (NRD)

The NRD is a nationally representative survey of hospitalisations, conducted by the HCUP in collaboration with participating American states and contains 50% of all hospital admissions in the U.S (88). The NRD is made up of c.15 million in-patient discharge records and over 100 clinical and non-clinical data elements. Each in-patient encounter can have up to 25 clinical diagnoses and 25 procedural codes (uses ICD9 until 2015 and ICD10 thereafter) (91). Akin to the NIS, the first diagnosis recorded is the primary cause of hospitalisation. Each entry contains information on demographic details, insurance status, primary and secondary procedures, hospitalisation outcomes, total cost, and length of stay. The NRD database contains clinical and resource use information, with safeguards to protect the privacy of patients, physicians, and hospitals (91). The NRD was built to enable analyses of both all-cause and condition-specific readmissions and its results have been shown to correlate well with other hospitalisation discharge databases in the US. National-level estimates can be produced by applying weighting and stratification methods. Unlike the NIS, the NRD, while compiled annually, has longitudinal records of readmissions for each calendar year. Therefore, 30- or 60-day readmissions for patients admitted in the latter part of the year may not be captured if the subsequent admission is in the next calendar year. Although the data is longitudinal for the calendar year, the NRD data cannot be combined across data years to create a multi-year database, i.e., the patient linkage identifier does not

track the same patient across years. While the HCUP family of databases includes information of both insured and uninsured hospitalisations, there is likely a selection bias as the uninsured population are less likely to get hospitalised. For my thesis, I used data from 2012 for specific aims 1, 2 and **4 (Table 2.1).**

Structure and organisation of Japanese data: Japanese Registry Of All Cardiac and Vascular Diseases\Diagnosis Procedure Combination- JROAD-DPC

Japan has a universal healthcare system, and its public healthcare system is known as the Social Health Insurance (SHI). SHI applies to everyone who is employed full-time with a medium- or large-sized company (92). The proportion of population that do not qualify under SHI are covered through the National Health Insurance (NHI) plan, by the government. In general, there are three modes of funding: government-managed plans, society-managed plans, and mutual aid associations (93).

There is high incidence of cardiovascular disease related mortality in Japan, accounting for more than a quarter of all deaths. In order to address this, the Japanese Circulation Society along with the Department of Health in 2012, established a nationwide claims database of cardiovascular diseases named the Japanese Registry of All Cardiac and Vascular Diseases – Diagnoses Procedure Combination (JROAD-DPC) (7). It is imperative to note the term 'registry' is somewhat unsuitable here, as JROAD-DPC captures all routine clinical encounters akin to electronic healthcare records, negating any selection bias that is otherwise endemic to a traditional registry. The database was instituted to assess the clinical activity of each Japanese institution with cardiovascular beds, to improve patient care. JROAD-DPC includes the unique hospital identifier, patient demographics, main diagnoses and comorbidities, drugs and devices, diagnostic and therapeutic procedures, length of hospital stay, discharge status and readmissions sourced from 1,022 hospitals (7). However, there is no information on longitudinal outpatient care. Data from JROAD-DPC has been extensively used to identify the status of cardiovascular care in Japan and has been shown as nationally representative.

Structure and organisation of Taiwanese data: National Health Insurance Research Database (NHIRD)

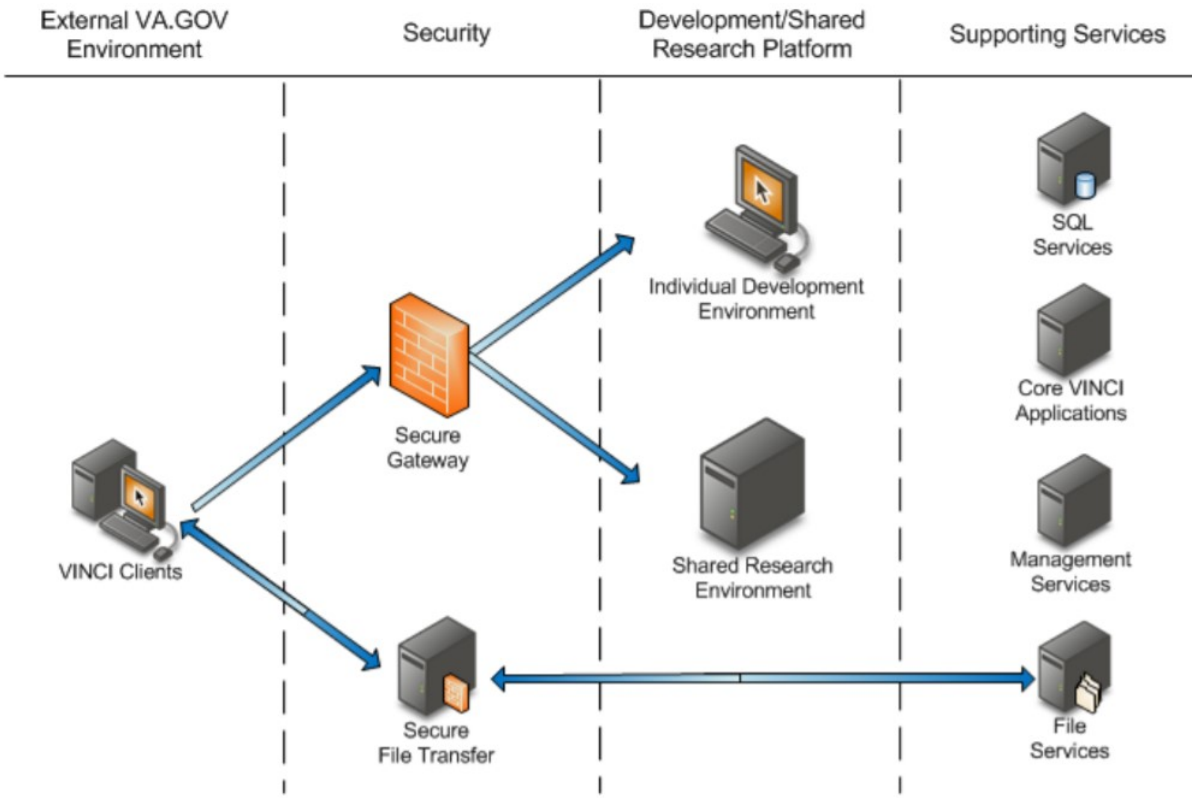
Taiwan adopted a government administered national health insurance system in 1995 for its 23 million residents. Similar to the UK, Taiwan has a single payer system for healthcare (94). Taiwan's National Health Insurance Research Database (NHIRD) was established to generate population level evidence to support clinical decisions and healthcare policy making. The NHIRD database (uses ICD-9-CM code) contains detailed information of all hospitalisations, outpatient visits, laboratory information,

accident and emergency visits and prescription information, thereby providing real-world data with great phenotyping depth and long term follow up for population-based research (95).

Structure and organisation of National Veteran Affairs data from the USA: Veteran Affairs Informatics and Computing Structure (VA-VINCI)

The Veteran Health Affairs Department has the largest integrated health care system in the United States, providing care at 170 hospitals and 1025 out-patient facilities (96).VA medical records are centrally stored in the corporate data warehouse (CDW). The VA Informatics and Computing Infrastructure (VINCI) allows researchers to query data to obtain information from patient health records. This contains clinical information regarding inpatient and outpatient visits, pharmacy prescription history and laboratory results (97). The VA Surgical Quality Initiative Project (VASQIP) for surgery was established prospectively in 1987 to evaluate and monitor surgical outcomes at all hospitals within the VA system. The VASQIP contains prospectively collected data on all Veterans undergoing surgery within the VA system. Also stored with in the CDW, VASQIP files can be linked to all other medical records available within VINCI (98). There are unique patient identifiers to link various flat datafiles together as well as longitudinally obtain data regarding patients in the study cohort. Vital status files are linked to the Social Security Index, Beneficiary Identification Records Locator Subsystem (BIRLS) and the Center for Medicare and Medicaid Services. This cross-linking of data enables researchers to accurately identify relevant long-term events for each patient (99,100). VA-VINCI was used for Aim 5 of this thesis. I identified patients that underwent isolated coronary artery bypass surgery (CABG) between January 2005 – September 2019 from the VASQIP database. Pre-operative demographic, clinical and laboratory data was available for all patients from the VASQIP.

Figure 2.5: VINCI (Veteran affairs Informatics and computing infrastructure) architecture



Adapted from https://www.hsrd.research.va.gov/for_researchers/vinci/

GOVERNANCE AND ETHICS APPROVAL

UK: This study was approved by the Independent Scientific Advisory Committee of the Medicine and Healthcare Products Regulatory Agency (MHRA) for database research (protocol number: 18_068R). The data are anonymous, and the requirement for informed consent was therefore waived.

US (NRD-NIS): Approval was obtained from the HCUP for the study. Additional approval was obtained to transfer the data to other countries (UK, Japan, and Taiwan) and for the merger at individual patient-level with data from the UK, Japan, and Taiwan (for Specific Aims 1 and 2).

Taiwan: The NHIRD was released by the Taiwan National Health Research Institutes with the approval for the research purposes. The data are anonymous, and the requirement for informed consent was therefore waived.

Japan: Approval for analyses of the Japanese data was obtained from the JROAD-DPC committee of the Japanese Circulation Society. This study was also approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center in Japan (M29-028).

US (VA-VINCI): Approval for analyses of the Veteran Affairs data was approved by the Institutional Review Board of the Louis Stokes Veteran Affairs Medical Center.

STORAGE AND ANALYSES OF DATA

The CPRD – HES data from the UK and HCUP data from the US was stored and analysed at Imperial College after obtaining necessary approvals. I carried out the entirety of the analyses for the UK and the US data. The data from Taiwan was stored in the Institute of Clinical Medicine, School of Medicine, National Yang-Ming University, Taipei. The JROAD-DPC data was stored at the National Cerebral and Cardiovascular Center in Japan. The Japanese and Taiwanese data analyses were performed by the respective institutions – National Cerebral and Cardiovascular Center in Japan and National Yang-Ming University, Taipei – under the direction of the author. Standardisation of analyses was ensured by rigorously monitoring every step along the way and the author providing the STATA do files (including codes) to these institutions. The data from VA-VINCI was stored in computer in the Cleveland Veteran Affairs Medical Center which I had access to. The analyses of VA data were performed by me with intermittent help from a bio statistician. The definitions employed for diagnoses, identification of comorbidities, procedures and outcomes in previous epidemiological studies comparing HF patients across different countries, were either not reported or standardised across countries. In order to overcome this limitation, I performed extensive standardisation of diagnosis across countries. For instance, matching similar diabetes codes in ICD 9 for US and Taiwan to ICD 10 in Japan and Read codes in the UK; so that codes for each of the comorbidities were individually matched across different healthcare coding systems to enable effective comparisons across countries

Chapter 3: **Transcultural lessons in the management of heart failure TRANSMED HF**

PREAMBLE

Geographic differences in patient characteristics, healthcare resource utilisation (HRU), and clinical outcomes of patients with heart failure (HF) are of significant policy interest. Post-hoc analysis from contemporary clinical trials and registries have revealed significant differences in patient characteristics and HRU among patients with heart failure hospitalisation (HFH) (17–23,38,101). However, clinical trials and registries do not necessarily represent the real-world environment as these are prone to selection bias (54,102). Conversely, nationally representative electronic health records (EHR) capture routine clinical encounters with the ability to mitigate the selection bias introduced by trials and registries. I have, therefore, compared individual patient-level data of more than 1 million consecutive unselected HFH, using large nationally representative EHR and administrative databases from developed countries across three different continents – UK, US, Taiwan, and Japan. In this chapter, I provide detailed epidemiological differences in individual patient characteristics, length of hospital stays (LOHS) and HRU of patients with HFH with similar attributes in the four countries.

EVIDENCE BEFORE THE STUDY

I searched PUBMED (January 1, 2000 to December 31st, 2018) using the Medical Subject Headings (MeSH) terms “heart failure” or “acute heart failure” or “hospitalised heart failure” or “hospitalized heart failure” or “heart failure hospitalisation” or “heart failure hospitalisation” and “Asia” or “Asians” or “United Kingdom” or “United States” or “Japan” or “Japanese” or “Taiwan” or “Taiwanese” or “ North America” or “procedural utilisation” or “procedural utilization” or “procedures” or “healthcare resource” or “length of stay” or “length of hospital stay” with no language restrictions. I also identified publications using searches on Google Scholar and via citations in peer-reviewed publications. Studies thus identified, evaluated international differences among patients hospitalised for HF by including samples primarily from clinical trials or patient registries (2,16,19–21,23). There were no investigations on differences in patient characteristics and HRU based on individual patient-level data from nationally representative EHR across countries.

METHODS

3.1.1 Data sources

A diverse global population (Europe, North America, and Asia) of patients with heart failure hospitalisation (HFH) were identified using i) Nationwide electronic health records from the UK, ii) the largest administrative healthcare database in the US, iii) the National Health Insurance Research Database from Taiwan, and iv) the national administrative database in Japan. *These nations were selected given their varied health system structures, and notably the availability of good quality source of nationally representative healthcare records across which analyses could be standardised*. The methodology of data extraction, strengths and limitations of the individual datasets have been explained in detail in Chapter 2 of this thesis.

3.1.2 Case ascertainment: Identification of unplanned primary HFH in individual countries

3.1.2.1 Study population

Patients aged 18 years or older with heart failure hospitalisation (HFH) between 2012 to 2014 from the British, Taiwanese, and Japanese cohorts **(Figure 3.1)** were included in the study. Patients with HFH from January to December 2012 were included from the American cohort as follow-up data was available only for this period. Patients with missing data on age, gender, and elective admissions were excluded from the final analyses **(Figure 3.1)**. The specifics of case ascertainment i.e., identification of HF patient population, are explained in the following sections.

3.1.2.2 Differentiating primary HFH from secondary HFH

The primary HFH was differentiated from secondary HFH in the respective datasets using the following methods:

A. **HES-UK:** The HES data has multiple individual files. Patients with a primary HFH were differentiated from secondary HFH using the 'HES primary diagnosis hospitalisation file' (i.e., hes_primary_diag_hosp_18_068R) that was provided at the time of data extraction.
B. **NRD-US:** There are 20 diagnosis codes (diagnosis, clinical classification software code [DXCCS1-DXCCS20]) for each hospitalisation episode in the NRD. Hospitalisations with the first diagnosis code (diagnosis, clinical classification software code, 1 [DXCCS1]) of HF (DXCCS1=108, includes ICD9CM codes for HF) were included as primary HFH. [https://www.hcup-us.ahrq.gov/toolssoftware/ccs/CCSUsersGuide.pdf]
C. **NHIRD-Taiwan:** There are five diagnosis codes (ICD9CM codes) for each hospitalisation in the Taiwanese NHIRD. Hospitalisations with the first diagnosis code (ICD9CM codes for HF) were identified as the primary HFH.

D. **JROAD-DPC–Japan:** The JROAD-DPC administrative database has an inbuilt column for the primary cause of hospitalisation. Hospitalisations with the primary diagnosis ICD-10 codes for HF in the DPC were identified as the primary HFH.

3.1.2.3 Differentiating unplanned HFH from elective/planned HFH

The planned or elective hospitalisations were differentiated from unplanned hospitalisations in the respective databases using the following methods:

A. **HES-UK:** Codes for elective hospitalisations (11 = Elective: from waiting list, 12 = Elective: booked, and 13 = Elective: planned) were identified using the Hospital Episode Statistics Data Dictionary. Patients with elective hospitalisation for HF were excluded from the final analysis. [https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics]
B. **NRD-USA:** Patients with elective hospitalisations were identified using the variable "elective" in the NRD 2012 Core files. [https://www.hcupus.ahrq.gov/db/nation/nrd/nrdfilespecs.jsp#2012NRD]
C. **NHIRD-Taiwan:** Unable to differentiate unplanned from planned HF hospitalisations in Taiwan.
D. **JROAD-DPC-Japan:** Elective hospitalisations were differentiated from unplanned using the variable "elective hospitalisations (100 = Elective/Planned)" in JROAD-DPC. The physicians caring for the patient are responsible for filling this column in the DPC database during hospitalisation.

3.1.3 Standardisation of diagnoses and procedure codes

The definitions employed for diagnoses, identification of comorbidities, procedures and outcomes in previous epidemiological studies comparing HF patients across different countries, were either not reported or standardised across countries. In order to overcome this limitation, I performed extensive standardisation of diagnosis across countries. For instance, matching similar diabetes codes in ICD 9 for US and Taiwan to ICD 10 in Japan and *Read* codes in the UK; so that codes for each of the comorbidities were individually matched across different healthcare coding systems to enable effective comparisons across countries **(Table 3.1 and Supplementary Appendix Table 1).**

Data on 12 frequently occurring comorbidities in HF were extracted using respective diagnosis codes from each country: Coronary artery disease (CAD), atrial fibrillation (AF), diabetes mellitus (DM), hypertension (HTN), chronic lung disease, chronic kidney disease (CKD) (codes specific for CKD stage 3 and above), chronic liver disease, peripheral arterial disease (PAD), obesity, chronic anaemia, pulmonary circulation disorders and alcohol abuse **(Table 3.1 and Supplementary Appendix Table**

1). Procedures performed were identified using ICD-9CM procedure codes in the US, Taiwan, and Japan, and using Operating Procedure Code Supplement Fourth Revision (OPCS-4.6) in the UK cohort. The procedure codes were individually matched across countries; for example, coronary angiogram codes in ICD9 used in the US, Taiwan, and Japan, were individually OPCS4.6 codes in the UK **(Table 3.1 and Supplementary Appendix Table 2)**

3.1.4 Outcomes of interest

The main outcomes of interest were differences in patient characteristics, length of hospital stay and healthcare resource utilisation during index hospital admission of patients with heart failure hospitalisation across the 4 countries.

3.1.5 Statistical analyses

All of the analyses were performed with STATA MP64 version 15 (StataCorp, College Station, TX). Baseline characteristics were presented as mean ± standard deviations (SD) when normally distributed, and as medians and interquartile (IQR) ranges when not normally distributed. Length of hospital stays were presented as median and interquartile ranges. Healthcare resource utilisation was analysed using the proportion of patients receiving coronary angiogram, right heart catheterisation, mechanical ventilation (invasive and non-invasive), device implantation (permanent pacemakers, implantable cardioverter defibrillator and cardiac resynchronisation therapy), coronary revascularisations (percutaneous coronary intervention and coronary artery bypass grafting), ablations for arrhythmias, cardioversion, and mechanical hemodynamic support during the index hospital stay. Mechanical hemodynamic support was defined as the use of either intra-aortic balloon pump, percutaneous ventricular assisted device or extracorporeal membrane oxygenation in patients not undergoing cardiac surgery.

Table 3.1 Data Source, Diagnosis and Procedural Coding Systems in 4 Countries

Country	Data Source	Generalisability	HF diagnosis	Coding system for comorbidities	Coding system for procedures during index hospitalisation
United States	NRD	50% of all hospitalisations	Hospitalisation with a primary ICD-9-CM diagnosis code for HF	ICD-9-CM: comorbidities recorded at the time of admission	ICD-9-CM procedural codes
United Kingdom (England & Wales only)	HES linked to CPRD and ONS	7% of the population	Hospitalisation with a primary ICD-10 diagnosis code for HF	READ codes: comorbidities recorded at outpatient encounter prior to the admission	OPCS 4.6 procedural codes
Taiwan	NHIRD	99% of the entire population	Hospitalisation with a primary ICD-9-CM diagnosis code for HF	ICD-9-CM: comorbidities recorded at outpatient encounter prior to the admission	ICD-9-CM procedural codes

Japan	JROAD-DPC	~ 600 health systems	Hospitalisation with a primary ICD-10 diagnosis code for HF	ICD-10: comorbidities recorded at the time of admission	ICD-9-CM procedural codes

NRD: National Readmissions Database; HES: Hospital Episode Statistics; CPRD: Clinical Practice Research Datalink; NHIRD: National Health Insurance Research Database; JROAD-DPC: Japanese Cardiovascular Administrative Database-Diagnosis Procedure Combination; OPCS: Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (4th revision); ICD: International Classification of Diseases

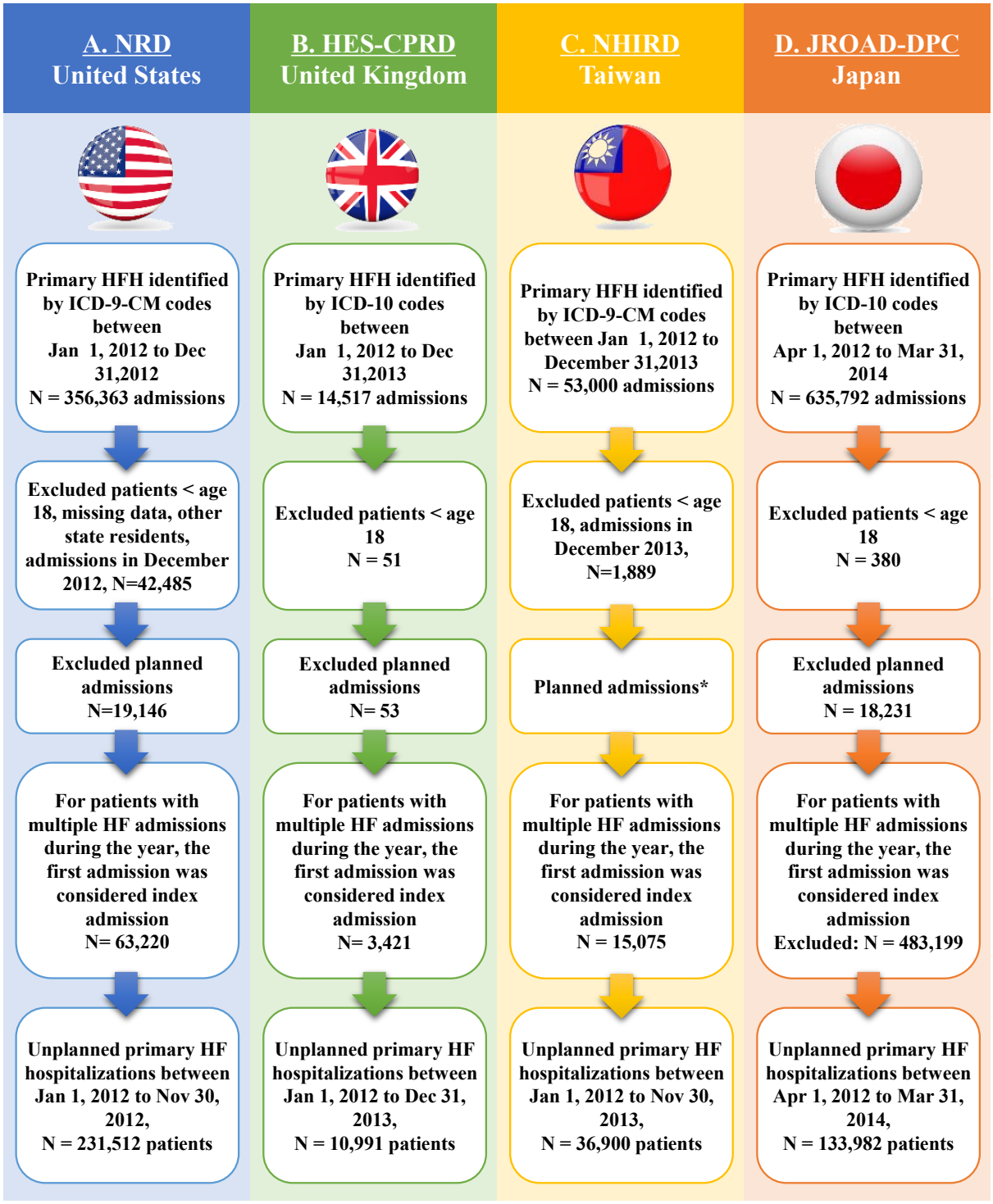
RESULTS

3.1.6 Differences in patient characteristics

I identified 231,512, 10,991, 36,000 and 133,982 eligible patients who had unplanned primary hospitalisations for HF in the US, UK, Taiwan, and Japan, respectively **(Figure 3.1)**. The baseline characteristics of patients with HFH across the countries are outlined in **Table 3.2** with wide variation in comorbidities. The mean age of patients in the study sample were 73, 79, 74 and 79 years in the US, the UK, Taiwan, and Japan, respectively. In the UK and Japan, patients aged >75 years comprised a much greater proportion of HFH compared to the US and Taiwanese population **(Table 3.2 and Figure 3.2).**

Taiwanese HF patients had the highest prevalence of CAD, DM and HTN (CAD 73%, DM 56.3%, HTN 90%) with lowest prevalence in Japanese HF patients (CAD 34.2%, DM 23.6%, HTN 56.2%). Taiwanese HF patients also had the highest rates of non-cardiac comorbidities including chronic liver disease, chronic lung disease, and chronic anaemia. In contrast, Western HF populations had higher rates of obesity (US 18%, UK 10.8%, Taiwan 1.4%, Japan 0.1%) and CKD (US 40.1%, UK 33.9%, Taiwan 19.2%, Japan 12.4%). A significantly higher proportion of patients in the US (26.7%) and UK (23.6%) were discharged within 24 hours of admission compared to Japan (5.5%) and Taiwan (2.1%) indicative of varying severity, practice patterns, thresholds for HFH and discharge across these regions.

Figure 3.1. Flow Diagram for Identifying Study Population in the US, UK, Taiwan, and Japan



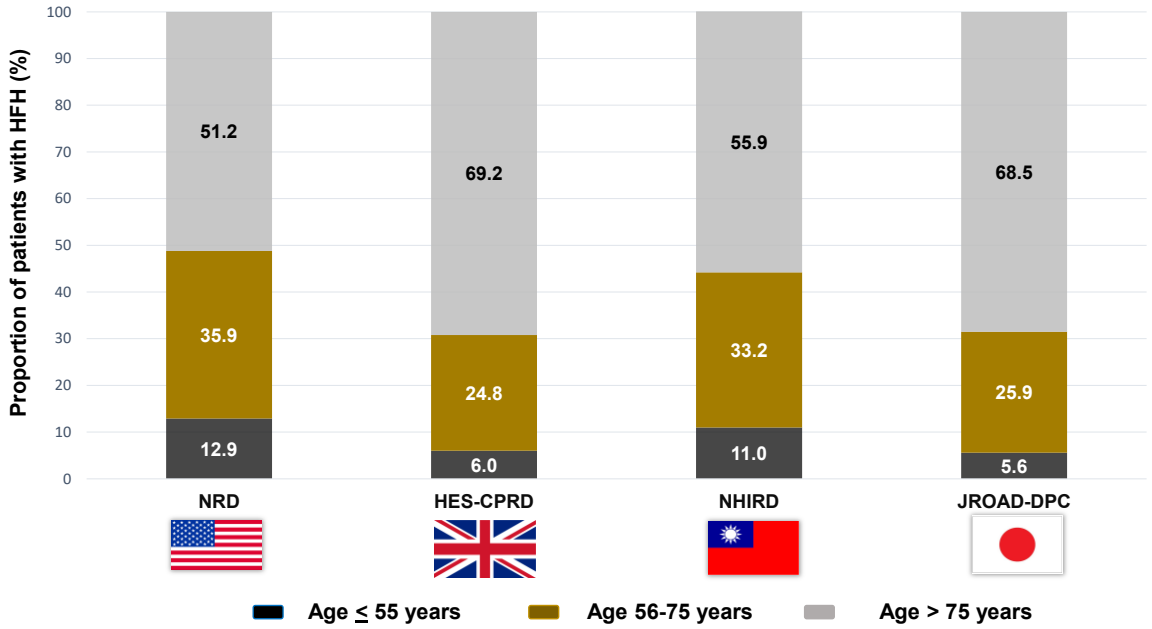
NRD: National Readmissions Database; HES: Hospital Episode Statistics; CPRD: Clinical Practice Research Datalink; NHIRD: National Health Insurance Research Database; JROAD-DPC: Japanese Cardiovascular Administrative Database-Diagnosis Procedure Combination; HFH: Heart Failure Hospitalisation

Table 3.2 Baseline Characteristics of Patients with HF Hospitalisation

Variable	NRD United States (n = 231,512)	HES-CPRD United Kingdom (n = 10,991)	NHIRD Taiwan (n = 36,900)	JROAD-DPC Japan (n = 133,982)
Mean age in years	73.1±14.1	78.8±12.9	74 ± 11.9	78.7±12.5
Age, n (%)				
18-35	2,802 (1.2)	62 (0.6)	426 (1.2)	793 (0.6)
36-45	7,083 (3.1)	146 (1.3)	1.077 (2.9)	2,212 (1.6)
46-55	20,091(8.6)	454 (4.1)	2,542 (6.9)	4,444 (3.3)
56-65	35,431 (15.3)	870 (7.9)	5,122 (13.9)	12,092 (9.0)
66-75	47,678 (20.6)	1,856 (16.9)	7,120 (19.3)	22,613 (16.9)
76-85	64,756 (28.0)	3,812 (34.6)	12,558 (34.0)	47,943 (35.8)
>85	53, 760 (23.2)	3,791 (34.5)	8,055 (21.8)	43,885 (32.8)
Female sex, n (%)	116,066 (50.1)	5,665 (48.5)	18,735 (50.8)	66,424 (49.6)
Comorbidities, n (%)				
Coronary artery disease	127,533 (53.2)	4,329 (39.4)	27,773 (75.3)	45,802 (34.2)
Atrial fibrillation	97,173 (40.6)	3,640 (33.1)	13,652 (37.0)	40,472 (30.2)
Diabetes mellitus	102,409 (44.1)	3,076 (28.0)	20,785 (56.3)	31,627 (23.6)
Hypertension	177,840 (76.8)	6,827 (62.1)	33,214 (90.0)	75,234 (56.2)
Chronic lung disease	83,743 (36.2)	2,691 (24.5)	23,161 (62.8)	10,809 (8.1)
Chronic kidney disease	92,797 (40.1)	3,731 (33.9)	7,201 (19.2)	16,581 (12.4)
Chronic liver disease	6,881 (3.0)	133 (1.2)	12,310 (33.4)	3,949 (3.0)
Peripheral arterial disease	28,127 (12.2)	1,440 (13.1)	7,041 (19.1)	7,093 (5.3)
Obesity	41,589 (18.0)	1,186 (10.8)	524 (1.4)	148 (0.1)
Chronic anaemia	69,853 (30.2)	1,352 (12.3)	12,815 (34.7)	14,220 (10.6)
Pulmonary circulation disorders	878 (0.4)	131 (1.2)	2,258 (6.1)	1,850 (1.4)
Alcohol abuse	7,229 (3.1)	218 (2.0)	535 (1.4)	82 (0.1)
***Discharged within 24 hours of admission, n (%)**	22,764 (10.1)	1,872 (19.1)	421 (1.2)	5,428 (4.5)
***Discharged within 48 hours of admission, n (%)**	63,969 (28.5)	2,591 (26.9)	783 (2.2)	7,351 (6.2)

* *Patient with in-hospital mortality were accounted for while estimating discharges within 24 and 48 hours of admission. Have now mentioned this in the footnote of the table.*

Figure 3.2. Break Up of HF Hospitalisations by Age Groups in the US, UK, Taiwan, and Japan



NRD: National Readmissions Database; HES: Hospital Episode Statistics; CPRD: Clinical Practice Research Datalink; NHIRD: National Health Insurance Research Database; JROAD-DPC: Japanese Cardiovascular Administrative Database-Diagnosis Procedure Combination; HFH: Heart Failure Hospitalisation

3.1.7 Length of hospital stay and healthcare resource utilisation during index hospitalisation

The US patients with HFH had the shortest stay (median LOHS: 4 days, 25th to 75th percentile: 2-6 days), whereas HF admissions in UK (median LOHS: 7 days, 25th to 75th percentile: 3-15 days), Taiwan (median LOHS: 9 days, 25th to 75th percentile: 4-10 days), and Japan (median LOHS: 17 days, 25th to 75th percentile: 10-28 days), were characterised by longer hospital stays **(Figure 3.3)**. The proportion of patients with HFH receiving diagnostic procedures including coronary angiogram and right heart catheterisation during hospitalisation were the highest in Japan (CAG 20.7%; RHC 11.9%) and the lowest in the UK (CAG 4.3%; RHC 0.2%). Similar trends were observed in the use of mechanical ventilation, invasive and non-invasive, and mechanical hemodynamic support, which are surrogate markers of HF severity at the time of admission. The utilisation of other common cardiovascular procedures during HFH such as coronary revascularisation: percutaneous coronary intervention and coronary artery bypass grafting; device implantations: Implantable Cardioverter Defibrillation, Cardiac Resynchronisation Therapy and Pacemakers; and ablations: ablation and cardioversion for atrial and ventricular arrythmias, during index hospitalisation are outlined in **Table 3.3**. In general, HRU during index hospitalisation was the highest in Japan and the lowest in the UK.

Figure 3.3: Length of hospital stay during index hospitalisation in days, (median, 25-75 IQR) in the US, UK, Taiwan, and Japan

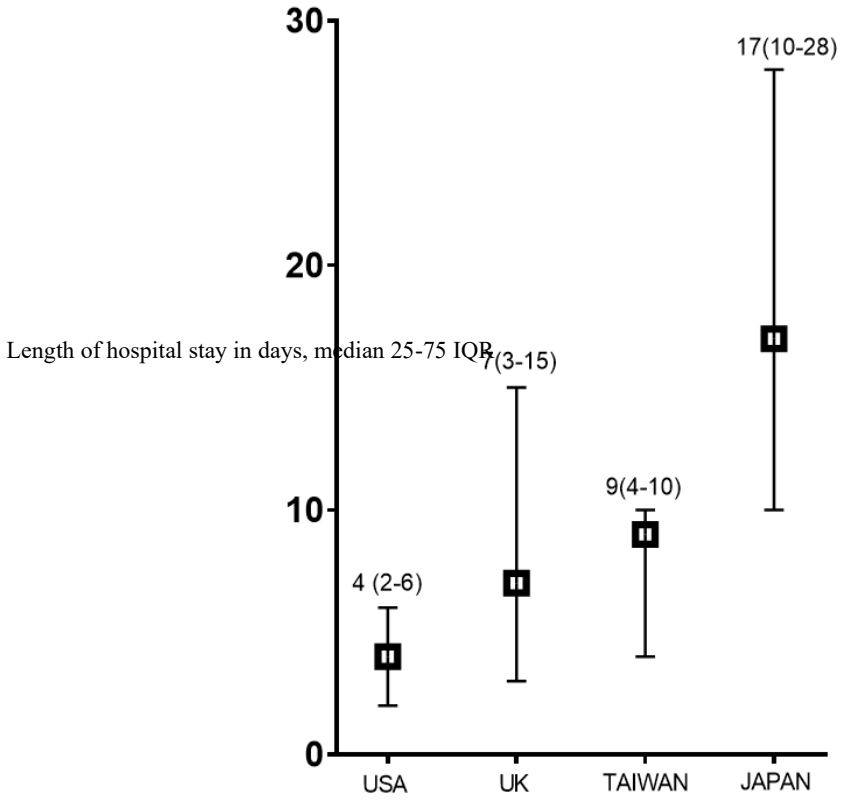


Table 3.3 Healthcare Resource Utilisation during Hospital Stay

Variable	NRD United States (n = 231,512)	HES-CPRD United Kingdom (n = 10,991)	NHIRD Taiwan (n = 36,900)	JROAD-DPC Japan (n = 133,982)
In-hospital procedures, n (%)				
Coronary angiogram	17,583 (7.3)	474 (4.3)	3,818 (10.3)	27,785 (20.7)
Right heart catheterisation	9,634 (4.0)	16 (0.2)	637 (1.7)	15,877 (11.9)
****Mechanical ventilation**	20,852 (9.0)	594 (5.4)	2,772 (7.5)	24,852 (18.6)
***** Device implantation**	5,374 (2.2)	308 (2.8)	319 (0.9)	3,300 (2.5)
Coronary Revascularisation	2,941 (1.2)	63 (0.6)	1,232 (3.3)	7,284 (5.4)
PCI	2,211 (1.0)	51 (0.5)	1,114 (3.0)	6,517 (4.9)
CABG	730 (0.3)	12 (0.1)	118 (0.3)	767 (0.6)
Ablations / Cardioversion	2,869 (1.2)	52 (0.53)	121 (0.3)	4,396 (3.3)
Cardioversion	2,342 (1.0)	49 (0.5)	101 (0.3)	3,729 (2.8)
Ablations for atrial or ventricular arrhythmias	525 (0.2)	3 (0.03)	20 (0.1)	667 (0.5)
****** Mechanical hemodynamic support**	1,137 (0.4)	23 (0.2)	164 (0.4)	2,828 (2.1)

PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting

*NRD: National Readmissions Database; HES: Hospital Episode Statistics; CPRD: Clinical Practice Research Datalink; NHIRD: National Health Insurance Research Database; JROAD-DPC: Japanese Cardiovascular Administrative Database-Diagnosis Procedure Combination; HFH: Heart Failure Hospitalisation

**Mechanical ventilation included both non-invasive and invasive ventilation.

***Device implantations included permanent pacemaker, implantable cardioverter defibrillator and cardiac resynchronisation therapy implantations.

****Mechanical hemodynamic support was defined as the use of either intra-aortic balloon pump, percutaneous ventricular assisted device or extracorporeal membrane oxygenation in patients not undergoing cardiac surgery

3.1.8 Threshold for heart failure hospitalisation across the UK, US, Taiwan, and Japan

The proportion of HF hospitalisations per 100,000 people varied widely across the 4 countries. This was calculated using the total population size and estimated prevalence of HF in 2012 in respective countries using published literature. US had the highest number of HFHs per 100,000 people for the study period (225/100,000) while Taiwan had the highest threshold for HFH among the four countries (115/100,000) **(Table 3.4).** HFH per 100,00 people in the UK and Japan were 180/100,000 and 157/100,000 respectively.

Table 3.4: Estimates of heart failure hospitalisations per 100,000 people (4,103–105)

Country	Population in 2012 (in million)	Total HF admissions/year 2012 (estimates)	Prevalence of HF (estimates)	HF admissions /100,000 in 2012
England and Wales**	56.5	~103,000	~1.6%	180
United States	314	~700,000	~2.4%	225
Taiwan	23	~26,500	~2.4%	115
Japan ***	127	~200,000	N/A	157

HF = heart failure.

*Age-sex standardised.

** Data obtained from https://www.bhf.org.uk/for-professionals/press-centre/facts-and-figures

*** There are no population-based studies estimating the nationwide prevalence of HF in Japan

**** The estimates of HF admissions per year (2012) were derived from my analyses using the nationally representative datasets in the US, England & Wales, and Taiwan. I used previously published data for estimates of HF admissions/year in Japan (105)

DISCUSSION

To my knowledge this is the first international comparative study using nationally representative electronic and administrative healthcare records providing vital insights into the epidemiological differences in patient characteristics, length of hospital stays, and healthcare resource utilisation of patients hospitalised for HF in the US, UK, Taiwan, and Japan.

3.1.9 Major findings

The major findings of this chapter could be summarised as follows

i) There was marked heterogeneity in comorbidities among patients hospitalised for HF in the UK, US Taiwan, and Japan.
ii) HF admissions in the US had the shortest median length of hospital stay while UK, Taiwan, and Japanese HF hospitalisations where characterised by progressively longer stays.
iii) Healthcare resource utilisation during index hospitalisation was highest in Japan and lowest in the UK.
iv) Threshold for HFH was the lowest in US and highest in Japan.

3.1.10 Heterogeneities in baseline characteristics

The mean age of Asian patients in this study was over a decade higher compared to the mean age of Asian HFH patients (especially Taiwan) in the ADHERE-Asia Pacific and REPORT-HF registries, and Asian HF patients enrolled in the PARADIGM-HF and ATMOSPHERE trials (17,20,33). A considerably higher proportion of elderly patients accounted for HF admissions in the Asian countries compared to their Western counterparts **(Figure 3.2)**. The reasons for this could be manifold.

i) Firstly, a substantially higher proportion of elderly population, due to higher life expectancy, in countries like Japan compared to the Western countries could partly explain my observations (106,107).
ii) Second, the threshold to admit elderly HF patients may be different across countries due to the disparities in the infrastructure for elderly care in the community (107,108).
iii) Thirdly, the prevalence of obesity, a common risk factor for HF in the young – especially HF with preserved ejection fraction (HFpEF), is higher in the West (compared to the East) plausibly contributing to a higher proportion of young patients with HFH as opposed to elderly patients in Asia, who are more predisposed to senescent and comorbidity driven HFpEF (38,109).
iv) Finally, patients in Japan and Taiwan may be developing HF much later in their life compared to the US and the UK.

This study confirms previous reports of high DM prevalence despite a near absence of overt obesity in Asian HF patients, unlike the western HF population (38,110). This analyses also revealed significant diversity in the prevalence of certain cardiac and non-cardiac comorbidities within the Asian population (Japan vs Taiwan), indicating that Asian HF patients are not necessarily a single homogenous phenotype. In contrast to the Japanese patients, Taiwanese patients had the highest prevalence of risk factors for HF (HTN, DM, CAD) among other non-cardiac comorbidities including chronic lung (due to high rates of smoking in Taiwan) and liver disease (related to increased prevalence of hepatitis B and hepatitis C in Taiwan) (111–113).

3.1.11 Differences in length of hospital stay and healthcare resource utilisation

To my knowledge, this is the first study to compare procedural utilisation in patients with HFH using equivalent procedural codes (i.e., individual matching of procedural codes across different countries) in large nationally representative cohorts. Notably, despite having the lowest prevalence of CAD among the 4 countries, almost 20% of patients with HFH in Japan had in-patient coronary angiograms. This was followed by Taiwan where 10% of the HF patients received coronary angiograms during index hospitalisation. Despite ischemia being the most common cause for HF in the West, only a small fraction of the patients with HFH in the US (7.3%) and the UK (4.3%) underwent coronary angiograms during index hospitalisation. This could also indicate differences in the mode of ischemia assessment, with more non-invasive assessment of ischemia (e.g., using CT coronary angiography, nuclear testing, or assessment with cardiac magnetic resonance imaging) in the Western countries compared to their counterparts in Japan and Taiwan. However, this study was not designed to address this specific question. Hemodynamic assessment using pulmonary artery catheters was strikingly high in Japan at 12%, while only 0.2% of patients with HFH in the UK received right heart catheterisation (US: 4.0%, Taiwan: 1.7%). There are multiple factors which could have driven the geographic differences in HRU including per capita healthcare expenditure, reimbursement mechanisms, differences in patient characteristics, severity of HF at the time of admission along with varying cultural and practice patterns. These differences in procedural utilisation require further investigation to determine optimal practice patterns by region.

3.1.12 Varying threshold for HFH across different countries

This analysis revealed that a significant proportion of patients hospitalised in the US were discharged within 24 hours of admission, possibly indicating less severe HF admissions than other countries. A much higher proportion of HF hospitalisations per 100,000 people was observed in the US healthcare system compared to other countries, despite a lower estimated HF prevalence than Taiwan and a similar prevalence rate to the UK. (4,26,103,114,115) This potentially signifies a lower threshold for HFH in the US, akin to what has been observed with acute myocardial infarction and stroke in the US(116). The varying thresholds for HFH may be attributable to the differences in healthcare financing and

delivery, medical litigation, earlier identification of HF decompensation, or hospitalisation of less severe HF patients.

3.1.13 Strengths and limitations

Extensive standardisation of diagnosis and procedure codes across countries, such as matching similar DM codes in ICD 9 for US and Taiwan to ICD 10 for Japan and *Read* codes in the UK, or coronary angiogram codes in ICD9 for US, Taiwan, and Japan to OPCS4.6 codes in the UK, was performed by me (cardiologist by training) enabling effective cross-country comparisons of patient characteristics and HRU. To the best of my knowledge, this analysis is the first to compare multiple nationally representative EHR and administrative databases capturing more than 1 million unselected HF hospitalisations, while simultaneously utilising standardised coding algorithms, thereby avoiding significant selection bias.

While my study has several strengths, it does have some important limitations. I was not able to differentiate de novo HF admissions from acute decompensations of chronic HF. Importantly, the first hospitalisation included is the first for the study period and not necessarily the first hospitalisation for the patient however this should not impact the population level estimates of the HF hospitalisation burden across these countries. Direct markers of severity of HF including natriuretic peptides, vital signs at the time of admission, laboratory tests such as serum sodium and creatinine among others, were not available. Another limitation of research using EHR, is the potential for misclassification of diseases as ultimately, I was limited by the clinical judgment of the physician recording the diagnosis. Wherever possible, definitions and algorithms that have been validated in these data sources were preferentially used to identify both the diseases of interest as well as complications. Despite performing extensive coding conversions across these countries, coding patterns could have still been influenced by differences in healthcare reimbursements. Finally, I was not able to present a measure of effect size (p value or standardized difference for differences in baseline characteristics) due to inability to merge data from all 4 countries due to data privacy regulations. Adjusted analyses for mortality were performed by merging individual patient data from the USA with that from the UK and Japan. However, I believe that qualitative assessment of 4 large nationally representative EHR provides key insights into the differences in baseline characteristics of patients hospitalized for heart failure in the real world.

CONCLUDING REMARKS

Among patients hospitalised for HF, there were significant differences in the patient characteristics, length of hospital stays, threshold for hospitalisation and healthcare resource utilisation between the UK, US, Taiwan, and Japan. My results provide hypothesis generating findings into the quality and efficiency of healthcare for patients with HFH and a basis for future cross-country research in chronic HF using geographically representative real-world healthcare records. The next chapter of my thesis elaborates the clinical outcomes, including mortality and readmissions, of patients with HFH across these 4 countries.

Chapter 4: **Transcultural lessons in the management of Heart Failure TRANSMED HF: comparison of mortality and readmissions among patients hospitalised for HF in UK, US, Taiwan, and Japan**

PREAMBLE

Previous studies using registries from the UK and Japan revealed that while existing mortality prediction models predominantly derived from the US population provided fairly good discrimination for mortality amongst patients with heart failure hospitalisation (HFH) in the UK, they overestimated mortality in Japanese patients with HFH (116). Earlier studies from global multi-centre HF clinical trials databases and from patient registries have shown that short and long-term mortality rates for patients with heart failure hospitalisation (HFH) were dissimilar across countries (2,19). It remains unclear whether such regional differences are related to selection bias or differing aetiologies and practice pattern across diverse health-care systems. In this chapter, I report the differences in outcomes and 30-day readmissions using nationally representative data across the Western and Asian countries. Additionally, I evaluated the patient specific factors predicting mortality and readmission across the 4 countries.

EVIDENCE BEFORE THE STUDY

I searched PUBMED (January 1, 2000 to December 31st, 2018) using the Medical Subject Headings (MeSH) terms “heart failure” or “acute heart failure” or “hospitalised heart failure” or “heart failure hospitalisation” and “Asia” or “Asians” or “United Kingdom” or “United States” or “Japan” or “Japanese” or “Taiwan” or “Taiwanese” or “North America” or “mortality” or “in-hospital mortality” or “readmissions” with no language restrictions. I also identified publications using searches on Google Scholar and via citations in peer-reviewed publications. Previous reports have primarily included samples from clinical trials or patient registries. There were no reports on standardised or adjusted mortality based on individual patient level data from nationally representative EHR across countries.

METHODS

4.1.1 Data sources

I used the same data sources used for *specific aim 1*, namely, the CPRD/HES from UK, NRD from the US, NHIRD from Taiwan and JROAD-DPC from Japan. The methodology of data extraction, strengths and limitations of the individual datasets have been explained in Chapter 2 of this thesis.

4.1.2 Study population

Patients aged 18 years or older hospitalised with HF between 2012 to 2014 from the UK, Taiwanese, and Japanese cohorts **(Figure 3.1 and Table 3.1)** were included in the study. Patients hospitalised with HF between January and December 2012 were included from the US cohort as the follow-up data was only available for this period. Patients with missing data on age, gender, and elective admissions were excluded from the final analyses **(Figure 3.1)**. The specifics of case ascertainment i.e., identification of HF patient population, have been outlined in section 3.3.2

4.1.3 Outcomes of interest

The main outcomes of interest are differences in crude, standardised and adjusted rates of in-hospital mortality and 30-day readmissions between the 4 countries. Factors associated with in-hospital mortality and 30-day readmissions in each country.

4.1.4 Statistical analyses

All analyses were performed with STATA MP64 version 15 (StataCorp, College Station, TX). Patient characteristics were presented as mean ± standard deviations (SD) when normally distributed, and as medians and interquartile (IQR) ranges when not normally distributed.

4.1.4.1 Mortality analyses

I compared in-hospital mortality rates across all countries using the following methods

i) Crude in-hospital mortality rates per 100 hospitalisations for HF were calculated for each country.

ii) Standardised mortality rates were computed individually for each country on the basis of standard population distribution of age and sex in each country.

iii) Direct standardised mortality rates were also calculated for UK, Taiwan, Japan and US using the standard population distribution for age in the US in 2010 (direct method of standardisation using US as the standard population). Direct standardisation for age, using US as the reference population, was performed so that the mortality rate refers to a rate relative to a 'standard' population. When mortality rates in US, UK, Taiwan and Japan are standardised to a reference population (US age distribution for 2010), it makes it possible

to compare the mortality rates across countries by accounting for differences in age structures across the countries.

iv) Finally, analyses were performed by merging US data individually with the UK and the Japanese data. Merging of US data with Taiwan data was not performed due to data privacy regulations. Multivariable logistic regression and inverse probability treatment weighting (IPTW) propensity score analyses were employed to calculate in adjusted in-hospital mortality for UK and Japan patients with HFH using US patients with HFH as the reference population. The model was adjusted for age, sex, relevant co-morbidities including, DM, CKD, AF, CAD, PAD, HTN, obesity, chronic lung and liver disease, anaemia, and pulmonary circulation disorders. The variables used in the multivariable regression model were used for the IPTW analyses. Age, sex, relevant co-morbidities including, Diabetes mellitus, chronic kidney disease, atrial fibrillation, coronary artery disease, hypertension, chronic lung disease, chronic liver disease, anemia, peripheral artery disease and pulmonary circulation analyses were used for the propensity score calculation (1/p). Standardized difference was used to estimate balance of individual covariates before and after propensity matching and was less than 10%.

4.1.4.2 Factors predicting in-hospital mortality and 30-day readmissions across the countries

To identify patient characteristics that predict a high probability of in-hospital mortality and 30-day all-cause readmission within each country, I performed logistic regression analysis and co-morbidity specific adjusted odds ratio (OR) for all 4 (USA, UK, Taiwan, and Japan) HF cohorts. The model was adjusted for age, sex, CAD, PAD, AF, DM, HTN, chronic lung disease, CKD (codes specific for CKD stage 3 and above), chronic liver disease, obesity, chronic anaemia, and pulmonary circulation disorders. Furthermore, adjusted odds for in-hospital mortality and 30-day all-cause readmission stratified by different age categories (18-34, 35-49, 50-74 and over 75 years) were calculated individually for each country. The analyses for readmissions were restricted only to the patients discharged alive.

4.1.4.3 Sensitivity analyses

In addition to the main analyses, 3 sensitivity analyses, defined a priori, were performed to assess the robustness of the results.

i) Patients discharged within 24 hours are likely to have less severe HF and would possibly serve as an indirect method of identifying less severe HF patients at the time of admission. Crude, standardised and adjusted in-hospital mortality rates were computed by excluding patients discharged within 24 hours of admission.

ii) The in-hospital mortality rates were compared by excluding patients receiving major cardiovascular procedures (defined as percutaneous coronary intervention, coronary artery

bypass surgery, implantable cardioverter defibrillator, cardiac resynchronisation therapy and ablations) as it is typical practice in countries like Japan to keep patients in-hospital until all relevant procedures have been performed (to negate the effect of peri-procedural mortality) even if earlier safe discharge would be possible.(2)

iii) Finally, crude, standardised and adjusted in-hospital mortality rates were calculated by excluding patients admitted in the weekends as the weekend healthcare delivery mechanism may be different across countries.

RESULTS

I identified the following eligible patients who had unplanned primary hospitalisations for HF: 10,991 in the UK, 231,512 in the US, 36,900 in Taiwan and 133,982 in Japan. **(Figure 3.1)**

4.1.5 Outcomes; Crude and standardised rates (direct and indirect standardisation) for mortality and 30-day readmissions

The shortest stay for patients with HFH was in the US, whereas UK, Taiwan, and Japan HF admissions had much longer hospital stays **(Figure 3.3)**. The crude in-hospital all-cause mortality rate (per 100 HFH), age and sex standardised in-hospital mortality rate (standardised for age distribution with each country), direct age standardised in-hospital mortality rate (standardised for US age distribution in 2010) and adjusted odds ratio for mortality (for UK and Japan using US as a reference) for each country are described in **Table 4.1 and Figure 4.1.**

Table 4.1 Clinical Outcomes

Variable	NRD US (n = 231,512)	HES-CPRD UK (n = 10,991)	NHIRD Taiwan (n = 36,900)	JROAD-DPC Japan (n = 133,982)
Crude in-hospital mortality, n	7,264	1,350	2,243	15,823
(rate per 100 hospitalisations for HF)	(3.2)	(12.2)	(6.1)	(11.8)
***Age and sex standardised in-hospital mortality, rate per 100 hospitalisations for HF**	1.8	6.7	3.8	7.0
(95% CI)	(1.7-1.9)	(6.6-7.1)	(3.6-3.9)	(6.9-7.2)
Direct age and sex standardisation using United States age distribution for 2010 in-hospital mortality, rate per 100 hospitalisations for HF	1.8	6.4	3.9	6.7
(95% CI),	(1.7-1.9)	(6.1-6.7)	(3.8-4.1)	(6.6-6.8)
30-day all-cause readmission, n	57,880	2,237	8,100	14,055
(%)	(25.8)	(25.1)	(22.0)	(11.9)
30-day HF readmission, n	16,147	486	2,058	5,977
(%)	(7.2)	(5.5)	(5.6)	(5.1)

* *Indirect age and sex standardisation are based on 2010 population in United States and Japan, and 2013 European standardised population for the United Kingdom*

The crude and standardised rates for in-hospital mortality among HHF patients were highest in Japan (crude rates: 11.8 per 100 HFH; standardised rates: 7.0 per 100 HFH; 95% CI: 6.9 - 7.2; direct standardised rates for US age distribution: 6.7 per 100 HFH; 95% CI: 6.6 - 6.8), followed by UK (crude rates: 12.2 per 100 HFH; standardised rates: 6.7 per 100 HFH; 95% CI: 6.6 - 7.1; direct standardised rates for US age distribution: 6.4 per 100 HFH, 95% CI: 6.1 - 6.7), Taiwan (crude rates: 6.1 per 100 HFH; standardised rates: 3.8 per 100 HFH; 95% CI: 3.6 - 3.9; direct standardised rates for US age distribution: 3.9 per 100 HFH; 95% CI: 3.8 - 4.1) and the US (crude rates: 3.2 per 100 HFH; standardised rates 1.8 per 100 HFH; 95% CI: 1.7 - 1.9). Proportion of patients readmitted in 30 days due to any cause

and due to HF were similar in the US, UK, and Taiwanese cohorts (c.22-25%) and much lower in the Japanese HFH patients (12%).

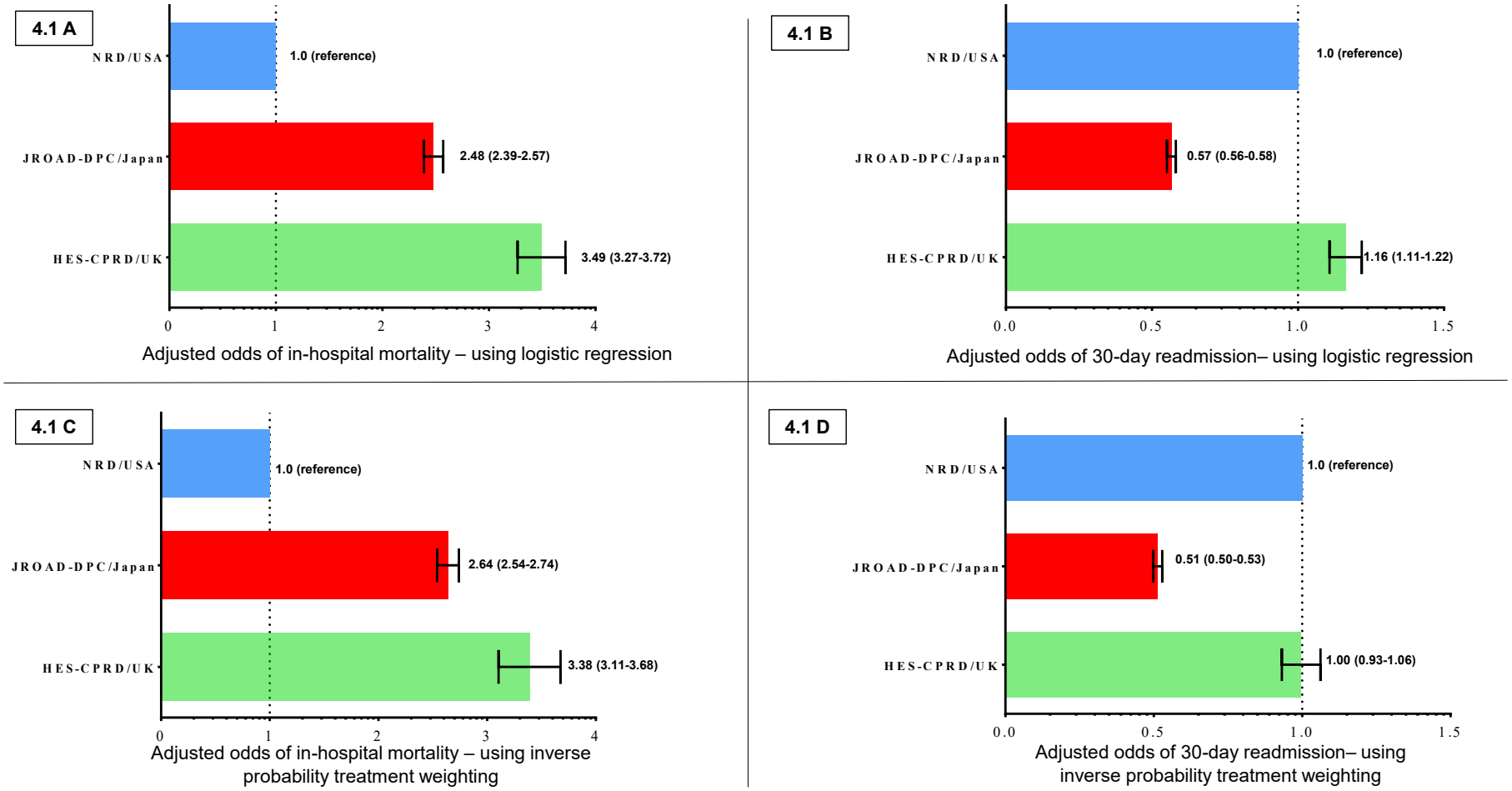
4.1.6 Adjusted odds ratio of in-hospital mortality and 30-day readmissions

Multivariable logistic regression and inverse probability treatment weighting (IPTW) propensity score analyses were used to calculate in adjusted in-hospital mortality for UK and Japan patients with HFH using US patients with HFH as the reference population. The adjusted odds ratio (OR) of in-hospital mortality was the highest in the UK using both logistic regression (UK: OR 3.49, 95% CI: 3.27-3.72; Japan: OR 2.48, 95% CI: 2.39-2.57; US: reference) and IPTW (UK: OR 3.38, 95% CI: 3.11-3.68; Japan: OR 2.48, 95% CI: 2.39-2.57; US: reference) **(Figures 4.1 A&C)**. The adjusted odds for 30-day readmission were similar in the US and the UK and lower in Japan (Logistic regression - UK: OR 1.16, 95% CI: 1.11-1.22; Japan: OR 0.57, 95% CI: 0.56-0.58; US: reference) and IPTW (UK: OR 1.00, 95% CI: 0.93-1.06; Japan: OR 0.51, 95% CI: 0.50-0.53; US: reference) **(Figures 4.1 B&D)**

4.1.7 Patient specific factors predicting in-hospital mortality and 30-day readmissions

In general, older age (older than 65 years) and chronic kidney disease (CKD) were the most important predictors of in-hospital mortality in all four countries **(Figure 4.2).** The association between AF and in-hospital mortality was observed only in the American and the Japanese HF patient population. Patients with history of stable CAD and obesity had lower odds for in-hospital mortality **(Figure 4.2).** The relationship between patient specific factors and 30-day readmissions were largely similar in the British, American, Taiwanese, and Japanese HFH **(Figure 4.3).** The adjusted odds for 30-day readmissions were lower in the advanced age group (older than 75 years) compared to the other age groups in all countries, except Taiwan. The adjusted odds for in-hospital mortality and 30-day readmissions stratified by different age groups are outlined in **Table 4.2.**

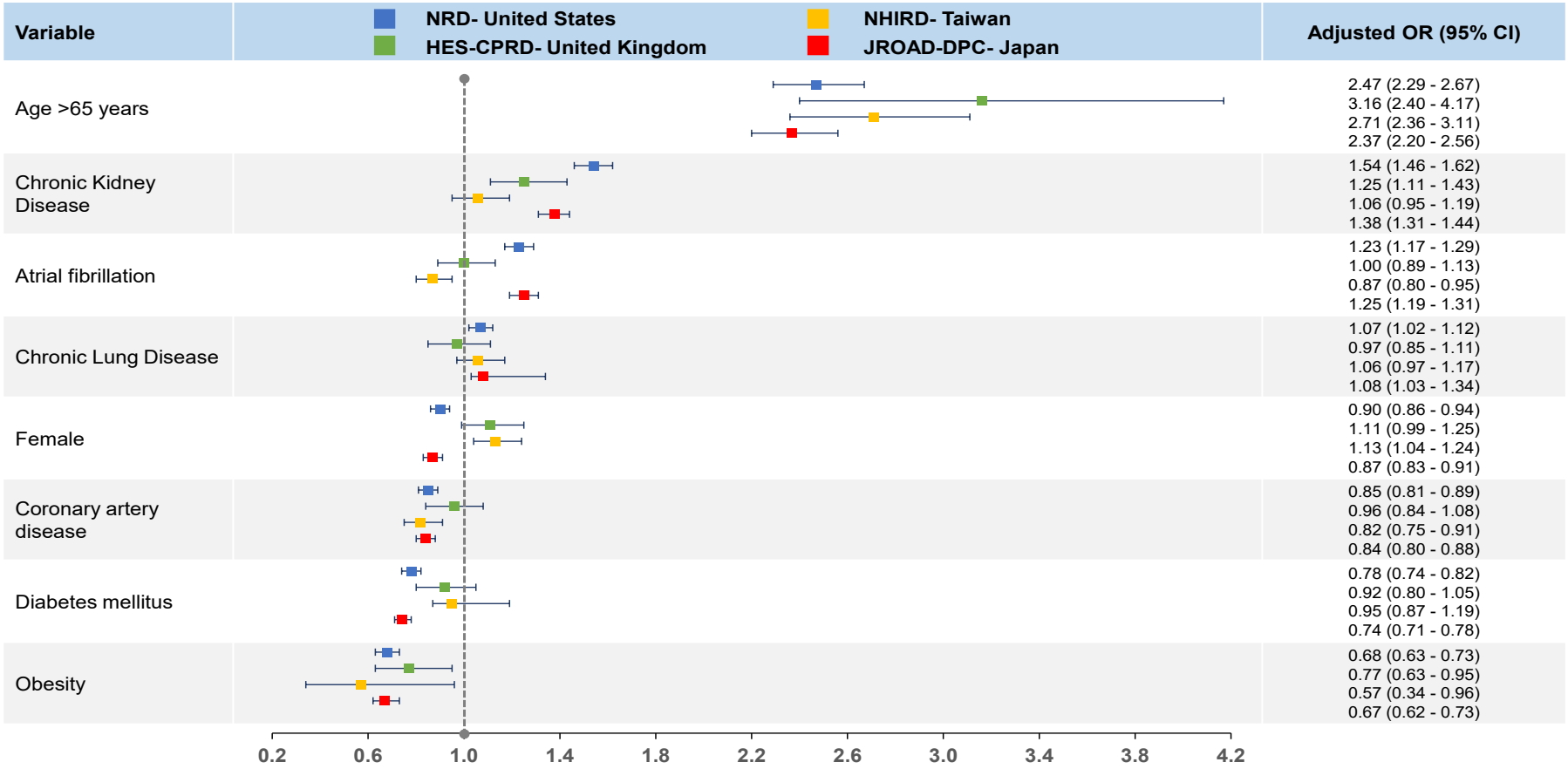
Figure 4.1. (A-B) Adjusted Differences In-hospital Mortality and (C-D) 30-day Readmissions in the UK and Japan Using Multivariate Logistic Regression and Inverse Probability Treatment Weighting (US as the Reference Population)



NRD: National Readmissions Database; HES-CPRD: Hospital Episode Statistics-Clinical Practice Research Datalink; JROAD-DPC: Japanese Registry of All cardiac and vascular Diseases - Diagnosis Procedure Combination; HFH: Heart Failure Hospitalisation; IPTW: inverse probability treatment weighting.

Model was adjusted for age, sex, relevant co-morbidities including, DM, CKD, AF, CAD, PAD, HTN, obesity, chronic lung and liver disease, anaemia, and pulmonary circulation disorders

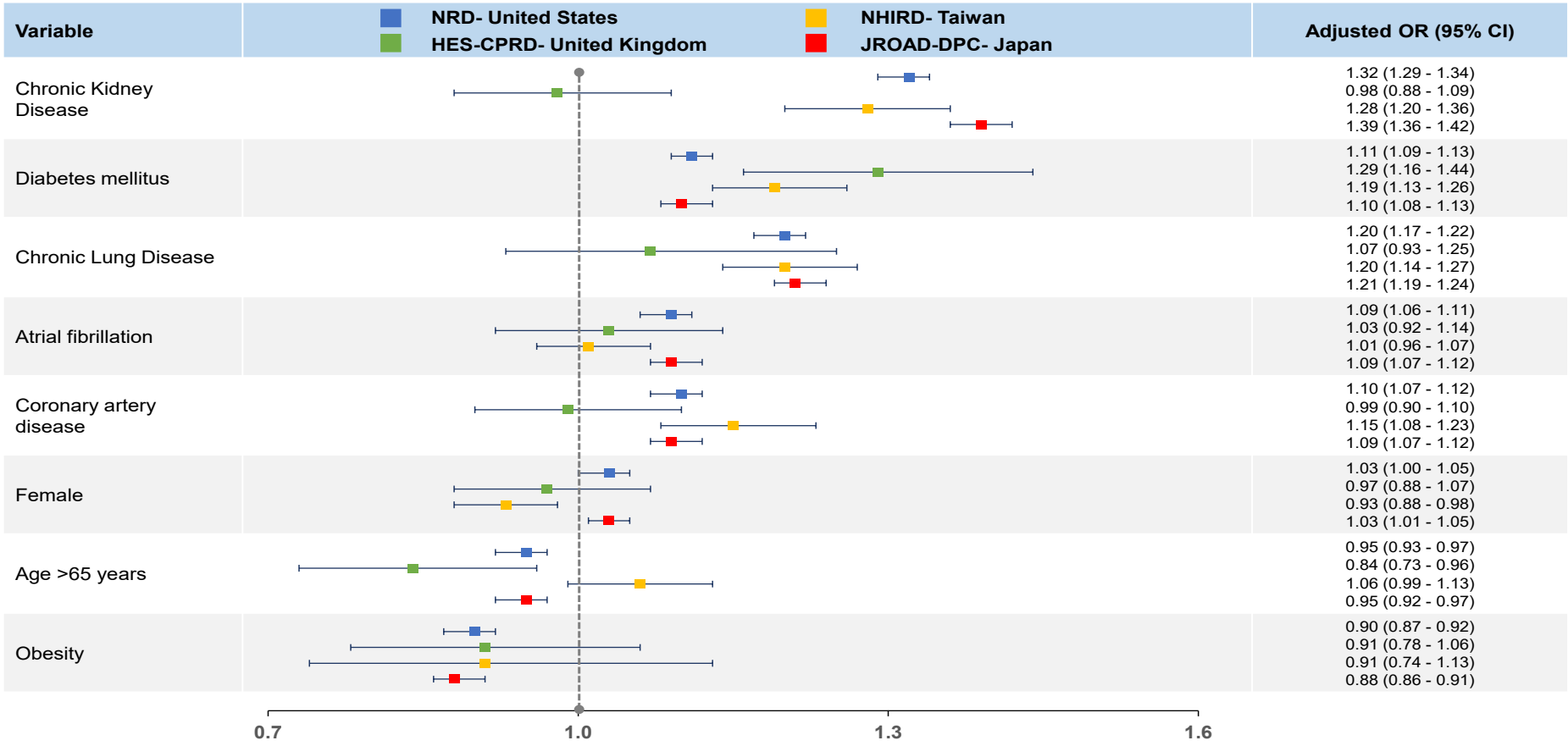
Figure 4.2 Factors Predicting In-hospital Mortality in the US, UK, Taiwan, and Japan



Model was adjusted for age, sex, relevant co-morbidities including, DM, CKD, AF, CAD, HTN, obesity, chronic lung and liver disease, anaemia, PAD, and pulmonary circulation disorders

NRD: National Readmissions Database; HES-CPRD: Hospital Episode Statistics-Clinical Practice Research Datalink; JROAD-DPC: Japanese Registry Of All Cardiac And Vascular Diseases - Diagnosis Procedure Combination; HFH: Heart Failure Hospitalisation;

Figure 4.3 Factors Predicting 30-day readmissions in the US, UK, Taiwan, and Japan.



Model was adjusted for age, sex, relevant co-morbidities including, DM, CKD, AF, CAD, HTN, obesity, chronic lung and liver disease, anaemia, PAD, and pulmonary circulation disorder

Table 4.2 Adjusted Odds of In-hospital mortality and 30-day All-cause Readmission Stratified Across Age Categories

Variable	NRD United States (n = 231,512)	HES-CPRD United Kingdom (n = 10,991)	NHIRD Taiwan (n = 36,900)	JROAD-DPC Japan (n = 133,982)
Age categories for in-hospital mortality, OR (95% CI)				
18-34	Reference	Reference	Reference	Reference
35-49	0.76 (0.53 - 1.08)	0.47 (0.14 - 1.60)	0.60 (0.33 - 1.09)	0.85 (0.66 - 1.08)
50-74	1.48 (1.08 - 2.02)	0.98 (0.35 - 2.75)	0.90 (0.53 - 1.53)	1.60 (1.28 - 2.00)
≥75	3.07 (2.25 - 4.20)	2.43 (0.88 - 6.71)	2.06 (1.21 - 3.49)	3.64 (2.92 - 4.53)
Age categories for 30-day all-cause readmission, OR (95% CI)				
18-34	Reference	Reference	Reference	Reference
35-49	0.82 (0.74 - 0.89)	0.64 (0.36 - 1.15)	1.10 (0.81 - 1.50)	0.78 (0.71 - 0.86)
50-74	0.82 (0.75 - 0.90)	0.49 (0.29 - 0.83)	1.16 (0.87 - 1.56)	0.83 (0.76 - 0.91)
≥75	0.76 (0.71 - 0.85)	0.45 (0.27 - 0.76)	1.25 (0.94 - 1.68)	0.77 (0.71 - 0.85)

The above-mentioned estimates are adjusted for sex, relevant co-morbidities including, DM, CKD, AF, CAD, HTN, obesity, chronic lung and liver disease, anaemia, PAD, and pulmonary circulation disorder

NRD: National Readmissions Database.
HES: Hospital Episode Statistics.
CPRD: Clinical Practice Research Datalink.
NHIRD: National Health Insurance Research Database.
JROAD-DPC: Japanese Cardiovascular Administrative Database-Diagnosis Procedure Combination.
HFH: Heart Failure Hospitalisation

4.1.8 Sensitivity analyses

Sensitivity analyses were performed for each country by excluding patients discharged within 24 hours, patients who underwent major cardiovascular procedures during hospitalisation and those admitted over the weekends. All three sensitivity analyses yielded results similar to the original analyses. The results of the sensitivity analyses for crude, standardised and adjusted odds for in-hospital mortality are outlined in **Tables 4.3, 4.4 and 4.5.**

Table 4.3 Sensitivity Analyses Excluding Patients Discharged Within 24 Hours

Variable	NRD United States	HES-CPRD United Kingdom	NHIRD Taiwan	JROAD-DPC Japan
Number, n	209,551	9,139	36,479	130,833
Crude in-hospital mortality, n (rate per 100 hospitalisations for HF)	6,100 (2.9)	1,178 (12.9)	2,243 (6.1)	13,107 (10.0)
***Age standardised in-hospital mortality, rate per 100 hospitalisations for HF (95% CI)**	1.7 (1.6-1.7)	7.4 (6.9-7.8)	4.0 (3.8-4.1)	5.0 (4.9-5.1)
Direct age standardisation using United States age distribution for 2010 in-hospital mortality, rate per 100 hospitalisations for HF (95% CI),	1.7 (1.6-1.7)	7.1 (6.7-7.5)	3.8 (3.6-4.0)	4.6 (4.5-4.7)
****Adjusted odds for mortality, OR (95%CI) (LR)**	Reference	4.1 (3.8-4.4)	N/A	2.4 (2.3-2.5)
****Adjusted odds for mortality, OR (95%CI) (IPW)**	Reference	3.8 (3.4-4.1)	N/A	2.52 (2.4-2.6)

Values are n (%) or median (interquartile range), unless otherwise indicated.
OR: Odds Ratio.
LR: Logistic Regression.
IPW: Inverse Probability Weighting.
N/A: Not Available
HFH: Heart Failure Hospitalisation

Age standardised rates are based on 2010 population in United States and Japan, and 2013 European standardised population for the United Kingdom; Direct age standardisation was performed for all countries using 2010 age distribution in the United States

Model was adjusted for age, sex, relevant co-morbidities including, DM, CKD, AF, CAD, HTN, obesity, chronic lung and liver disease, anaemia, PAD, and pulmonary circulation disorder

NRD: National Readmissions Database; HES: Hospital Episode Statistics; CPRD: Clinical Practice Research Datalink; NHIRD: National Health Insurance Research Database; JROAD-DPC: Japanese Cardiovascular Administrative Database-Diagnosis Procedure Combination

Table 4.4 Sensitivity Analyses Excluding Patients with Major Cardiovascular Procedures*

Variable	NRD United States	HES-CPRD United Kingdom	NHIRD Taiwan	JROAD-DPC Japan
Number, n	223,462	10,889	36,357	123,229
Crude in-hospital mortality, n (rate per 100 hospitalisations for HF)	7,048 (3.2)	1,348 (12.4)	2,148 (5.9)	15,199 (12.3)
Median length of hospital stay, days	4 (2 - 6)	7 (3 - 15)	N/A	17 (11 - 27)
****Adjusted odds for mortality, OR (95%CI) (LR)**	Reference	3.5 (3.3 - 3.8)	N/A	2.5 (2.4 - 2.6)
****Adjusted odds for mortality, OR (95%CI) (IPW)**	Reference	3.3 (3.0 - 3.6)	N/A	2.8 (2.6 - 2.9)

Values are n (%) or median (interquartile range), unless otherwise indicated.
OR: Odds Ratio.
LR: Logistic Regression.
IPW: Inverse Probability Weighting.
N/A: Not Available
Other abbreviations as in **Table 4.3**

Major cardiovascular procedures are defined as percutaneous coronary intervention, coronary artery bypass surgery, implantable cardioverter defibrillator, cardiac resynchronisation therapy, ablations, and cardioversions.

Model was adjusted for age, sex, relevant co-morbidities including, DM, CKD, AF, CAD, HTN, obesity, chronic lung and liver disease, anaemia, PAD, and pulmonary circulation disorder

Table 4.5 Sensitivity Analyses Excluding Patients Admitted in the Weekend

Variable	NRD United States	HES-CPRD United Kingdom	JROAD-DPC Japan
Number, n	176,589	8,747	107,818
Crude in-hospital mortality, n (rate per 100 hospitalisations for HF)	5,467 (3.1)	1,053 (12.0)	12,267 (11.4)
****Adjusted odds for mortality, OR (95%CI) (LR)**	Reference	3.4 (3.2-3.7)	2.4 (2.3-2.5)

Values are n (%) or median (interquartile range), unless otherwise indicated.
OR: Odds Ratio.
LR: Logistic Regression.
IPW: Inverse Probability Weighting.
N/A: Not Available
Other abbreviations as in **Table 4.3**

Model was adjusted for age, sex, relevant co-morbidities including, DM, CKD, AF, CAD, HTN, obesity, chronic lung and liver disease, anaemia, PAD, and pulmonary circulation disorder

Data on weekend admissions was not available in Taiwan

DISCUSSION

This international comparative study using nationally representative real-world data provides vital insights into the clinical outcomes of patients hospitalised for HF in US, UK, Taiwan, and Japan.

4.1.9 Major findings

The major findings of this study could be summarised as follows:

i) This analysis revealed that HFH patients in the US had the lowest crude, direct standardised and adjusted in-hospital mortality rates, whereas Japan and the UK were among the highest, with Taiwan falling in between
ii) The crude, direct standardised and adjusted 30-day readmission rates in patients with HFH were higher in the Western countries compared to the Asian healthcare systems
iii) Factors predicting in-hospital mortality and 30-day readmissions were largely similar across the countries. Interestingly, older patients (older than 75 years) were less likely to get readmitted within 30 days of discharge in all countries except for Taiwan

4.1.10 Transcultural differences in clinical outcomes

The differences among the in-hospital mortality rates across the four countries could be due to myriad reasons. Whether this difference represents a younger population of obese HF patients being admitted in the US, differences in thresholds for hospitalisation, variations in practice patterns, length of hospital stays, procedural utilisation, or approach to out of hospital care (nursing facility, home care and end of life care) is unclear.

i) The higher in-hospital mortality rates observed in UK and Japan, along with a higher proportion of patients requiring mechanical ventilation and mechanical hemodynamic support (both indirect markers of HF severity), probably reflects more severe HFH or more patients with advanced HF in these countries compared to the others (108,116,117). The higher in-hospital mortality rates could also be driven by a higher threshold for admissions, possibly driven by patient behaviour and/or institutionalised practice patterns within their respective healthcare systems, resulting in patients being admitted at an advanced phase of decompensation.
ii) My analyses revealed a much higher proportion of HFH per 100,000 people in the American healthcare system compared to the other countries, despite a lower estimated HF prevalence than Taiwan and similar prevalence rates to the UK. This might point to a much lower threshold for HFH in the US and plausibly hospitalisation of less sick patients, further evidenced by a higher proportion of patients being discharged within 24 hours of admission

and a much lower need for mechanical ventilation and hemodynamic support in the US. It is imperative to note that the financial incentives institutionalised within the US healthcare system could have also contributed to the lower threshold for hospitalisations (118,119).

iii) In Japan, longer hospital stays may have exposed patients to a prolonged period at risk of cardiac and non-cardiac events, resulting in increased in-hospital mortality.

iv) The results also highlight the complex relationship between in-patient healthcare resource utilisation (HRU) and in-hospital mortality, with both the UK and Japan having higher in-hospital mortality rates, despite the sharp disparities in HRU (highest HRU in Japan and lowest in the UK).

v) Finally, differences in mortality could be partially explained by the differences in the provision of out of hospital care, including community HF services and end of life care, which is crucial in patients with advanced HF (patients at highest risk for in-hospital mortality). In the US, a significant proportion of patients with advanced chronic illness die outside the hospital,(120) whereas end of life care in England and Japan is predominantly hospital centric (121). Wide availability of out of hospital services and the shorter LOHS in the US could be explained by patient preferences, higher per day hospital cost, and the economic pressure to find alternatives to hospitalisation (hospice, home care services and palliative care) (122–124).

4.1.11 Comparison of patient factors predicting mortality and readmissions

Keeping in line with the historical evidence, I observed a strong association between advanced patient age and in-hospital mortality among patients with HFH in all four countries (19,20,125,126). It has been well established that geriatric HF patients often have a wide range of non-cardiac comorbidities including renal dysfunction, chronic lung disease, cognitive impairment, anaemia, and poor functional status (127–131). While these non-cardiac comorbidities are independently associated with adverse outcomes, they can also alter the treatment response to HF in elderly(132–134). This coupled with polypharmacy, unavoidable in the geriatric population, could further alter the biological response to HF therapy(135). The phenotype of the HF patient population, especially the elderly, has changed substantially in the last decade; and a significant proportion of the elderly HFH is attributed to HFpEF, with no effective disease modifying interventions (27). The association between advanced age and in-hospital mortality was consistent with similar OR for HF patient population in all countries, after adjusting for conventional patient-specific risk factors for mortality.

Another patient factor common to all countries was chronic kidney disease, stage 3 and above, which was associated with increased odds for in-hospital mortality. Fonarow GC et al demonstrated using the ADHERE-HF cohort, one of the largest HFH registries, that renal function at admission was one of the

best discriminators between hospital survivors and non-survivors. Renal dysfunction plays an important role in the pathophysiologic progression of HF and may aggravate or trigger an episode of HF, resulting in decompensation and poor overall outcomes (136,137). Additionally, CKD may complicate HF management by increasing the propensity to hyperkalaemia with HF medications, mainly with neurohormonal antagonists(138,139). The phenomenon of the obesity heart failure paradox, i.e., a paradoxically improved survival for patients with obesity, was observed in this study for short term clinical outcomes (in-hospital mortality and 30-day readmissions) regardless of the geographical location. This topic is addressed in length in chapter 6 of this thesis. While previous analysis from large HF registries including the Organised Program To Initiate Lifesaving Treatment In Hospitalised Patients With Heart Failure (OPTIMIZE-HF) cohort revealed no increased risk of in-hospital mortality with DM and CAD (140,141), I observed an inverse association between CAD, DM and in-hospital mortality in all four countries.

Readmissions following HFH is quite common, with 30-day and 6-month readmission rates exceeding 10% and 50% respectively (74,142–144). In this analysis, factors influencing 30-day readmissions were largely uniform across the countries. CKD, chronic lung diseases, DM, AF were particularly associated with an increased risk of 30-day readmissions, while obesity and advanced age were associated with a lower risk. Interestingly, younger HF patients were more likely to get readmitted within 30 days of discharge, compared to the elderly patient population (older than 75 years) in all countries except Taiwan. In general, the geriatric patients are likely to be discharged to an out of hospital care unit such as nursing facilities or discharged with community care and/or home health aide nurse support systems as opposed to being discharged home (145). In these instances, the elderly HF patients are closely followed-up with better medication adherence and earlier identification of decompensation. Consequently, this could be the cause for lower hospital readmissions in this age group. However, further studies are warranted to evaluate the reasons behind this trend and its trajectory in long-term follow-up.

4.1.12 Limitations

While the study has many strengths, I recognise the important limitations, which are:

i) Several prognostic variables in HF such as vital signs at the time of admission (i.e., blood pressure, heart rate, respiratory rate among others), biomarkers and imaging data were not available.
ii) HF patients in this study could not be classified into specific phenotypes, HFrEF and HFpEF, due to absence of ejection fraction measurements.

iii) Unavailability of laboratory data such as serum haemoglobin, blood urea nitrogen, albumin among others, precluded the use of established HF mortality prediction models such as The Acute Decompensated Heart Failure National Registry (ADHERE-HF), Organised Program to Initiate Lifesaving Treatment in Hospitalised Patients with Heart Failure (OPTIMIZE-HF), and Get With The Guidelines – Heart Failure (GWTG-HF)(137,146,147) .

iv) Information on out of hospital mortality in the US and Japan were not obtainable, which could have led to an underestimation of their 30-day readmission rates in these countries. However, prior research has estimated this to not be a major issue for short-term readmissions up to 60 days.

v) A limitation of EHR-based research is the potential for misclassification of diseases. While I acknowledge that there is a potential for misclassification in electronic health records and administrative healthcare databases, I believe that the large and diverse sampling nature of the data in all four countries, renders our results close to the true underlying population mean.

vi) Other limitations involved with using these individual datasets have been described in chapter 2 and in the limitations section in chapter 3.

I believe that these limitations are outweighed by the many advantages of the study design. One of the biggest strengths of this study was the substantial samples size of the database comprising over 1 million HF hospitalisations. A vast array of data was available on a range of variables, providing a large representative dataset of information for analysis.

CONCLUDING REMARKS

This robust comparative study of HFH across three different continents has demonstrated marked cross-country differences in short term mortality and readmission rates. These findings merit further research into finding the cause for these differences, which might provide insights for physicians, healthcare systems and policy makers to improve care for patients with HF globally. Furthermore, as HF clinical trials become increasingly globalised, sufficient understanding of regional factors which influence HF outcomes is imperative for their successful design, interpretation, and implementation.

Chapter 5: **Identification of algorithms for identification of HFrEF and HFpEF in nationwide electronic healthcare records in the UK**

PREAMBLE

Heart failure (HF) is classified into two main phenotypes, heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF), based on the left ventricular ejection fraction measurements, obtained from echocardiogram (27). Another phenotype, namely heart failure with mid-range ejection fraction (HFmrEF), has been described in the 2016 European Society of Cardiology guidelines (9). However, recent studies suggest that the pathophysiology and response to treatment in HFmrEF might be similar to HFrEF, indicating that both HFrEF and HFmrEF might possibly be one phenotype with varying severity (148,149).

In the UK, electronic health records (EHR) provide an excellent resource for understanding the natural history of HF and perform comparative effectiveness research in HF. However, a major limitation of EHR is the unavailability of left ventricular ejection fraction measurements, impeding compartmentalisation of HF patient population into their specific phenotypes. Identification of the two main HF phenotypes, namely HFrEF and HFpEF, in EHR is crucial, as aetiology, prognosis and response to therapy varies based on the specific phenotype. In the UK, *Read* codes used in primary care provides diagnoses codes specific for the HF phenotypes (e.g., 33BA.00: Impaired left ventricular function for HFrEF, G583.11: heart failure with normal ejection fraction for HFpEF) (24,26). However, more than 70% of the HF diagnoses recorded in primary care EHR have non-specific HF *Read* codes such as heart failure, congestive heart failure etc (e.g., G580.00: congestive heart failure) (26). Hence, it is imperative to establish and validate algorithms as proxies to left ventricular ejection fraction in EHR. In this chapter, I explain the results of my prospective study performed to develop and validate algorithms for identification of specific HF phenotypes, using *Read* codes in combination with additional patient characteristics that are shown to differ across patients with different HF phenotypes.

EVIDENCE BEFORE THE STUDY

I searched PUBMED (January 1, 2000 to August 30th, 2018) using the Medical Subject Headings (MeSH) terms "heart failure" or "heart failure reduced ejection fraction" or "heart failure with preserved ejection fraction" and "identification" or "validation" or "prediction" and "electronic healthcare records" or "electronic medical records" or "Claims database" or "registry". I identified four studies relevant to the research question (150–153). Bovitz et al performed a study to identify HF phenotypes in a single centre study using administrative claims database (150). Another study was performed using the Veteran Affairs Medical Centre in the US for identification of HFpEF (152). However, I was not able to find any study validating algorithms for identification of HFpEF and HFrEF using nationwide EHR, especially from the UK.

METHODS

5.1.1 Data source

I used The Healthcare Improvement Network (THIN), an electronic medical data collection scheme that sources anonymised patient data from more than 3.7 million active patients across 587 general practices in the UK (81). The THIN database accounts for c.6% of the British population and these patients have been shown to be representative of the population in terms of age, gender, medical conditions, and death rates **(Figure 2.8 and Table 2.4)** (80,82). Primary use of data is for patient management and not medical research and hence, data in THIN reflects only those events that are considered to be relevant to the patient's care. THIN data are subjected to computerised validation to quantify the completeness and accuracy of recording. These results are fed back to the practices with information on how to improve quality and correct omissions. The information on data quality of individual practices is shared with researchers and the dataset is subject to data quality threshold.

THIN EHR was preferred over CPRD due to the nature of the contract with the GPs, which allows sending questionnaires to the GPs, a key step in this prospective validation study. The methodology of data extraction, strengths and limitations of THIN database have been explained in detail in Chapter 2 of this thesis.

5.1.2 Study population

The study population for the validation study included random sample of individuals with HF codes (HFrEF, HFpEF and non-specific HF) selected from all participants registered in THIN database. I obtained a random sample of 500 patients with HF from January 1, 2015 to September 30, 2017 from the UK. The inclusion and exclusion criteria of the study are outlined below

Inclusion criteria

•Patients had to be over 18 years of age.

•Diagnosis of HF defined by either specific or non-specific codes suggestive of HF

•Registered at their general practice for > 1 year

•At-least 6 months of historical data

Exclusion criteria

•Patients with history of congenital heart disease, rheumatic heart disease, primary valvular disease, infiltrative cardiomyopathies (sarcoidosis, amyloidosis etc.), hypertrophic cardiomyopathy, and constrictive pericarditis were excluded (codes provided in supplementary file). These patients were excluded as they mimic HFpEF and have a different pathogenesis of heart failure

•Patients with multiple HF codes (e.g., those with both non-specific HF codes and HFrEF codes etc.)

One questionnaire consisting of 7 questions **(Supplementary Table 4)** was sent to the GPs in charge of randomly selected patients, requesting confirmation of HF status as well as any specific information from individual's records such as echocardiograms, laboratory tests including HF biomarkers (natriuretic peptides), hospital cardiology outpatient and discharge letters **(Figure 5.1).**

5.1.3 Algorithms for identification of different HF phenotypes

Medical conditions are recorded using the *Read* Clinical Classification version 2 in the THIN database. In the *Read* coding system, HF codes are listed either as HF or HF related codes e.g., left ventricular failure, cardiac failure etc. **(Supplementary Table 5)**. Combination of code lists and additional information such as echocardiogram, heart failure medications including angiotensin converting enzyme inhibitors (ACEI)/Angiotensin Receptor Blockers (ARB), betablockers, Mineralocorticoid receptor antagonists (MRA) and loop diuretics, were used to create algorithms. The algorithms for HFpEF were built based on the clinical risk factors of specific HF phenotypes and from the most recently published H2FpEF score. (165) The compositions are presented in **Table 5.2 for HFrEF (16 Algorithms) and for HFpEF (24 Algorithms) in Table 5.3**. The construct of algorithms is based on binary classification of variables (e.g., diabetes: yes/no, hypertension: yes/no).

HFrEF algorithms were based on the following facets

1. One of the three codes: Definite HFrEF (e.g., diagnoses codes of systolic heart failure etc), Possible HFrEF codes (e.g., cardiomyopathy) or non-specific HF codes (e.g., congestive heart failure
2. Use of Guideline directed medical therapy: Guideline directed medical therapy included the use of angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs), beta-blockers and mineralocorticoid antagonist (MRA)

HFpEF algorithms were based on the following facets

1. One of the two HF codes: HFpEF (e.g., diagnoses codes of heart failure with normal ejection fraction etc), or non-specific HF codes (e.g., congestive heart failure
2. Use of loop diuretics: furosemide, torsemide, bumetanide and ethacrynic acid
3. Risk factors for heart failure, primary driven from historical studies and H2FPEF score; obesity (BMI > 30 kg/m2), hypertension, atrial fibrillation, elderly (age > 65 years), diabetes mellitus and chronic kidney disease

5.1.4 Outcomes of interest

Estimation of positive predictive value (PPV) of predefined algorithms to identify HFpEF and HFrEF in the THIN database. The criteria's (gold standard) for the diagnosis of HFrEF and HFpEF are mentioned in Table 5.1

Table 5.1 Gold standard diagnosis of HFpEF and HFrEF

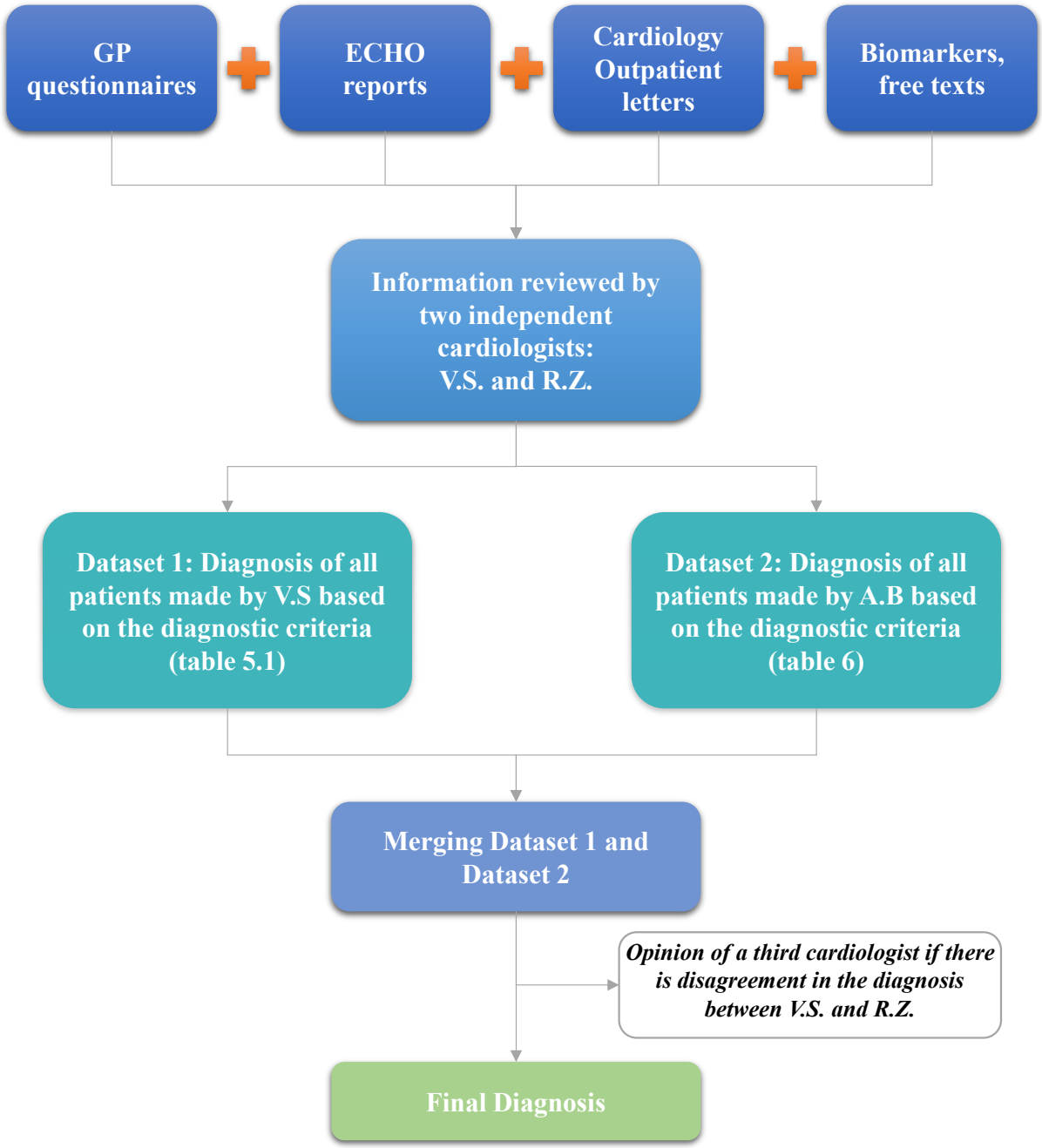
Criteria	Diagnosis of HFpEF and HFrEF
1	Based on European Society of Cardiology guidelines; HF diagnosis (GP questionnaire or cardiology outpatient letter or free texts) + Echocardiogram results + biomarker
2	Based on GP diagnosis of HFpEF or HFrEF (from the questionnaire) only
3	Based on echocardiogram only
4	Based on cardiology outpatient letters only

Patients falling into one of the 4 criteria were considered to have a diagnosis of heart failure with preserved ejection fraction (HFpEF) or heart failure with reserved ejection fraction (HFrEF)

5.1.5 Overall study design

Two independent cardiologists (V.S and R.Z) reviewed all questionnaires from GPs, hospital outpatient letters, echocardiograms, biomarkers, and free texts and built two independent datasets with specific phenotype diagnosis for each patient **(Dataset 1; created by V.S and Dataset 2: created by R.Z)**. The overall study design is outlined in **Figure 5.1**

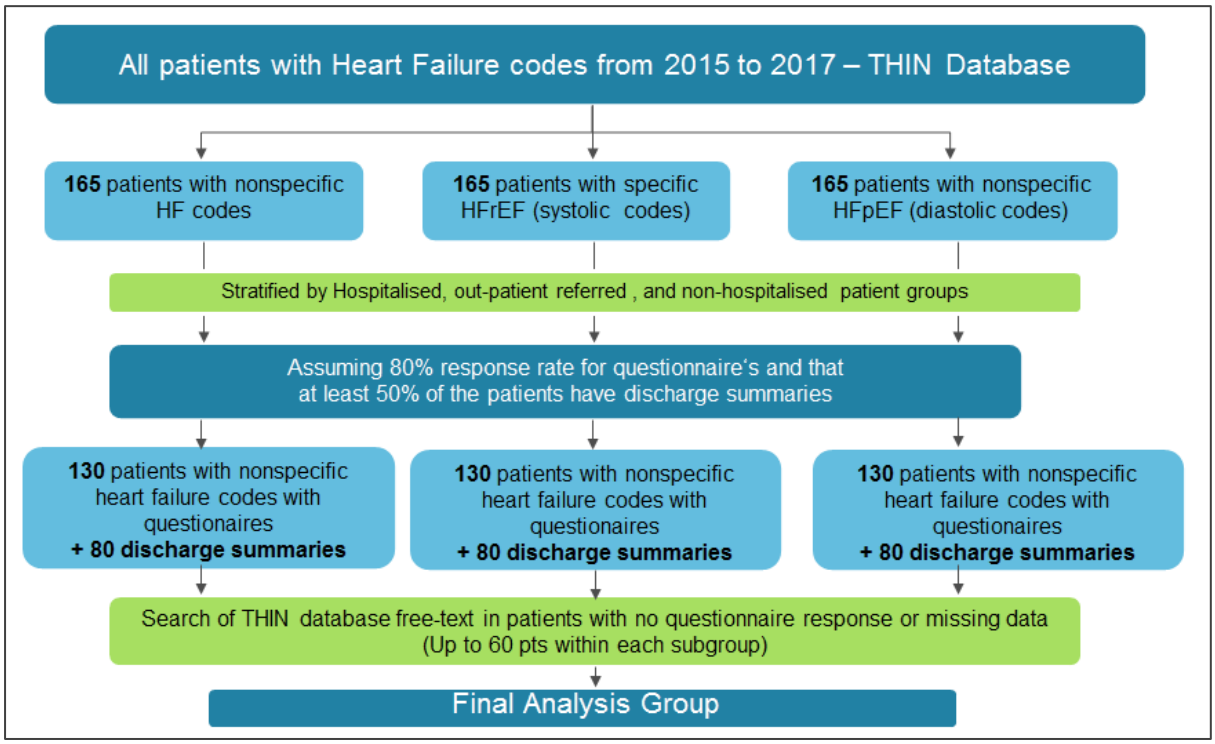
Figure 5.1 Gold standard diagnosis of HFpEF and HFrEF



5.1.6 Statistical analysis

All of the analyses were performed with STATA MP64 version 15 (StataCorp, College Station, TX). Baseline characteristics were presented as mean ± standard deviations (SD) when normally distributed, and as medians and interquartile (IQR) ranges when not normally distributed. The $\chi 2$ test was used for categorical data; depending upon distribution, continuous data were compared with the analysis of variance or the Kruskal-Wallis test to identify differences in baseline characteristics across different heart failure phenotypes. The details of sample size estimation are outlined in **Figure 5.2**

Figure 5.2 Sample size estimation for the validation study



Sample size for each algorithm was chosen to achieve a PPV of 0.85 based on the reviewing physician's judgment as the gold standard. The cut off 0.85 for PPV was chosen based on previous validation studies. The crude prevalence of HF in the THIN database is 0.9% and is comparable with data from the UK National Quality and Outcome framework (0.8%). The proportion of patients with HFrEF is ~ 70%.

For HFrEF

The prevalence in the population is 0.7%. Therefore with 130 patients in the sample, to aim for a PPV of 0.85 the 95% CI is 0.78-0.89.

For HFpEF

The prevalence in the population is 0.3%. Therefore with 130 patients in the sample, to aim for a PPV of 0.85 the 95% CI is 0.72-0.92.

Confidence intervals for PPV are estimated using the method from Mercaldo et al (154). The PPV values of all the algorithms were based on the reference standard (i.e., cardiologist confirmed diagnosis of HFrEF and HFpEF). The number of patients chosen in each group was felt to provide a reasonable

sample size to be representative of the HF patients in the database across the spectrum from more sensitive to more specific definitions.

5.1.7 Final Study Population

I identified 32,066 patients with HF between January 1, 2015 and September 30, 2017 in the THIN database. 16,144 patients were excluded from this initial cohort as their general practices had not consented for research. I identified a final cohort of 10,275 HF patients after applying the study inclusion and exclusion criteria. Out of the overall cohort of 10,275 HF patients, 1,595 (15.5%) patients had specific HFrEF codes (includes both definite and possible HFrEF codes) and 256 (2.5%) patients specific HFpEF codes. Majority of the patients had non-specific HF codes (n=8,424, 82%) (**Figure 5.2)**

From the final cohort of 10,275 patients, 500 patients were randomly sampled based on the prespecified algorithms **(Tables 5.3 and 5.4).** The response rate from GPs was 77.2% (n=386/500). On further reviewal of questionnaires, 99 patients (99/386) were excluded as there was either no data on ejection fraction (EF), did not have true HF (e.g., coronary artery disease) or they had HF from severe valvular heart disease (e.g., severe aortic stenosis), pericardial disease (constriction) or hypertrophic obstructive cardiomyopathy. Patients with heart failure and recovered EF i.e., previously low EF which had recovered at the time of the study, were still categorised under HFrEF (n=6)

5.1.8 Cohort characteristics: Overall HFrEF vs HFpEF

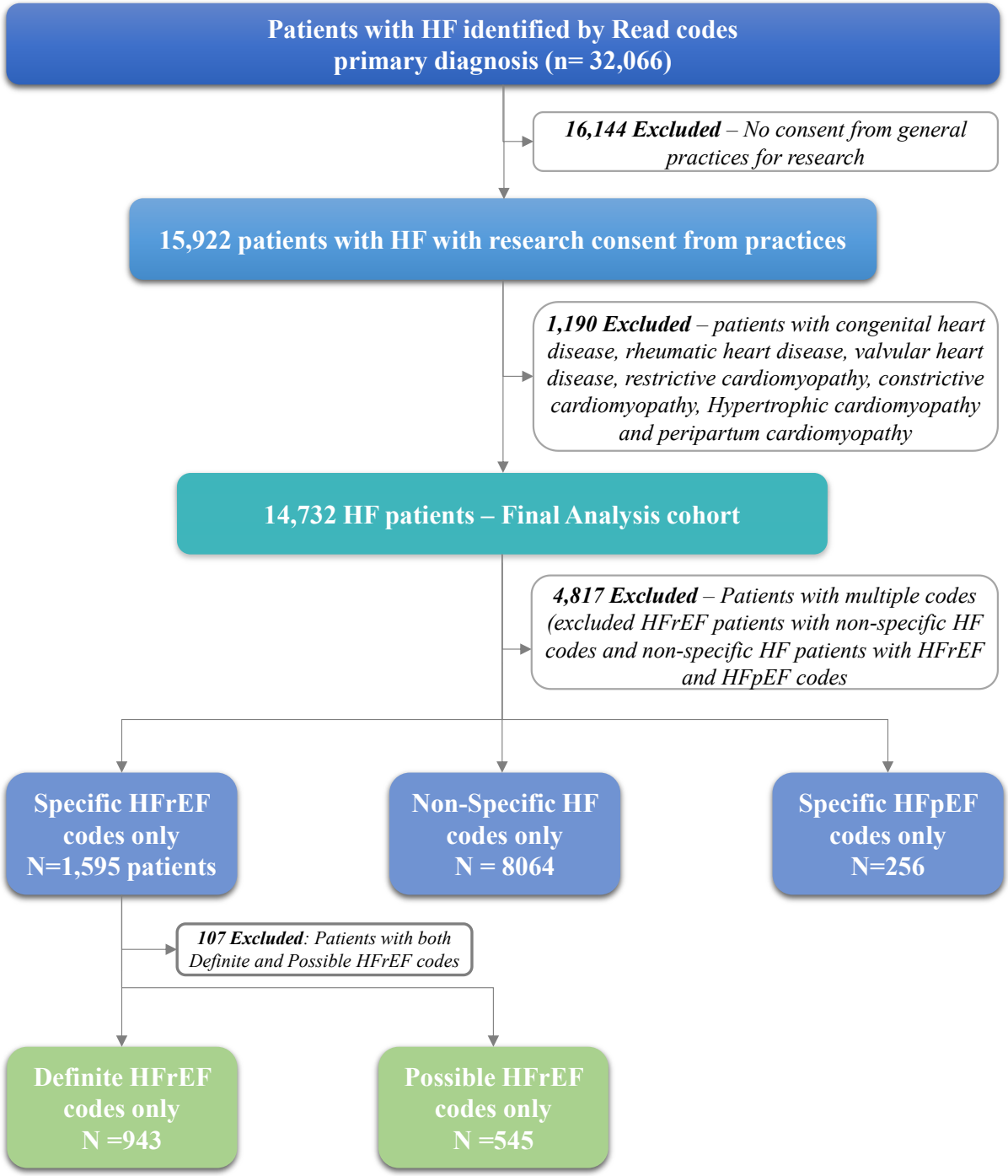
Final analyses included 90 patients with HFpEF and 197 patients with HFrEF. The baseline characteristics of patients with HFrEF and HFpEF are outlined in **Table 5.2**. In this sample population, patients with HFpEF were much older (mean age 76.2 $\pm$ 8.9 years) than HFrEF (mean age 68.2 $\pm$ 8.9 years). There was a higher prevalence of obesity, chronic kidney disease, atrial fibrillation, and hypertension in HFpEF patients compared to those with HFrEF. Higher proportion of HFrEF patients were on angiotensin converting enzyme inhibitors, betablockers and mineralocorticoid receptor antagonists compared to HFpEF. The baseline characteristics presented here in the HFpEF population, are likely to be an overestimate of the true burden of comorbidities. This is because HFpEF patients were sampled based on the pre-existing co-morbidities (i.e., risk factors) to increase the likelihood of capturing the patient population.

5.1.9 Cohort characteristics: HFsrEF (Heart Failure with severely reduced EF) vs HFmrEF (heart failure with mid-range or mildly reduced EF)

Patients with low EF (overall HFrEF: EF <50%) were further categorised into those with HF with severely reduced EF (HFsrEF; EF < 40%) and heart failure with mildly reduced EF (HFmrEF; EF 40-49%) as per the 2016 European Society of Cardiology guidelines. The overall HFrEF patient population were not sampled based the baseline characteristics or the risk factors and hence the co-morbidity burden is likely to be a true reflection of the real world HFrEF patient population. Patients within the

two groups (HFsrEF and HFmrEF) were sampled together and hence comparisons of differences in baseline characteristics across these two groups are valid. There were no significant differences in baseline characteristics and comorbidities between those with HFsrEF and those with HFmrEF except for the prevalence of CAD. Patients with HFmrEF were more likely to have CAD compared to those with HFsrEF **(Table 5.3)**. There was no significant difference in the mean age between HFsrEF (mean age 68.1 $\pm$ 13.6 years) and HFmrEF (mean age 68.4 +/-12.9 years) patients. The prevalence of obesity, chronic kidney disease, diabetes mellitus, atrial fibrillation, chronic obstructive pulmonary disease, and hypertension were comparable between HFsrEF and HFmrEF. The use of ACEI, betablockers and loop diuretics were similar between the two groups, however, significantly higher proportion of patients with HFsrEF were on MRA.

Figure 5.2 Identification of study population



HF: Heart Failure; HFrEF: Heart Failure with reduced ejection fraction; HFpEF: Heart Failure with preserved ejection fraction.

Definite HFrEF codes: codes are outlined in Supplementary appendix e.g., heart failure with reduced ejection fraction, Left ventricular systolic dysfunction. Possible HFrEF codes only: codes are outlined in Supplementary appendix e.g., cardiomyopathy, ischemic cardiomyopathy etc

Table 5.2 Patient characteristics, HFpEF vs HFrEF

	HFpEF (n=90) EF > 50%	Overall HFrEF (n=197) EF < 49%	P value
Demographics			
Age, mean +/- SD	76.2 +/- 8.9	68.2 +/- 13.4	< 0.001
Elderly (age > 75), n (%)	49 (55.5)	66 (33.5)	< 0.001
Female	50 (55.6)	54 (27.4)	< 0.001
BMI, mean +/- SD	34.2 +/- 8.2	29.7 +/- 6.2	0.001
Co-morbidities, n (%)			
Diabetes	33 (36.7)	64 (32.4)	0.77
Hypertension	80 (88.9)	117 (59.4)	< 0.001
Coronary artery disease	36 (40.0)	134 (68.0)	< 0.001
Chronic Kidney Disease > stage 3	15 (16.7)	19 (9.6)	0.11
Atrial fibrillation	66 (73.3)	91 (45.7)	0.001
COPD	9 (10.0)	38 (19.3)	0.09
Baseline medications			
Loop diuretics	82 (90.0)	153 (76.9)	0.02
ACEI/ARB	72 (80.0)	189 (95.6)	< 0.001
Betablockers	61 (67.8)	187 (94.5)	< 0.001
MRA	6 (6.7)	80 (40.6)	< 0.001

Table 5.3 Patient characteristics, HFsrEF vs HFmrEF

	HFmrEF (n=42) EF 40-49%	HFsrEF (n=155) EF < 40%	P value
Demographics			
Age, mean +/- SD	68.4 +/-12.9	68.1 +/- 13.6	0.96
Elderly (age > 75), n (%)	14 (33.3)	52 (33.5)	0.41
Female	11 (26.1)	43 (27.4)	0.74
BMI, mean +/- SD	30.4 +/-5.4	28.6 +/-6.2	0.79
Co-morbidities, n (%)			
Diabetes	13 (30.1)	52 (33.5)	0.41
Hypertension	25 (59.5)	92 (59.3)	0.97
Coronary artery disease	32 (76.2)	103 (66.5)	0.04
Chronic Kidney Disease > stage 3	3 (7.1)	16 (10.3)	0.67
Atrial fibrillation	20 (47.6)	71 (45.8)	0.26
COPD	7 (16.6)	32 (20.7)	0.41
Baseline medications			
Loop diuretics	28 (66.7)	125 (80.7)	0.27
ACEI/ARB	39 (92.9)	150 (96.8)	0.51
Betablockers	38 (90.5)	149 (96.1)	0.37
MRA	11 (26.2)	66 (44.5)	0.03

5.1.10 Positive predictive value of algorithms for HFrEF

The PPV of various HFrEF algorithms are summarised in **Table 5.4**. Out of all the algorithms, the one using definite HFrEF codes, 3/3 GDMT (ACEI + Betablocker + MRA), had the best PPV.

Algorithms with higher PPVs (>80%) were those that included:

- (i) usage of all three medications based on guidelines (GDMT), namely ACEI/ARB, betablockers and MRA & (ii) either definite HFrEF, possible HFrEF or non-specific HF codes.
- (i) usage of 2 out of three medications based on GDMT (ACEI, betablockers and MRA) & (ii) either definite HFrEF or possible HFrEF diagnoses codes

The PPV of non-specific HF codes were high when used in combination with 3/3 GDMT or with 2/3 GDMT in combination with echocardiogram. The other algorithms with non-specific HF codes had much lower PPV (< 60%)

Table 5.4 HFrEF algorithms

Algorithms for HFrEF	Number of evaluations returned	Number with confirmed HFrEF	PPV	95% Confidence intervals
Definite HFrEF codes + 3/3 GDMT	9	8	88.9	51.8-99.7
Definite HFrEF codes + 2/3 GDMT	12	10	83.3	51.6-97.9
Definite HFrEF codes	6	5	83.3	36.0-99.6
Possible HFrEF codes + 3/3 GDMT	13	12	92.3	64.0-99.8
Possible HFrEF codes + 2/3 GDMT	10	9	90.0	55.5-99.7
Possible HFrEF codes	10	6	60.0	26.2-87.8
Non-specific HF codes + 3/3 GDMT	16	14	87.5	61.7-98.4
Non-specific HF codes + 2/3 GDMT	12	6	50.0	21.1-78.9
Non-specific HF codes + 3/3 GDMT + ECHO	12	11	91.7	61.5-99.8
Non-specific HF codes + 2/3 GDMT + ECHO	8	6	75.0	34.5-96.8

**** ECHO indicates *Read* diagnosis code of ordering echocardiograms**

5.1.11 Positive predictive value of algorithms for HFpEF

The PPV of various HFpEF algorithms are summarised in **Table 5.5**. In general, all algorithms using non-specific HF codes and risk factors of HFpEF had a very low PPV. The algorithms with the best PPVs included those with specific HFpEF codes with and without loop diuretics use.

Table 5.5 HFpEF algorithms

Algorithms for HFpEF	Number of evaluations returned	Number with confirmed HFpEF	PPV	95%, Confidence intervals
HFpEF codes	40	33	82.5	67.2-92.7
HFpEF codes + LD	31	27	87.1	70.2-96.4
Non-specific HF codes + LD	126	45	35.7	27.4-44.7
Non-specific HF codes + LD + AF	81	33	40.7	29.9-52.2
Non-specific HF codes + LD+ HTN + AF	14	6	42.9	17.7-71.1
Non-specific HF codes + LD+ obesity	73	31	42.5	31.0-54.6
Non-specific HF codes + LD+ HTN	102	43	42.2	32.1-51.9
Non-specific HF codes + LD+ elderly	114	43	37.7	28.8-47.2
Non-specific HF codes + LD + DM	50	17	34.0	21.2-48.8
Non-specific HF codes + LD + CKD	15	7	47.0	21.2-73.4
Non-specific HF codes + LD + CAD	77	20	26.0	16.6-37.2

5.1.12 Major findings

The major findings of the study are as follows

i) A very small proportion (18%) of the overall heart failure patient population got coded with specific HF phenotype *Read* codes in the UK primary care practice

ii) The patient characteristics of those with HFsrEF and HFmrEF are largely similar signifying that these two groups could possibly be similar phenotypes with varying severity. Moreover, the treatment pattern in real world clinical practice (use of ACEI/ARB, betablockers and MRA) are comparable in these two groups indicating that clinicians may have been treating these two groups similarly.

iii) Tracking of HF medications prescriptions (guideline directed medical therapy) could be used as a proxy to left ventricular ejection fraction to identify HFrEF patient population in the primary care EHR.

iv) No algorithms using non-specific HF codes could reliably identify HFpEF patient population in THIN EHR.

5.1.13 Difficulties in the identification of HF phenotypes in EHR

Population based HF research using EHR has been historically limited due to the unavailability of left ventricular ejection fraction measurements. It is therefore vital to establish proxies to left ventricular ejection fraction to precisely curate HFrEF and HFpEF in large EHR. As expected, in this study I observed that >80% of patients with HF in the UK primary care practice had only non-specific HF code documentation. In order to overcome this limitation, I combined structured elements such as *Read* codes, patient characteristics, risk factors (especially for identification of HFpEF) and prescriptions to accurately recognise different HF phenotypes from EHR. While I was able to identify HFrEF patients using non-specific HF *Read* codes and medications prescribed, such approach for the identification of HFpEF patients did not yield similar results. Moreover, additional algorithms using established risk factors of HFpEF did not improve the discriminative performance.

Unlike HFrEF, HFpEF is a more complicated diagnosis with no medications specific to the disease. HFpEF diagnosis in EHR can be extremely challenging as it requires clinical symptoms and signs, laboratory data (natriuretic peptides) and documentation of ejection fraction (155). Patel et al developed a highly sensitive algorithm for identification of detection of HFpEF in the Veteran's affair national database (152). However, the algorithms included a Natural Language Processing (NLP) to identify ejection fraction from the unstructured text files in EHR.

5.1.14 Differences between HF with severely reduced EF vs HF with mid-range EF in real world: HFmrEF resembles HFsrEF

The findings of this study reinforce the notion that HFmrEF might probably a phenotypic subset of HFrEF as opposed to a separate phenotype(148,149). The similarities in pharmacotherapy use between the two groups (HFmrEF and HFsrEF) signify that physicians in real world might also be approaching these two groups of patients as one. Contrary to previous registry and clinical trial data, the crude prevalence of coronary artery disease was higher in HFmrEF compared to HFsrEF (156–158), a finding which warrants confirmation with further studies.

5.1.15 Strength and Limitations

This study has several strengths but important limitations. While there was a reasonable response rate (> 75%), additional patients were excluded due to lack of data of ejection fraction. Few algorithms were able to identify patients with HFrEF, however, the wide confidence intervals underscore the uncertainty with these algorithms. This could plausibly be due to a small sample size. The findings of this study emphasize the importance of establishing alternative algorithms using Natural Language Processing (NLP) to identify ejection fraction from the unstructured text files in EHR. The extent to which the coding practices differ across the general practices could not be determined in this study. This study was performed in the UK, and hence may limit generalisability of the results to EHR databases from other countries.

CONCLUDING REMARKS

This prospective validation study from nationwide EHR showed that heart failure medication use could reliably be used to identify HFrEF patients in the UK. However, no algorithms using non-specific HF codes and structured clinical parameters could dependably identify HFpEF patient population in THIN EHR. The results of my study iterate the fact that future heart failure validation studies should focus on building natural language processing (NLP) tools to capture left ventricular ejection from unstructured data such as text files to accurately phenotype HF in EHR

Chapter 6: **Trends in the prevalence, epidemiological characteristics, and outcomes of obese HFpEF; Complex interplay of diabetes mellitus and obesity in HFpEF**

PREAMBLE

Comorbidities such as hypertension, atrial fibrillation, diabetes mellitus (DM) and coronary artery disease have been identified as risk factors for HFpEF(159,160) but with increasing evidence, HFpEF associated with obesity is slowly being considered a new phenotype altogether (44,45,161–163). A prospective study evaluating postmenopausal women who participated in the Women's Health Initiative demonstrated obesity to be an independent risk factor for HFpEF (164). In this aim, I sought to evaluate the national trends in the prevalence of obese HFpEF from 2005 to 2014, characteristics of patients with obese HFpEF and the impact of obesity on outcomes in HFpEF, utilising national level data from the US.

I observed from my initial analysis **(from specific aim1)** that a considerably higher proportion of elderly patients accounted for HF admissions in the Asian countries compared to their Western counterparts **(table 6.1)**. The reasons for this could be manifold. The prevalence of obesity, a common risk factor for HF in the young, is higher in the West (compared to the East) plausibly contributing to a higher proportion of young patients with HFpEF as opposed to elderly patients in Asia, who are more predisposed to comorbidity driven HFpEF (38,39). Additionally, an interesting observation of the initial analysis was the prevalence of obesity and DM among HF patients **(Table 6.1)**. Despite a high prevalence of DM, there was a near absence of obesity among HF patients in Japan and Taiwan i.e., higher proportion of lean diabetics. On the contrary, the proportion of obese diabetics was much higher among HF patients in the West. While obesity is considered to an independent risk factor for HFpEF, it is also possible that the high prevalence of DM among the obese population, could explain the risk of HFpEF among obese patients(46,47,110). The residual risk of HFpEF in obese patients after accounting for DM at the is unclear. In this chapter, I also compared contemporary trends in the prevalence of obesity and diabetes among hospitalised HFpEF to determine which of these two comorbidities is driving the rising prevalence of HFpEF.

Table 6.1 Prevalence of obesity and diabetes mellitus among patients hospitalised with HF in the US, UK, Taiwan, and Japan (from specific aim1)

Variable	NRD United States (n = 231,512)	HES-CPRD United Kingdom (n = 10,991)	NHIRD Taiwan (n = 36,900)	JROAD-DPC Japan (n = 133,982)
Age >85, n (%)	53, 760 (23.2)	3,791 (34.5)	20,613 (55.9)	91,828 (68.5)
Comorbidities, n (%)				
Diabetes mellitus	102,409 (44.1)	3,076 (28.0)	20,785 (56.3)	31,627 (23.6)
Obesity	41,589 (18.0)	1,186 (10.8)	524 (1.4)	148 (0.1)

EVIDENCE BEFORE THE STUDY

I searched PUBMED (January 1, 2000 to December 31st, 2019) using the Medical Subject Headings (MeSH) terms “heart failure with preserved ejection fraction” or “heart failure with normal ejection fraction” and “obesity” or “obese” with no language restrictions. I also identified publications using searches on Google Scholar and via citations in peer-reviewed publications. Previous reports have primarily included post hoc analysis from clinical trials, registries and community cohorts including atherosclerosis risk in communities (ARIC).

In the most recently constructed H2FpEF score for the diagnosis of HFpEF, obesity and atrial fibrillation had the highest point allocations compared to other variables in the model (165). A secondary analysis of the RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction) trial between 2008 and 2012 which classified patients into categories of obese HFpEF and non-obese HFpEF showed that patients who had a body mass index (BMI)≥35kg/m2 had greater peripheral edema, orthopnoea and a worse New York Heart Association (NYHA) class, all factors contributing to a worse quality of life (31,161). Similarly, a post hoc analysis of the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial which enrolled 3,310 patients with HFpEF showed that patients with abdominal obesity had a higher all-cause mortality (adjusted HR: 1.52; 95% confidence interval [CI]: 1.16 to 1.99) compared to patients without abdominal obesity(40). Post hoc analysis from three large HFpEF trials (TOPCAT, I-Preserve and CHARM-Preserved) that younger HFpEF patients were more likely to obese compared to the elderly HFpEF patient population (109). There were no studies evaluating the trends in the national burden of obese HFpEF, and the impact of obesity on outcomes in HFpEF using nationwide data.

METHODS

6.1.1 Data sources

Data was obtained from the Agency for Healthcare Research and Quality Healthcare Cost and Utilisation Project—Nationwide Inpatient Sample (NIS) files from 2005-2014 and National Readmission Database (NRD) from 2012. The Nationwide Inpatient Sample (NIS) is a 20% stratified sample of all non-federal US hospitals (89). As mentioned earlier in Chapter 2, NIS database does not identify individual patients, and recurrent hospitalisations appear as distinct observations i.e., captured encounters represent hospitalisation records, and not distinct patients. Hence, for this specific aim, NIS was only used to assess the trends in the prevalence of obesity and DM among HFpEF hospitalisations over the last decade in the US. NRD which identifies distinct patients (sample of 50% of all hospitalisations in the US) was used to characterise obese HFpEF patients, and evaluate outcomes including mortality and readmissions (91).

6.1.2 Study population

All hospitalisations with a diagnosis of HFpEF among adults aged >18 years in 2005-2014 were included to assess trends in the prevalence of DM and obesity (from NIS). Patients with hospitalisation for HFpEF from NRD (2012 data) were used for the rest of the analyses. Hospitalisations for HFpEF were identified based on presence of diastolic heart failure codes, ICD-9-CM codes 428.31 and 428.33.

Diseases that can mimic HFpEF including rheumatic heart disease, hypertrophic cardiomyopathy, peripartum cardiomyopathy, valvular heart disease, amyloidosis, sarcoidosis, and myocarditis were excluded. Those with a secondary diagnosis of systolic heart failure were excluded from the analysis.

6.1.3 Identification of comorbidities

The Agency for Healthcare Research and Quality comorbidity measures, based on the previously validated Elixhauser methods, were used to identify comorbid conditions (88). Patient-level co-morbidities were identified using ICD 9 CM codes (Supplementary appendix). Hospital characteristics were derived from the American Hospital Association Annual Survey Database.

6.1.4 Statistical analyses

All of the analyses were performed with STATA MP64 version 15 (StataCorp, College Station, TX).

Trends in the prevalence of obese HFpEF between 2005 and 2014 was calculated by the number of ICD-9-CM diagnoses of obesity and HFpEF divided by the number of hospitalisations with a primary

ICD-9-CM diagnosis of HFpEF for that particular year (from NIS). The trends in the prevalence of diabetes mellitus (DM) in HFpEF was also calculated in a similar manner.

Data from the NRD was stratified based on obesity and diabetes mellitus status among patients with HFpEF. Each individual group (obese HFpEF and diabetic HFpEF) was further categorised based on the presence or absence of diabetes mellitus in the obese group and vice versa **(Figure 6.4)**. Baseline characteristics were presented as mean ± standard deviations (SD) when normally distributed, and as medians and interquartile (IQR) ranges when not normally distributed. $\chi 2$ test was used for categorical data; depending upon distribution, continuous data were compared with the analysis of variance or the Kruskal-Wallis test to identify differences in baseline characteristics across the groups. Length of hospital stays were presented as median and interquartile ranges. In-hospital mortality and 30-day readmissions were presented as crude rates and multivariable logistic regression analysis was performed to generate adjusted odds ratio.

To identify patient characteristics that predict a high probability of in-hospital mortality and 30-day all-cause readmission in obese and non-obese HFpEF, I performed multivariable logistic regression analysis and generated co-morbidity specific adjusted odds ratio (OR) for obese and non-obese HFpEF. The model was adjusted for age, sex, CAD, PAD, AF, DM, HTN, chronic lung disease, CKD (codes specific for CKD stage 3 and above), chronic liver disease, obesity, chronic anaemia, and pulmonary circulation disorders. Readmissions analyses was restricted to patients who were discharged alive.

RESULTS

6.1.5 Trends in the prevalence of obesity and diabetes among patients with HFpEF using NIS

There was a steady increase in the prevalence of obesity among HFpEF hospitalisations from 2005 to 2014 (13% in 2005 to 28% in 2014, **Figure 6.1**). The prevalence of DM in those hospitalised for HFpEF was largely steady during the same time period 2014 (13% in 2005 to 26% in 2014, **Figure 6.2**). The prevalence of obesity was much higher in HFpEF (28%) compared to systolic heart failure (19%) and the overall patient population (11%) **(Figure 6.3).**

Figure 6.1: Trends in the prevalence of obesity among patients hospitalised for HFpEF from 2005-2014 in the US

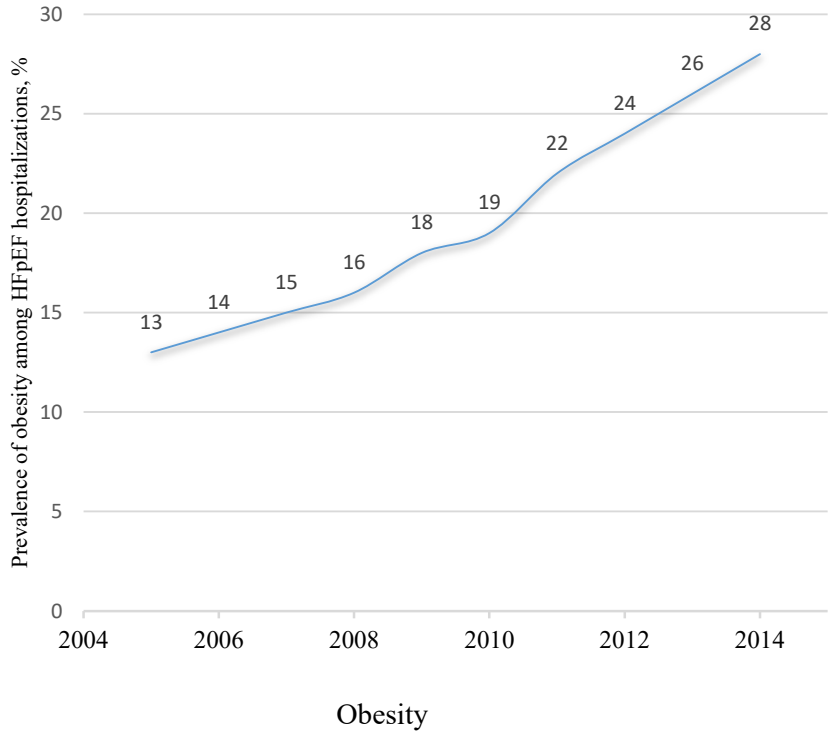


Figure 6.2: Trends in the prevalence of diabetes among patients hospitalised for HFpEF from 2005-2014 in the US

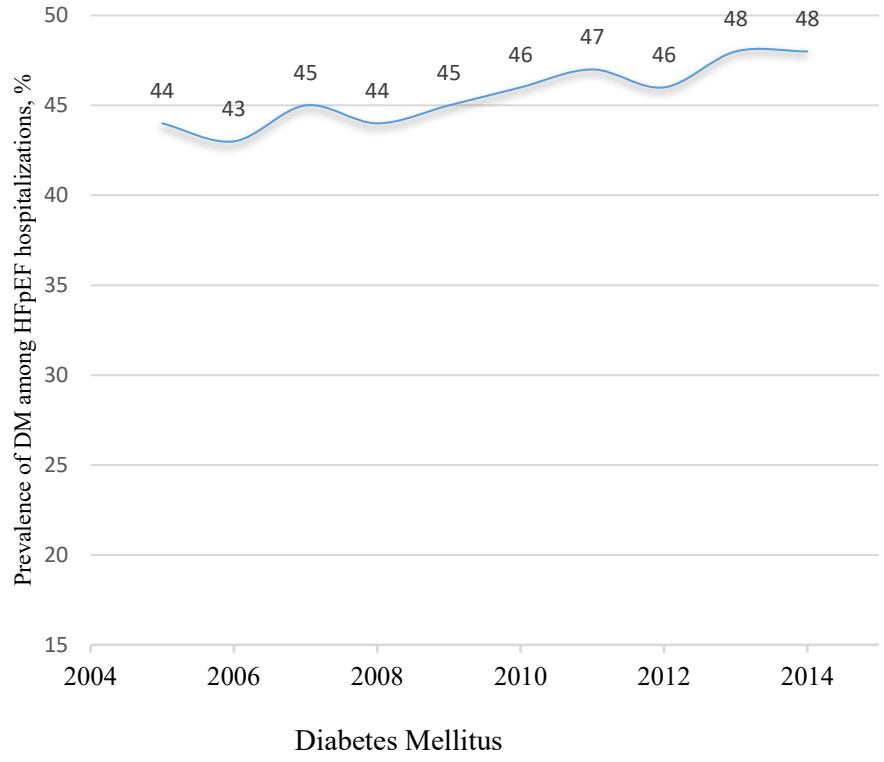


Figure 6.3: Prevalence of obesity among hospitalisations in the US, stratified by HF phenotype (2014)

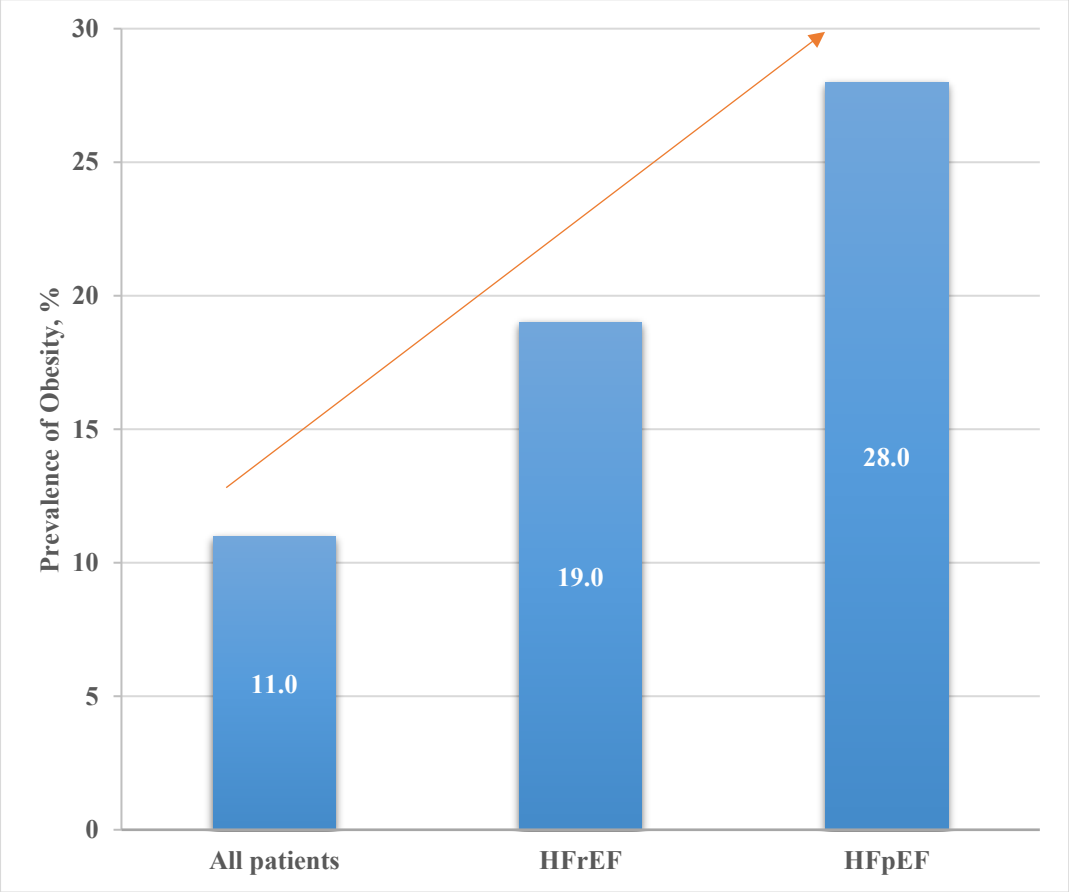
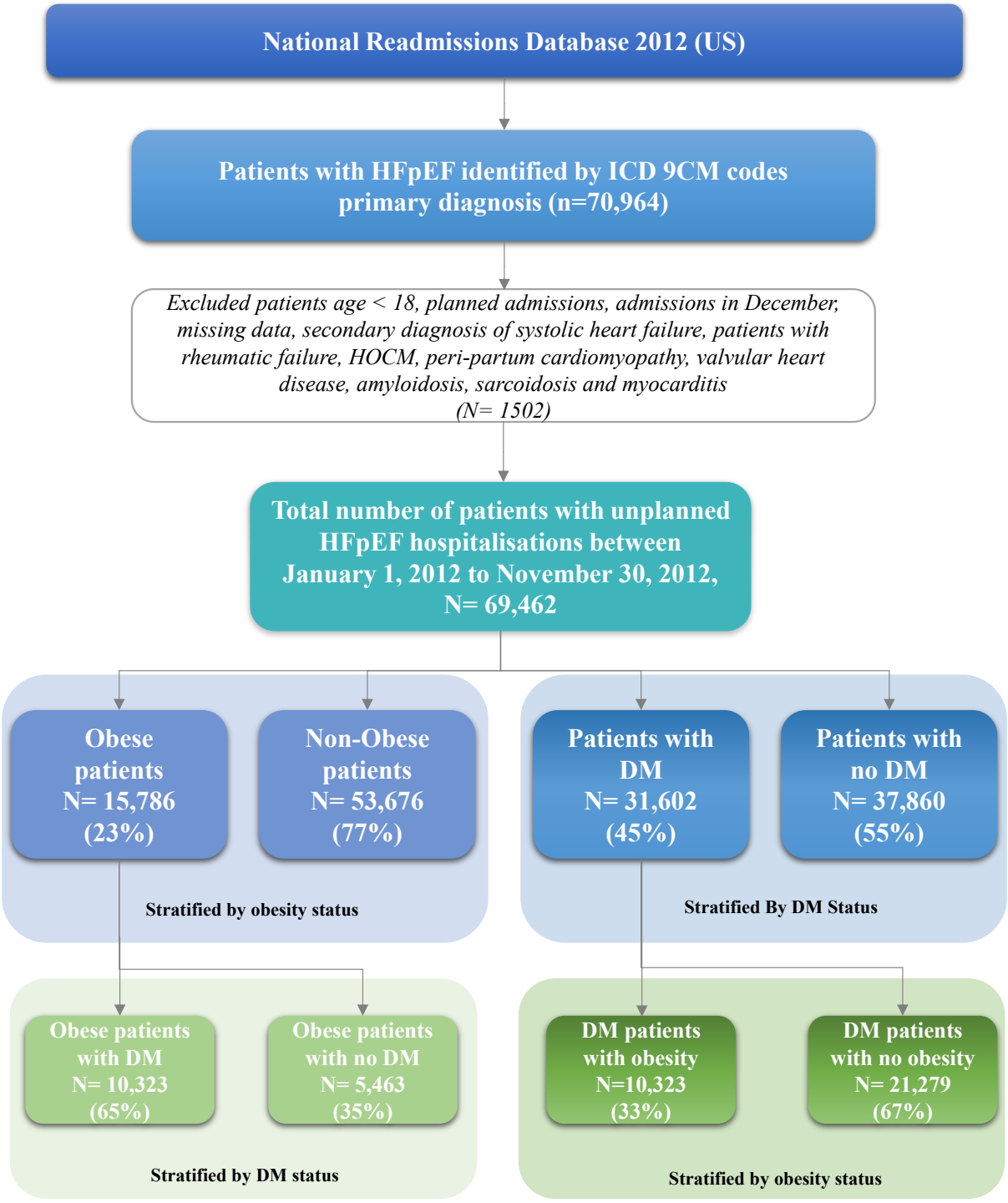


Figure 6.4: Flow diagram for identification of HFpEF (NRD, 2012)



- *HOCM: Hypertrophic obstructive cardiomyopathy; HFpEF: Heart Failure with preserved ejection fraction; DM: Diabetes Mellitus*

6.1.6 HFpEF patient characteristics stratified by obesity and diabetes using NRD from 2012

6.1.6.1 Obese vs non obese HFpEF

After applying the study inclusion and exclusion criteria, I identified 69,642 patients with HFpEF from 2012 NRD data **(Figure 6.4).** Patients with HFpEF were further stratified based on the presence or absence of obesity. 15,786 (23%) out of 69,642 patients with HFpEF were found to have obesity. Obese patients were further sub categorised based on the presence of DM. 35% of patients with obese HFpEF were non-diabetics **(Figure 6.4).** Obesity was present in almost half of the young HFpEF patients (age < 50 years) with the prevalence decreasing with age **(Figure 6.5).** The mean age of patients with obese HFpEF was much lower compared to those with non-obese HFpEF (67.6 +/- 11.5 vs 78.4 +/- 11.6 years, $p < 0.001$). The prevalence of hypertension, diabetes and chronic lung disease was much higher in obese HFpEF compared to non-obese HFpEF; whereas, coronary artery disease, atrial fibrillation, peripheral artery disease and chronic anaemia were more common in non-obese HFpEF patients **(Table 6.2)**

6.1.6.2 Stratification based on presence of obesity and DM in patients with HFpEF

Table 6.3 presents the characteristics of HFpEF patients when stratified by the presence or absence of obesity and DM. The mean age of obese HFpEF was much lower regardless of the presence or absence of DM. The mean age of non-diabetic non-obese HFpEF patients was almost 13 years higher than those with obese HFpEF (both with and without DM). Atrial fibrillation was the most common risk factor for HFpEF, with a prevalence of 50%, among the non-obese non-diabetic group.

The prevalence of hypertension, coronary artery disease, chronic kidney disease, chronic anaemia, peripheral artery disease and hypothyroidism was higher among obese HFpEF patients with DM compared to obese HFpEF patients without DM. The prevalence of AF, chronic lung disease and chronic liver disease was lower among obese HFpEF patient with DM compared to obese HFpEF patients without DM. The prevalence of pulmonary circulation disorders was similar in both groups **(Table 6.3).**

The differences in patient characteristics of HFpEF patients when stratified by the presence or absence of DM alone are outlined in **Table 6.4**

Table 6.2 Patient characteristics between Obese and Non-Obese HFpEF

Variables	Obese HFpEF	Non-obese HFpEF	P value
Number, n	15,786	53,676	
Mean age in years, SD	67.9 + 12.4	78.4 + 11.6	< 0.001
Age, n (%)			
18-35	163 (1.0)	176 (0.3)	
36-45	567 (3.6)	557 (1.0)	
46-55	1,921 (12.2)	2,162 (4.0)	
56-65	3,737 (23.7)	4,983 (9.2)	
66-75	4,681 (29.6)	9,386 (17.5)	
>75	4,717 (29.9)	36,412 (67.8)	
Female sex, n (%)	10,025 (63.4)	34,036 (63.4)	0.82
Co-morbidities, n (%)			
Hypertension	40,781 (82.0)	43,041 (80.1)	< 0.001
Diabetes Mellitus	10,363 (65.6)	21,340 (39.7)	< 0.001
Coronary artery disease	6,481 (41.1)	24,671 (45.9)	< 0.001
Chronic Kidney Disease	6,585 (42.6)	22,985 (42.8)	P 0.01
Atrial Fibrillation	5,674 (35.9)	25,067 (46.7)	< 0.001
Chronic Lung Disease	7,613 (48.6)	20,278 (37.7)	< 0.001
Chronic Anaemia	5,142 (32.5)	19,205 (35.7)	< 0.001
Hypothyroidism	2,852 (18.0)	10,624 (19.0)	< 0.001
Peripheral arterial disease	1,673 (10.6)	7,138 (13.2)	< 0.001
Chronic Liver Disease	566 (3.5)	1,448 (2.7)	< 0.001
Pulmonary circulation disorders	65 (0.4)	126 (0.2)	< 0.001

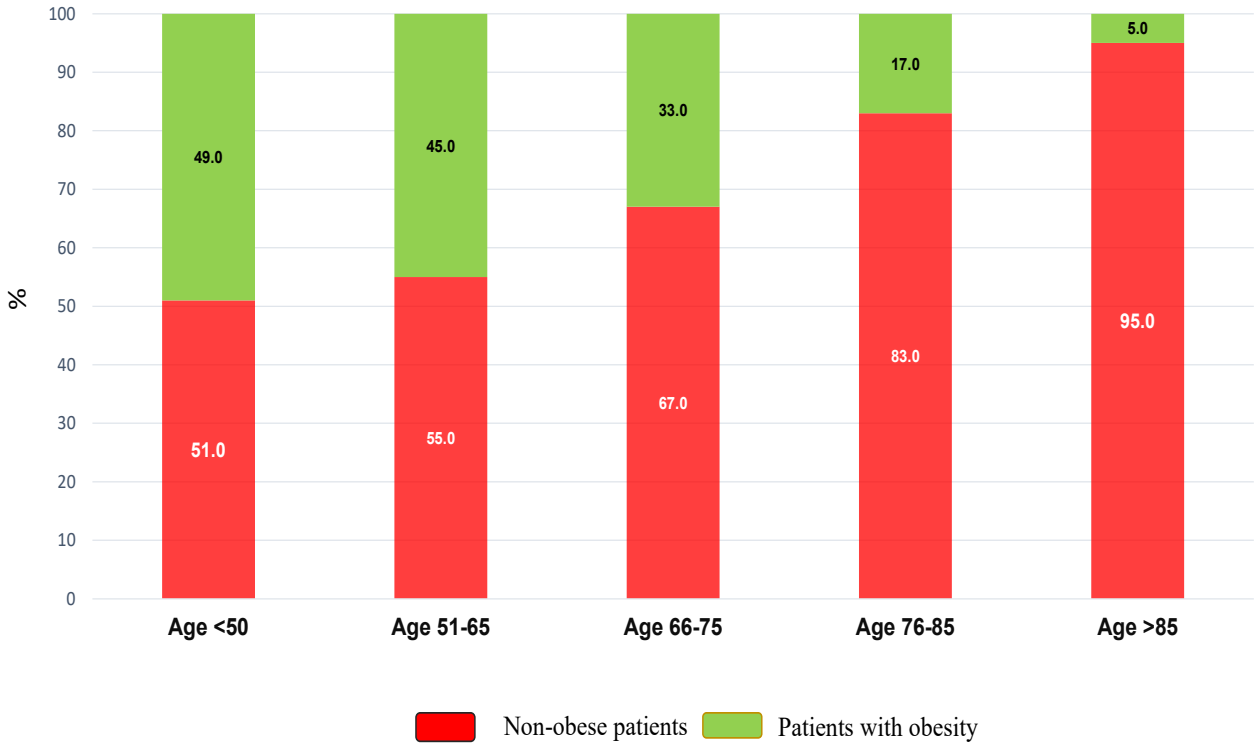
Table 6.3 HFpEF patient characteristics stratified by Obesity and Diabetes Mellitus status

Variables	Obese + DM + (N=10,323)	Obese + DM - (N=5,463)	DM + obesity - (N=21,279)	No Obesity, no DM (N=32,387)
Age in years, mean, SD	67.6 +/- 11.5	68.4 +/- 14	75.4 +/- 11.5	80.3 +/- 11.2
< 55	1,590 (28.7)	1,061 (19.1)	1,373 (24.8)	1,522 (27.4)
56 - 65	2,651 (30.4)	1,086 (12.5)	2,886 (33.1)	2,087 (24.0)
66 - 75	3,324 (23.6)	1,357 (9.6)	5,093 (36.2)	4,293 (30.5)
>75	2,758 (6.7)	1,959 (4.8)	11,927 (29.0)	24,485 (60.0)
Sex				
Female	6,553 (63.5)	3,472 (63.6)	12,758 (60.0)	21,278 (65.7)
Co-morbidities, N (%)				
Hypertension	8,729 (84.6)	4,210 (77.1)	18,088 (85.0)	24,953 (77.0)
Coronary Artery Disease	4,446 (43.1)	1,794 (32.8)	21,279 (51.1)	13,021 (40.2)
Atrial Fibrillation	3,333 (32.3)	2,173 (39.8)	8,098 (38.1)	16,189 (50.0)
Chronic Kidney Disease	10,323 (47.5)	1,680 (30.1)	11,274 (53.0)	32,387 (36.1)
Chronic Lung Disease	4,934 (47.8)	2,679 (49.0)	7,856 (36.9)	12,422 (38.3)
Chronic Anaemia	3,726 (36.1)	1,416 (25.9)	8,797 (41.3)	10,408 (32.1)
Peripheral Artery Disease	1,220 (11.8)	453 (8.3)	3,317 (15.6)	3,821 (11.8)
Chronic Liver Disease	355 (3.4)	211 (3.9)	635 (3.0)	813 (2.5)
Hypothyroidism	1,877 (18.2)	975 (17.8)	3,872 (18.2)	6,752 (20.8)
Pulmonary Circulation Disorders	44 (0.4)	21 (0.4)	58 (0.3)	68 (0.2)

Table 6.4 Patient characteristics between Diabetes Mellitus vs No Diabetes Mellitus among HFpEF

Variables	DM HFpEF	No DM HFpEF
Number, n	***31,602***	***37,861***
Mean age in years, SD	72.9 + 12.7	78.6 + 12.4
Age, n (%)		
18-35	114 (0.3)	225 (0.6)
36-45	534 (1.7)	590 (1.6)
46-55	2,315 (7.3)	1,768 (4.7)
56-65	5,537 (17.5)	3,183 (8.4)
66-75	8,457 (26.6)	5,650 (14.9)
>75	4,717 (46.4)	26,444 (69.8)
Female sex, n (%)	19,311 (61.1)	24,750 (65.4)
Co-morbidities, n (%)		
Hypertension	26,817 (84.9)	29,163 (77.0)
Obesity	10,363 (32.7)	5,463 (14.4)
Coronary artery disease	15,309 (48.4)	14,815 (39.1)
Chronic Kidney Disease	16,179 (51.2)	13,391 (35.4)
Atrial Fibrillation	11,431 (36.2)	18,362 (48.5)
Chronic Lung Disease	12,760 (40.4)	15,101 (39.9)
Chronic Anaemia	11,824 (31.2)	12,523 (39.6)
Hypothyroidism	5,749 (18.2)	7,727 (20.4)
Peripheral arterial disease	4,537 (14.4)	4,274 (11.3)
Chronic Liver Disease	566 (3.5)	1,448 (2.7)
Pulmonary circulation disorders	102 (0.3)	89 (0.2)

Figure 6.5: Prevalence of obesity among HFpEF hospitalisations stratified by age



6.1.7 Outcomes: short term mortality and readmissions; Obese HFpEF vs non obese HFpEF

Overall, the median length of hospital stay was similar on both obese and non-obese HFpEF **(table 6.5).** The crude in-hospital mortality rates (obese HFpEF: 1.4 % vs non-obese HFpEF 2.7%) and adjusted OR for in-hospital mortality of obese HFpEF patients was significantly lower than that of non-obese HFpEF patients (adjusted OR 0.61, 95% CI, 0.52-0.70). Crude rates and adjusted OR for 30-day all-cause readmissions were similar between the two groups **(Table 6.5)**

Table 6.5 Outcomes: Obese vs non-obese HFpEF

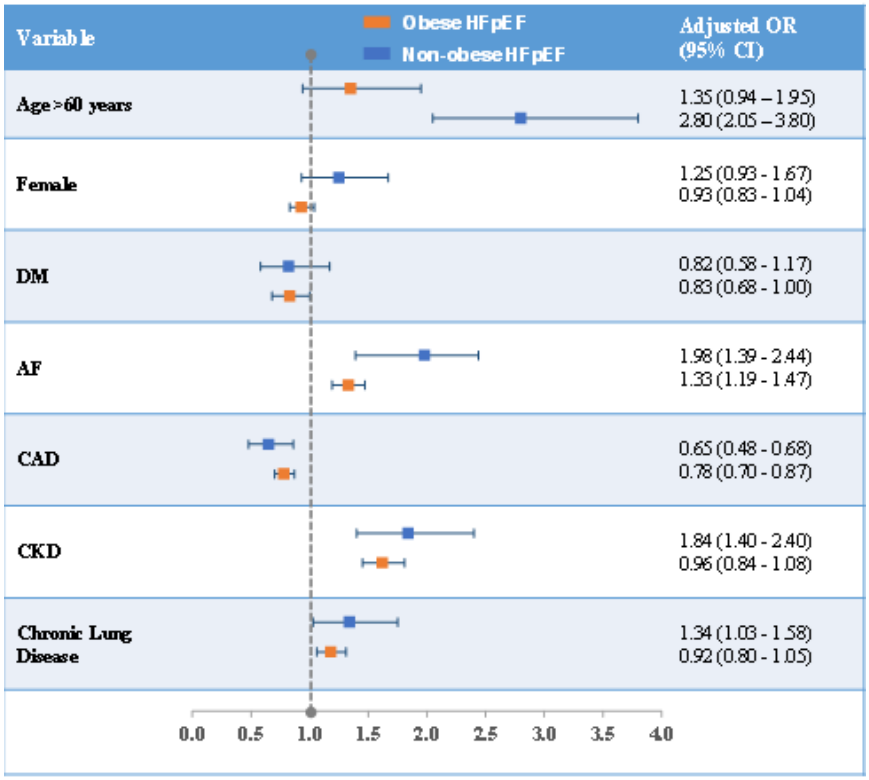
Variables	Non-obese HFpEF	Obese HFpEF
Median length of hospital stay, in days, (25th – 75th percentile)	4 (3-6)	4 (3-7)
Crude in-hospital mortality, rates per 100 hospitalisations for HF	2.7	1.4
Crude 30-day all-cause readmission rates, rates per 100 discharges	25.8	24.6
Crude 30-day readmission due to heart failure, rates per 100 discharges	5.9	5.6
Adjusted odds of in-hospital all- cause mortality, 95% CI	reference	0.61 (0.52 - 0.70)
Adjusted odds of 30-day all-cause readmission, 95% CI	reference	0.93 (0.89 - 0.97)
Adjusted odds of 30-day readmission due to heart failure, 95% CI	reference	0.95 (0.87 - 1.03)

6.1.8 Factors predicting in-hospital mortality and 30-day readmissions in obese and non-obese HFpEF

Figure 6.6 shows forest plots demonstrating adjusted OR for in-hospital mortality in obese HFpEF and non-obese HFpEF patients. Atrial fibrillation (adjusted OR 1.98, 95% CI 1.39 - 2.44), chronic lung disease (adjusted OR 1.34, 95% CI, 1.03-1.58) and chronic kidney disease (adjusted OR 1.84, 95% CI 1.40 - 2.40), were associated with a significantly increased risk for in-hospital mortality in obese HFpEF compared to the non-obese counterparts.

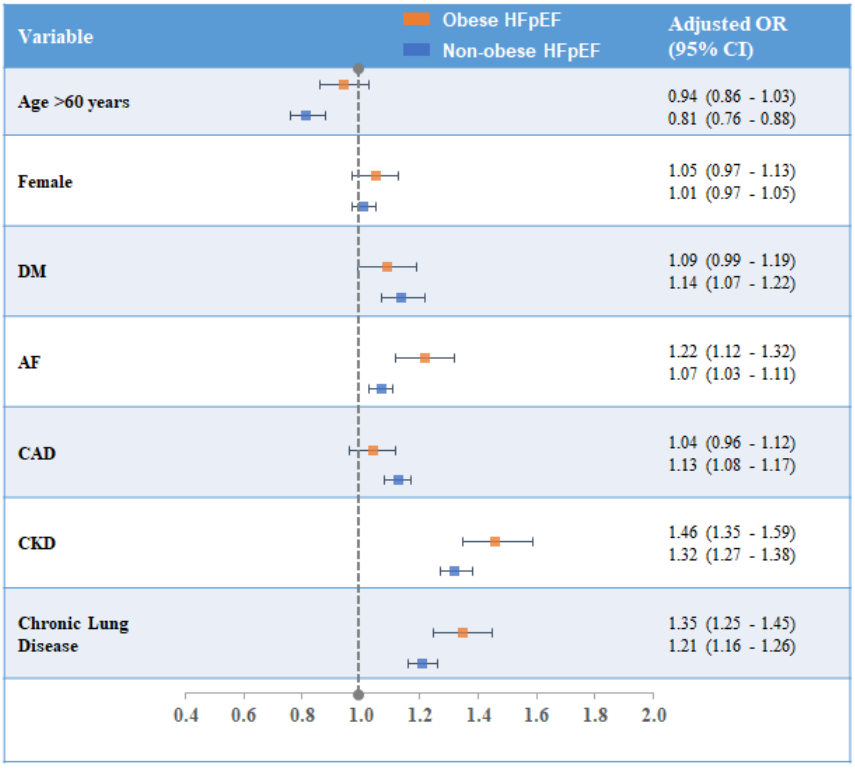
Figure 6.7 reveals forest plots demonstrating adjusted odds for 30-day readmissions in obese HFpEF and non-obese HFpEF patients. Analogous to in-hospital mortality, atrial fibrillation (adjusted OR 1.22, 95% CI 1.12-1.32), chronic lung disease (adjusted OR 1.35, 95% CI 1.25-1.45) and chronic kidney disease (adjusted OR 1.46, 95% CI 1.35-1.59) were associated with a much higher risk for 30-day readmissions in obese HFpEF compared to non-obese HFpEF.

Figure 6.6 Factors predicting in-hospital mortality; Obese vs non-obese HFpEF



DM: diabetes mellitus; AF: atrial fibrillation; CAD: coronary artery disease; CKD: chronic kidney disease

Figure 6.7 Factors predicting 30-day readmissions; Obese vs non-obese HFpEF



DM: diabetes mellitus; AF: atrial fibrillation; CAD: coronary artery disease; CKD: chronic kidney disease

6.1.9 Major findings

The major findings of the study are as follows

1. In the US, there was nearly a doubling in the prevalence of obese HFpEF from 2005 to 2014 (13% to 28%). In contrast, the prevalence of diabetes in those hospitalised for HFpEF was largely unchanged during the same time period.
2. The prevalence of obesity was much higher in HFpEF (28%) compared to systolic heart failure (19%) and the overall patient population (11%).
3. The mean age of obese HFpEF patients was almost a decade lower than non-obese HFpEF patients. In the US, obesity was a significant driver of HFpEF in young, with a prevalence of 50% among those HFpEF and age < 50 years.
4. Atrial fibrillation was the most common risk factor for HFpEF in the non-obese non-diabetic population (prevalence ~50%)
5. The phenomenon of obesity paradox was observed in obese HFpEF for short term clinical outcomes (in-hospital mortality)
6. Despite being a decade younger, the burden of hospitalisations in obese HFpEF was comparable to non-obese HFpEF patients.

6.1.10 Obese HFpEF: Increasing evidence for this new phenotype and its clinical implications

Obesity has recently been recognised to cause a unique form of HFpEF which differs from non-obese HFpEF(44,160–162,165). Although there is an emerging obesity epidemic, the relative changes in the obese phenotype of HFpEF over time remains unknown. Multiple mechanisms have been postulated in the pathogenesis of obesity related HFpEF and have been explained in detail in Chapter 1. A large-scale, population-based study found that weight gain over 4 years was associated with increases in left ventricular diastolic stiffness in both men and women, whereas weight loss led to a decrease in arterial load (166). A study on 22,681 participants from 4 community-based hospitals in the US showed that an increase in BMI was associated with a differential risk for HFpEF over HFrEF, particularly in obese women. 23% of the patients were obese with 37% meeting criteria for metabolic syndrome. Similar to my study, these patients were also young with a mean age of 60±13 years(41). As obese HFpEF patients are significantly younger, the years of life lost (YLL) is much higher than the non-obese HFpEF phenotype, necessitating further evidence to investigate the impact of treating obesity in this patient population.

6.1.11 Metabolic HFpEF: Complex interplay of diabetes and obesity in HFpEF; diabesity?

Obesity and DM frequently co-exist in the Western Population and are both important predisposing factors for HFpEF(167). Data from registries and observational studies have demonstrated a 45% prevalence of DM in HFpEF(168). Preclinical studies have shown that mice with obesity and Type 2 DM were more likely to develop myocardial hypertrophy in parallel with diastolic dysfunction without changes in systolic function (169). The DIG (Digitalis Investigation Group) trial followed 987 patients with LVEF>45% for 37 months and showed that diabetics had a 68% increased risk of HF hospitalisation, death and hazard of total mortality(170). These patients also had higher BMIs suggesting that obesity and DM together may accelerate the severity of HFpEF. I observed in my study a significant proportion of obese HFpEF patients with no DM (35%). This coupled with the doubling in the prevalence of obesity in HFpEF in the last decade, with constant prevalence of diabetes in HFpEF during the same time period indicate that there might be a residual risk of HFpEF attributable to obesity after accounting for DM.

6.1.12 Obesity paradox?

Previous studies have indicated an inverse relationship between obesity and the survival in patients with established cardiovascular disease - a phenomena known as *"the obesity paradox"*(163,171). In a retrospective cohort study of 7,767 outpatients with heart failure, obese HF patients had a lower crude and adjusted risks of all-cause mortality when compared with those with lower body mass index(172). Fonarow et al demonstrated from an analysis 108,927 hospitalised HF patients using the Acute Decompensated Heart Failure National Registry (ADHERE) that every 5 unit increase in body mass index was associated with 10% lower odds of risk adjusted mortality. This relationship was observed in both heart failure patients with preserved and reduced ejection fraction (173). Similarly, in my study I observed lower odds for in-hospital mortality in obese HFpEF patients compared to their non-obese counterparts. This relationship was unchanged even after accounting for the age difference between the two HFpEF phenotypes. However, despite being much younger, the burden of HF hospitalisations in obese HFpEF was similar to non-obese HFpEF.

6.1.13 Limitations

This study has several strengths but important limitations. I assumed that HFpEF patients with a diagnosis of obesity have obese HFpEF, while some patients may have had HFpEF unrelated to obesity. Data on serial body mass index and echocardiogram was not available. Unlike HFrEF, a significant part of HFpEF patients do not get hospitalised. This study included only hospitalised HFpEF, and these findings must be confirmed in the ambulatory HFpEF patient population. Information on out of hospital

mortality was not available which could have led to an underestimation of their 30-day readmission rates. However, prior research has estimated this to not be a major issue for short-term readmissions up to 60 days. The limitations of EHR and administrative database research have been explained in previous chapters. The phenomenon of obesity paradox observed for short term outcomes needs to be investigated for long term outcomes. The lower mortality rates observed in obese HFpEF patients could be due to reverse causation, i.e., were normal or lower weight is a consequence, probably due to cardiac cachexia in heart failure. This study was not designed to reduce the impact of reverse causation.

CONCLUDING REMARKS

In the US, there has been a substantial increase in the prevalence of obesity in hospitalised HFpEF patients in the last decade, which is far greater than the prevalence of diabetes, and disproportionately affects younger patients with substantial national disease burden. Further evaluation of the impact of treating obesity to prevent HFpEF hospitalisation is urgently needed.

Chapter 7: **Impact of coronary revascularisation in patients with HFpEF**

PREAMBLE

HFpEF has been postulated as heterogenous group of diseases based on the presence of key co-morbidities (48,174,175). While there is no proven therapy for HFpEF, they may possibly respond to treatment of co-morbidities implicated in the pathogenesis of the disease i.e., co-morbidity or sub-phenotype specific treatment (37,160,176). One such co-morbidity common in patients with HFpEF is coronary artery disease (CAD), with prevalence estimates between 40 to 60% (50,59). 6 Given HFpEF and CAD share risk factors such as hypertension, diabetes, ageing, and chronic kidney disease, it is possible that CAD may often be an innocent bystander in HFpEF. Therefore, investigating the role of coronary revascularisation in HFpEF may provide insights into their mechanistic link and serve as the basis for future randomised studies on co-morbidity specific treatment in HFpEF. Several studies have demonstrated a U-shaped relationship between left ventricular ejection fraction (LVEF) and outcomes in unselected HF cohorts (177,178). I hypothesised ischemic HF requiring coronary artery bypass grafting (CABG) exists on a continuous spectrum with the highest risk of outcomes with low EF and progressively lower risk with preserved EF. To address these questions, I evaluated a large national cohort of patients undergoing isolated elective CABG from the Veteran Affairs (VA) Medical Centres in the United States, stratified by baseline HF status and LVEF

EVIDENCE BEFORE THE STUDY

I searched PUBMED (January 1, 2000 to December 31st, 2020) using the Medical Subject Headings (MeSH) terms "heart failure with preserved ejection fraction" or "heart failure with normal ejection fraction" or "diastolic heart failure" and "percutaneous coronary revascularisation" or "coronary artery bypass grafting" or "revascularisation" or "coronary artery disease" with no language restrictions. I also identified publications using searches on Google Scholar and via citations in peer-reviewed publications.

The role of CABG in the treatment of patients with stable CAD and heart failure was evaluated in the Surgical Treatment for Ischemic Heart Failure (STICH) trial but the trial was limited to patients with left ventricular systolic dysfunction (179). Post-hoc analysis of a small subgroup of patients with heart failure from the ISCHEMIA trial (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) demonstrated better event free survival in patients with initial revascularisation strategy. However, this study predominantly included patients with heart failure with midrange ejection fraction (HFmrEF: EF of 35-45%), rather than HFpEF (180). A retrospective observational study investigating the role of coronary revascularisation in 205 patients with HFpEF and angiographically proven CAD, revealed greater preservation of left ventricular systolic function and improved survival with revascularisation (181). Two population-based studies of patients undergoing CABG, patients with HFpEF were found to have increased mortality compared to those with no HF (182,183). However, it is unclear if these two studies had excluded patients with acute coronary syndrome and HFpEF mimics such as valvular cardiomyopathy, constrictive pericardial disease, and cardiomyopathies.

METHODS

7.1.1 Data source

The Veteran Affairs (VA) Health Department has the largest integrated health system in the United States, with more than 170 hospitals and 1025 out-patient facilities (96). In the VA, EHR used for patient care are stored in a central repository managed by the Veterans Affairs Informatics and Computing Center (VINCI). Patients in VINCI are identified using Social Security information. The VA Surgical Quality Improvement Program (VASQIP) database, is a quality assurance activity-derived database containing information on all patients who undergo surgery within the VA (98). The primary purpose of this database is to improve the quality of care for Veterans undergoing surgery by providing information to provider teams for quality improvement purposes. VASQIP database is linked to the VA-VINCI and is available for research. I used the VASQIP database to identify patients who underwent cardiac surgery within the Veteran Affairs Health System.

7.1.2 Study population

7.1.2.1 Study inclusion and exclusion criteria

i) Patients who underwent CABG between January 1, 2005 and September 30,2019 within the National Veteran Affairs Health System in the US

ii) Patients with CABG indication for acute coronary syndrome (ST elevation myocardial infarction, Non-ST elevation myocardial infarction and unstable angina), surgery for valvular replacement or repair, surgery for constrictive pericarditis, emergent CABG and those with cardiogenic shock were excluded from the study.

7.1.2.2 Identification of different heart failure phenotypes

Patients were stratified into 4 groups, those with HFrEF, HFmrEF, HFpEF and patients with no diagnosis of HF. The criteria for identification of different phenotypes of HF are outlined in **Table 7.1.** The HFpEF identification criteria has already been validated in VA-VINCI with a sensitivity of 88%, specificity of 96% and a positive predictive value of 96% (152).

7.1.2.3 Selection of controls / reference group

Patients undergoing CABG with no HF diagnosis were included as controls. Patients with concurrent use of loop diuretic (for at-least 30 days prior to surgery) were excluded from the control group. This was done in order to exclude patients with unrecognised HFpEF and increase the accuracy of selecting true controls (with no HFpEF).

7.1.2.4 Ejection fraction measurements:

Left ventricular systolic function was assessed from preoperative 2-D echocardiogram. In the VASQIP database, left ventricular systolic function was categorised into 5 grades. Grade 1 Ejection fraction >55%, Grade 2: 45-54%, Grade 3a, 40-44%, Grade 3b 35-39%, Grade 4: 25-34% and Grade 5: <25%.

Table 7.1 Criteria used for identification of different heart failure phenotypes in National Veteran Affairs EHR

Heart Failure Phenotypes	Criteria used in VA-VINCI
Heart Failure with Preserved Ejection Fraction (HFpEF)	1. ICD 9 and 10 codes for heart failure. 2. Ejection Fraction $\geq$ 55% 3. Concurrent use of diuretic - for at least 30 days prior to cardiac surgery
Heart Failure with mid-range Ejection Fraction (HFmrEF)	1. ICD 9 and 10 codes for heart failure. 2. Ejection Fraction 41-54% 3. Concurrent use of diuretic - for at least 30 days prior to cardiac surgery
Heart Failure with reduced Ejection Fraction (HFrEF)	1. ICD 9 and 10 codes for heart failure. 2. Ejection Fraction < 40 %

7.1.3 Outcomes of interest

The primary outcome of interest is a composite of first heart failure hospitalisation and all-cause mortality. Other outcomes of interest include median time to first heart failure hospitalisation, recurrent heart failure hospitalisations, and myocardial infarction (MI) during follow up. Patients were considered to have observed the event if they underwent readmission with the corresponding primary diagnosis.

7.1.4 Statistical analyses

Baseline characteristics were presented as mean ± standard deviations (SD) when normally distributed, and as medians and interquartile (IQR) ranges when not normally distributed. Pre-operative baseline characteristics and outcomes were compared between the 4 groups: No HF, HFpEF, HFmrEF and

HFrEF. Chi-squared test was used for categorical data; depending upon distribution, continuous data were compared with the analysis of variance or the Kruskal-Wallis test.

Group-wise survival was estimated with the non-parametric Kaplan Meier method and tested with the log-rank test. To determine the risk of observing our primary endpoint, adjusted for clinically important covariates, a semi-parametric Cox proportional hazards model (CPH) was utilised. I observed a time-varying relationship between heart failure group variable and survival **(Figure 7.2 and 7.3).** Therneau & Grambsch test confirmed that this variable failed the proportional hazards test and thus, a segmented Cox model was fit splitting the follow-up period into three segments - 0-1 years, 1-5 years and beyond 5 years. Other variables included in the model were: age at surgery, sex, race, prior history of myocardial infarction, prior percutaneous intervention, prior stroke, chronic kidney disease, prior heart surgery, prior atrial fibrillation, peripheral vascular disease, and preoperative dialysis dependence. The hazard ratios (with 95% confidence intervals) were obtained for each HF group (HFpEF, HFmrEF and HFrEF) using the no HF group as control. This segmented Cox approach allowed me to reliably model the flexible time-varying hazard observed in the non-parametric Kaplan Meier curve.

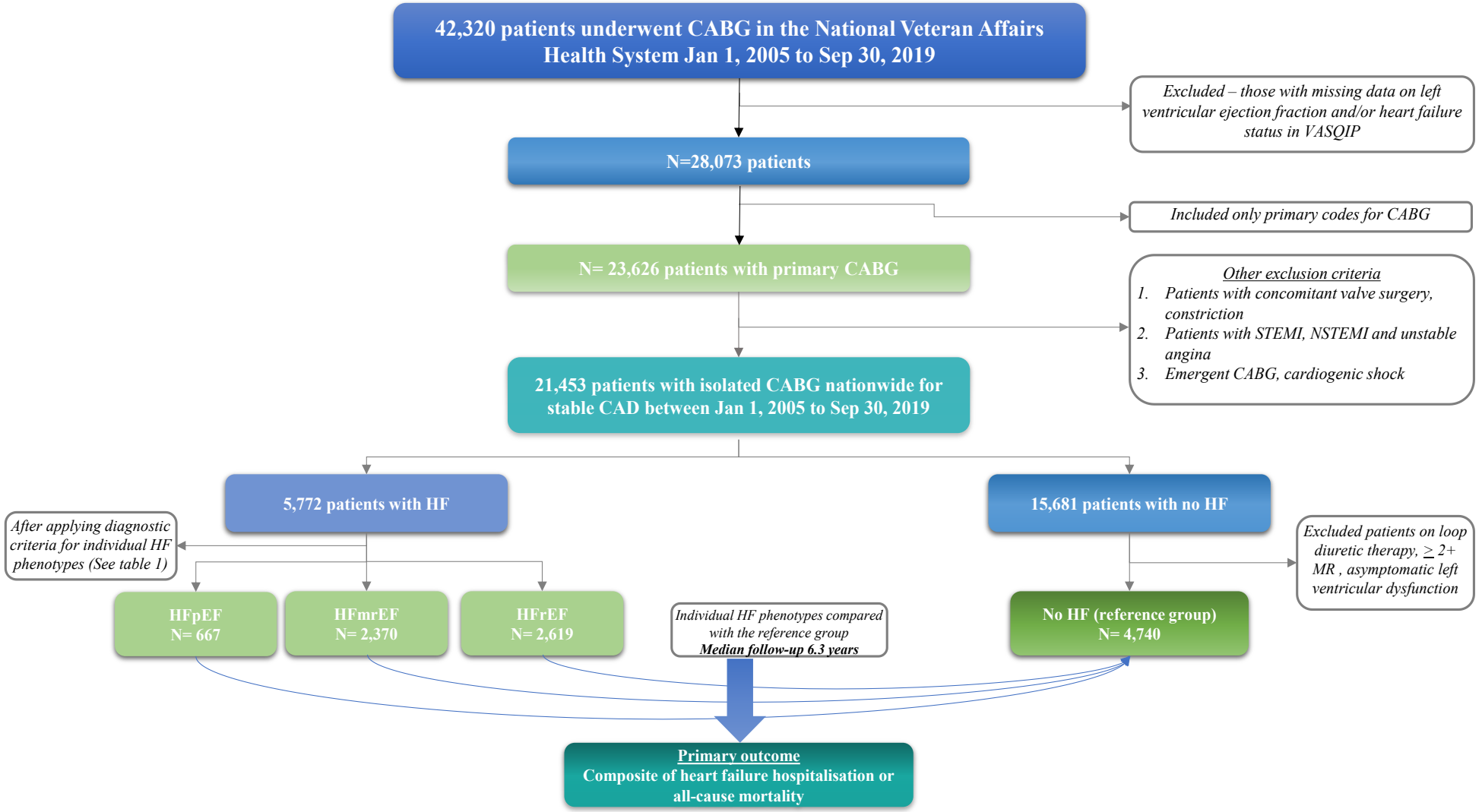
There is recent evidence to suggest that modelling heart failure as a recurrent event may provide a true estimate of HF burden (184,185) In my analyses, heart failure was modelled as (1) the cumulative incidence for the first HFH event in each group calculated as a competing-risk model, with mortality as the competing event. Recurrent HFH: modelled as a repeating event by taking the date of admission for each HFH. The mean cumulative count method was used to obtain adjusted event rates for each group (186,187) This method, introduced by Lin, et al has been recommended for modelling recurrent events in the presence of a competing terminal event (i.e., mortality).

Myocardial infarction was modelled with all-cause mortality being the competing risk event. The non-parametric cumulative incidence function was implemented to obtain event rates of myocardial infarction for each heart failure group during the study period. The median time to first heart failure hospitalisation in each heart failure group was obtained and compared with the no HF group with the Wilcoxon rank sum test. Heart failure hospitalisation was also modelled as a recurrent event. All heart failure hospitalisations for every patient during the study period were identified. A non-parametric mean cumulative count method was adopted to obtain the number of heart failure hospitalisations per 100 patient-years of follow-up in each HF group. Marginal means model was used to model the heart failure burden. A multivariable model, including the same variables listed earlier, was fit to obtain the adjusted hazard ratio (with 95% confidence intervals) for heart failure hospitalisations in HFpEF, HFmrEF and HFrEF patients compared to the reference group (no HF).

7.1.5 Cohort characteristics

After applying the study inclusion and exclusion criteria, I identified 10,396 patients who underwent isolated CABG for stable CAD **(Figure 7.1)**. Of the 10,396 patients who underwent isolated CABG, there were 4,740 patients with no HF, 667 with HFpEF, 2,370 with HFmrEF and 2,619 with HFrEF **(Table 7.2)**. The median age of patients in the study cohort 65 years (interquartile range 60 – 71) and did not significantly differ across the 4 groups **(Table 7.2)**. Patients with HFpEF were more likely to be obese, Caucasian, have atrial fibrillation and a higher mean eGFR compared to other groups **(Table 7.2).** Patients with HFrEF who had CABG were more likely to have advanced CKD (CKD stage >3), higher New York Heart Association (NYHA) score at baseline and prior myocardial infarction **(Table 7.2).**

Figure 7.1 Number of patients in the base cohort and study cohort.



VASQIP: The VA Surgical Quality Improvement Program (VASQIP) database; HF: Heart Failure; CABG: Coronary artery bypass surgery; STEMI: ST elevation myocardial infarction; NSTEMI: Non-ST elevation myocardial infarction; MR; Mitral regurgitation; CAD: Coronary artery disease

Table 7.2 Baseline characteristics of patients undergoing CABG stratified by different heart failure phenotypes and controls (no heart failure)

	No HF	HFpEF	HFmrEF	HFrEF	P-value
N	4,740	667	2,370	2,619	
Demographics					
Age (median [IQR])	65.0 [61.0, 71.0]	66.0 [62.0, 71.0]	65.0 [60.0, 72.0]	65.0 [60.0, 71.0]	0.03
Female, n (%)	46 (1.0)	7 (1.0)	22 (0.9)	17 (0.6)	0.51
Race, n (%)					<0.001
Black	357 (7.5)	51 (7.6)	220 (9.3)	296 (11.3)	
Others	958 (20.2)	102 (15.3)	423 (17.8)	515 (19.7)	
White	3425 (72.3)	514 (77.1)	1727 (72.9)	1808 (69.0)	
Co-morbidities, n (%)					
Diabetes	1,784 (37.6)	320 (48.0)	1,210 (51.1)	1,207 (46.1)	<0.001
Prior stroke	94 (2.0)	10 (1.5)	31 (1.3)	28 (1.1)	0.014
Prior MI	1,483 (31.3)	235 (35.2)	1,231 (51.9)	1,569 (59.9)	<0.001
Prior PCI	211 (4.5)	32 (4.8)	75 (3.2)	69 (2.6)	<0.001
CKD	693 (14.6)	107 (16.1)	500 (21.2)	636 (24.3)	<0.001
Obese	1,811 (38.2)	364 (54.6)	1,169 (49.3)	972 (37.1)	<0.001
Anaemia	1,441 (30.4)	252 (37.8)	1,008 (42.6)	1,152 (44.0)	<0.001
NYHA (mean (SD))	1.51 (0.50)	2.31 (0.92)	2.43 (0.97)	2.55 (0.97)	<0.001
Smoking	3,897 (82.2)	554 (83.1)	1,999 (84.3)	2,269 (86.6)	<0.001
Atrial Fibrillation	990 (20.9)	165 (24.7)	546 (23.0)	592 (22.6)	0.039
Mitral regurgitation severity					<0.001
0	3,324 (79.6)	429 (70.7)	1,292 (62.1)	1,100 (46.9)	
1+	851 (20.4)	138 (22.7)	575 (27.6)	830 (35.4)	
2+	0 (0.0)	23 (3.8)	136 (6.5)	342 (14.6)	
3+	0 (0.0)	17 (2.8)	78 (3.7)	71 (3.0)	
Baseline measurements					
BMI (median [IQR])	28.0 [25.6, 31.9]	30.7 [27.4, 34.8]	29.9 [26.3, 33.9]	28.3 [24.7, 31.9]	<0.001
HBA1c (mean (SD))	6.6 (1.4)	6.8 (1.3)	6.9 (1.5)	6.9 (1.6)	<0.001
Creatinine (median [IQR])	1.00 [0.9, 1.2]	1.1 [0.9, 1.3]	1.1 [0.9, 1.3]	1.1 [0.9, 1.3]	<0.001
eGFR (mean (SD))	90.7 (31.4)	90.4 (35.8)	88.2 (36.9)	83.7 (35.5)	<0.001
Hemoglobin (median [IQR])	13.8 [12.6, 14.8]	13.4 [12.2, 14.5]	13.3 [12.0, 14.4]	13.2 [11.8, 14.4]	<0.001
Serum albumin (median [IQR])	3.9 [3.6, 4.2]	3.9 [3.5, 4.2]	3.8 [3.40, 4.10]	3.7 [3.4, 4.1]	<0.001
Serum bilirubin (mean (SD))	0.6 (0.3)	0.6(0.3)	0. (0.32)	0.7 (0.4)	<0.001
Number of bypass grafts					
All Grafts, n (%)					0.089
1	363 (10.0)	55 (12.5)	195 (11.1)	189 (9.3)	
2	910 (24.9)	114 (26.0)	438 (24.9)	517 (25.5)	
3	1,614 (44.2)	188 (42.8)	716 (40.7)	865 (42.6)	
>3	761 (20.9)	82 (18.7)	409 (23.3)	459 (22.6)	
Medications at Discharge, n (%)					
ACEI/ARB	1,245 (26.3)	183 (27.4)	742 (31.3)	1,018 (38.9)	<0.001
Betablockers	4,584 (96.7)	643 (96.4)	2,267 (95.7)	2,511 (95.1)	0.105
Spironolactone	96 (2.0)	27 (4.0)	137 (5.8)	225 (8.6)	<0.001

Prior MI: Myocardial infarction, PCI: Percutaneous Coronary Intervention, NYHA: New York Heart Association, CKD, Chronic Kidney Disease, GFR: Glomerular Filtration Rate.

7.1.6 Primary outcome and overall survival following CABG stratified by heart failure phenotypes

Figure 7.2 reveals Kaplan-Meier estimates of overall survival for the 4 groups. The estimated 5-year all-cause mortality was observed in 14 +/- 0.5%, 16 +/- 1.3%, 24 + /- 0.9% and 29 +/- 0.9% in the no HF, HFpEF, HFmrEF and HFrEF groups respectively. At 10 years, 35 +/- 0.8%, 34 +/- 2.3%, 50 +/- 1.2% and 58 +/- 1.1% died in the no HF, HFpEF, HFmrEF and HFrEF groups respectively. At 5 years, the composite endpoint was observed in 18 +/- 0.5%, 21 +/- 1.6%, 35 +/- 1% and 43 +/- 1% in the no HF, HFpEF, HFmrEF and HFrEF groups respectively **(Figure 7.3)**. At 10 years, the composite endpoint occurred in 39 +/- 0.8%, 41 +/- 2.4%, 51 +/- 1.2% and 67 +/- 1% in the no HF, HFpEF, HFmrEF and HFrEF groups respectively **(Figure 7.3)**. The segmented hazard ratios with 95% CI for first one year of follow up, 1-5 years and the beyond 5 years are outlined in **Figure 7.4A-C**. Among all the groups, survival of patients with HFrEF following revascularisation was the lowest, followed by HFmrEF and HFpEF (**Figure 7.4 A-C)** Despite increasing hazard in the first year following revascularisation, the long-term survival of HFpEF post CABG was comparable to CABG patients with no history of HF (HR 0.85, 95% CI 0.68-1.06) (**Figure 7.4 A-C)**

When primary outcome was analysed stratified by the degree of systolic function, patients with HF and EF > 55% and those 45-54% had outcomes which were comparable to the reference group. There was graded increased in adjusted hazard ratio for primary outcome with declining EF **(Figure 7.5)**

Table 7.3 Segmented Hazard Ratios for the primary outcome of composite of HF hospitalisation and mortality stratified by heart failure phenotypes for 1 year, 1-5 years, 10 years

Variables	0-1 year	1-5 years	5-10 years
Heart Failure Phenotypes			
HFpEF	1.9 (1.5 - 2.6)	0.8 (0.6 - 1.0)	0.9 (0.7 - 1.1)
HFmrEF	2.6 (2.1 - 3.1)	1.5 (1.3 - 1.7)	1.3 (1.2 - 1.5)
HFrEF	3.2 (2.7 - 3.7)	2.0 (1.8 - 2.2)	1.6 (1.4 - 1.8)
Demographics			
Age	1.0 (0.9 - 1.1)	1.1 (1.0 - 1.2)	1.1 (1.0 - 1.2)
Caucasian race	0.9 (0.7 - 1.1)	0.9 (0.8 - 1.1)	1.0 (0.9 - 1.2)
Co-morbidities			
Diabetes Mellitus	1.4 (1.2 - 1.6)	1.8 (1.6 - 2.0)	1.7 (1.5 - 1.9)
Chronic Kidney Disease	1.4 (1.2 - 1.7)	1.4 (1.2 - 1.6)	1.4 (1.2 - 1.6)
Prior Myocardial Infarction	1.2 (1.1 - 1.4)	1.1 (1.0 - 1.2)	1.0 (0.9 - 1.1)
Prior Stroke	0.9 (0.5 - 1.6)	0.9 (0.6 - 1.4)	0.6 (0.3 - 1.1)
Atrial Fibrillation	1.1 (1.0 - 1.3)	1.3 (1.1 - 1.4)	1.2 (1.1 - 1.3)
COPD	1.5 (1.3 - 1.7)	1.4 (1.3 - 1.6)	1.4 (1.3 - 1.5)
Anaemia	1.5 (1.3 - 1.7)	1.6 (1.5 - 1.8)	1.3 (1.1 - 1.4)
Smoking	1.1 (0.9 - 1.3)	1.1 (1.0 - 1.3)	1.3 (1.1 - 1.4)
Body Mass Index	1.1 (1.0 - 1.1)	1.0 (0.9 - 1.1)	0.9 (1.0 - 1.1)
Prior PCI	1.0 (0.7 - 1.5)	0.9 (0.7 - 1.2)	0.9 (0.7 - 1.2)

HFpEF: Heart Failure with preserved Ejection Fraction; HFmrEF: Heart Failure with mid-range Ejection Fraction; HFrEF: Heart Failure with reduced Ejection Fraction

Figure 7.2 Overall survival following CABG stratified by HF phenotypes

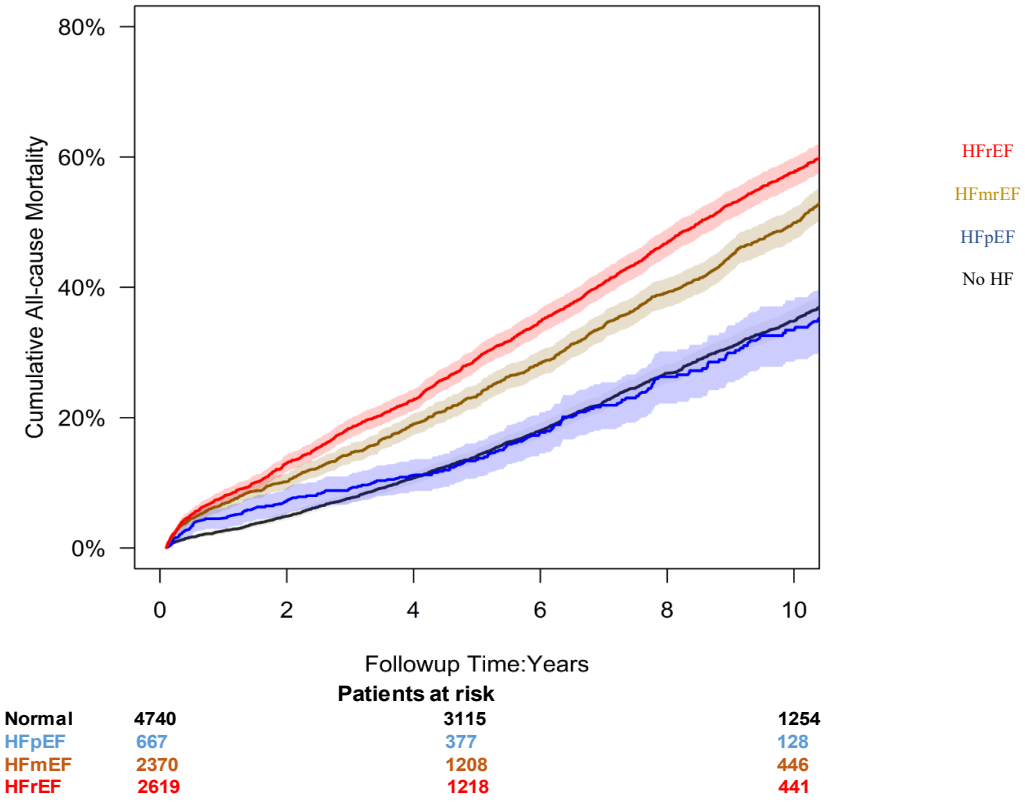


Figure 7.3 Primary outcome following CABG stratified by HF phenotypes; Outcome: Composite of all-cause mortality/heart failure hospitalisation

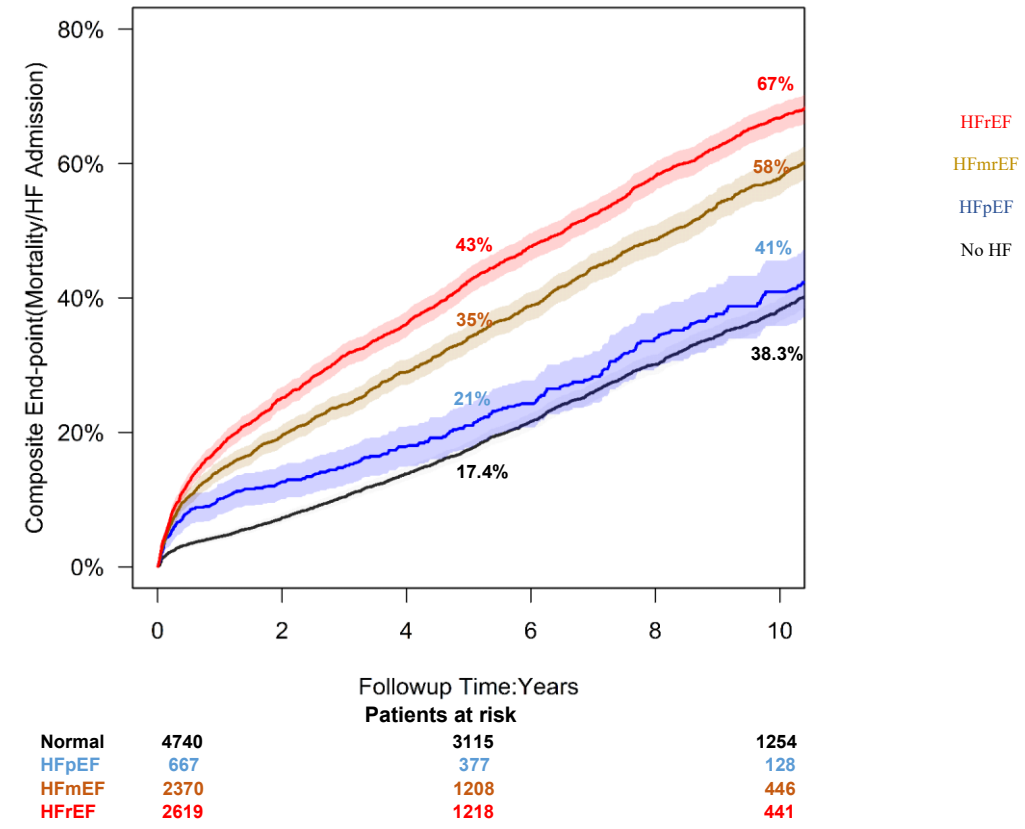
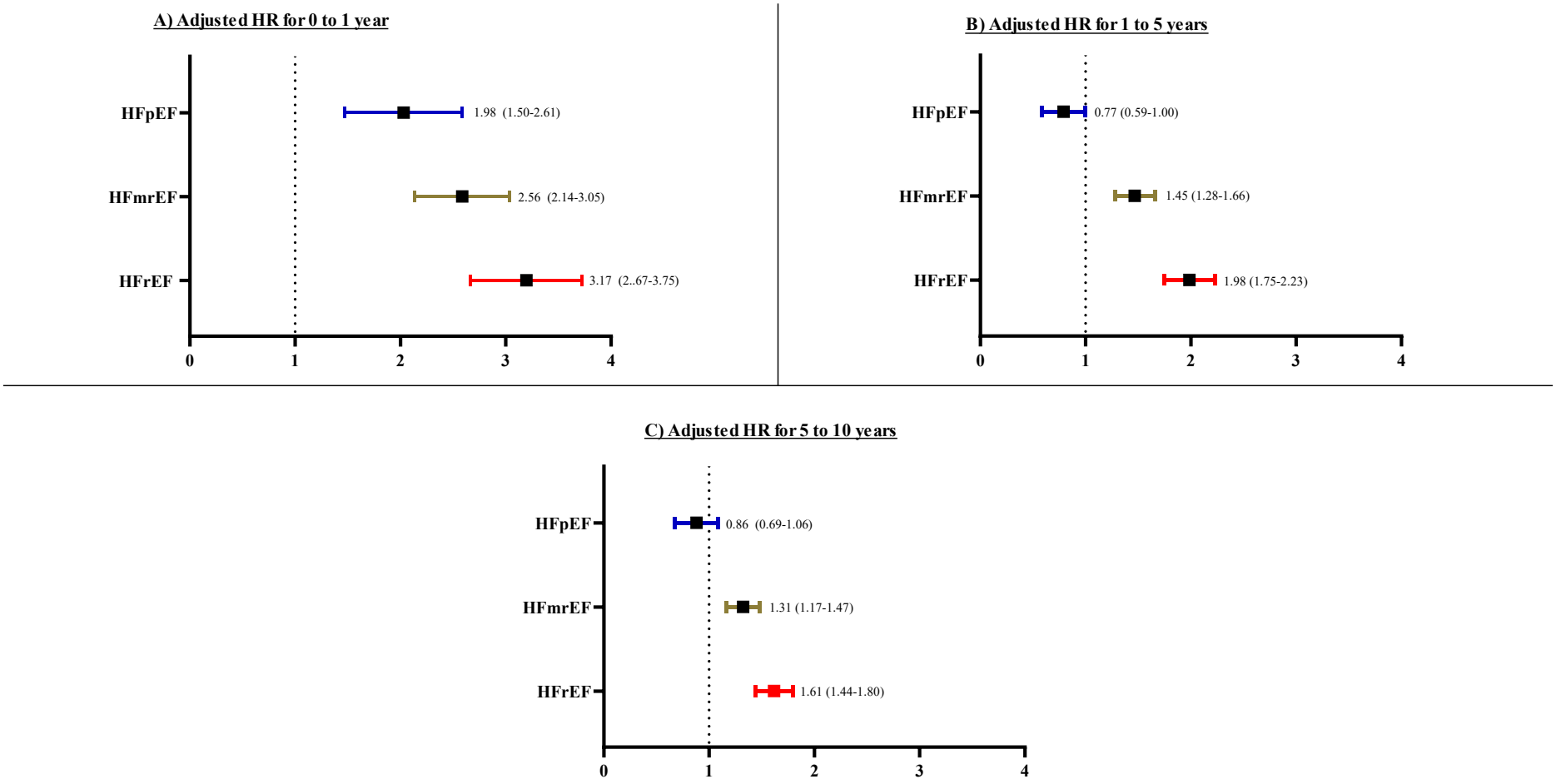


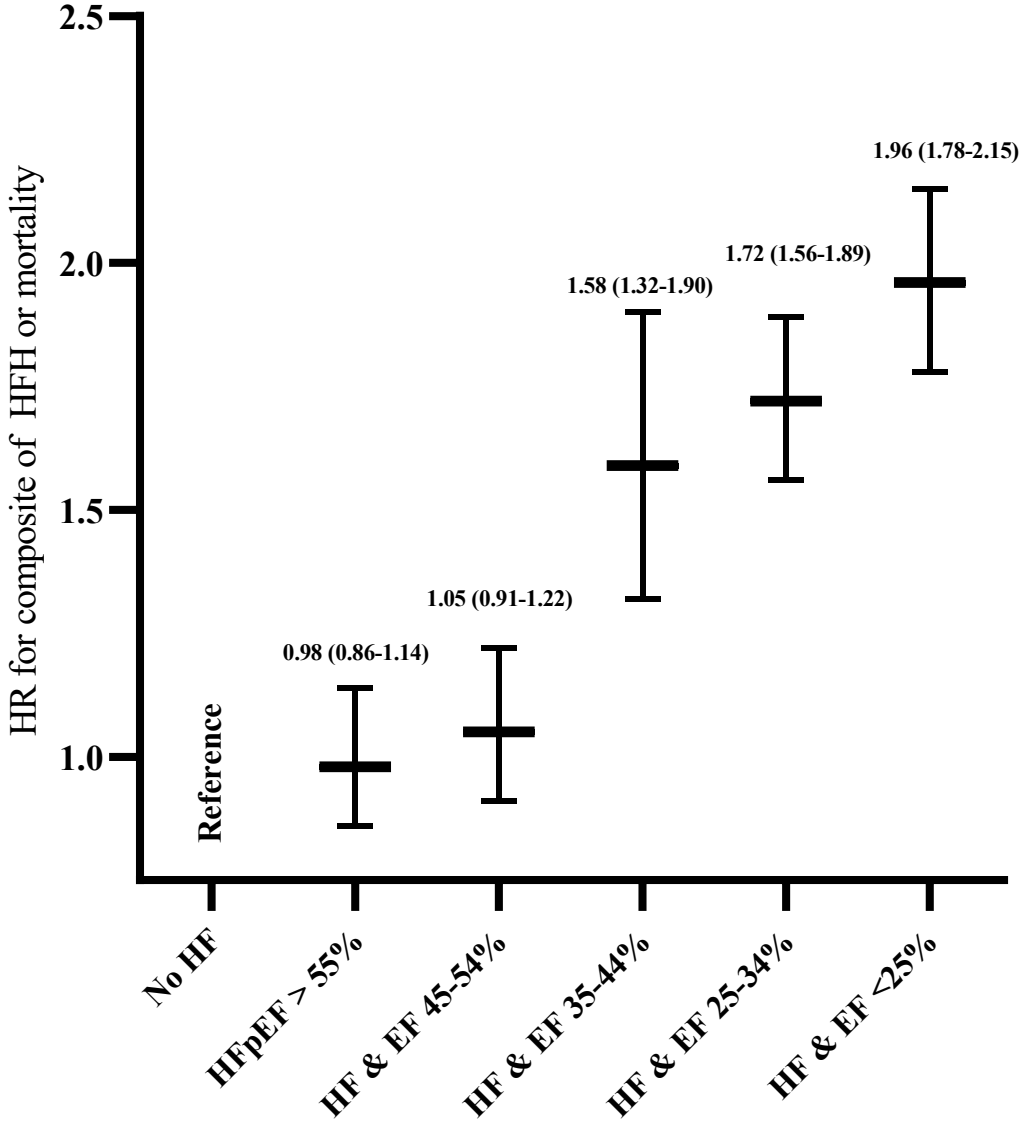
Figure 7.4 A-C Multisegmented Cox model for primary outcome stratified by different time periods (no HF as the reference group



HR: adjusted hazard ratio; HF: Heart Failure; HFH: Heart Failure Hospitalisation; HFpEF: Heart Failure with preserved ejection fraction; x axis: follow up time in years

** Group with no heart failure was used as the reference* Model was adjusted for surgery, sex, race, prior history of myocardial infarction, prior percutaneous intervention, prior stroke, chronic kidney disease, prior heart surgery, prior atrial fibrillation, peripheral vascular disease, and preoperative dialysis dependence*

Figure 7.5 Primary outcome stratified by different grades of systolic function



EF: left ventricular ejection fraction; HR: adjusted hazard ratio; HF: Heart Failure; HFH: Heart Failure Hospitalisation; HFpEF: Heart Failure with preserved ejection fraction

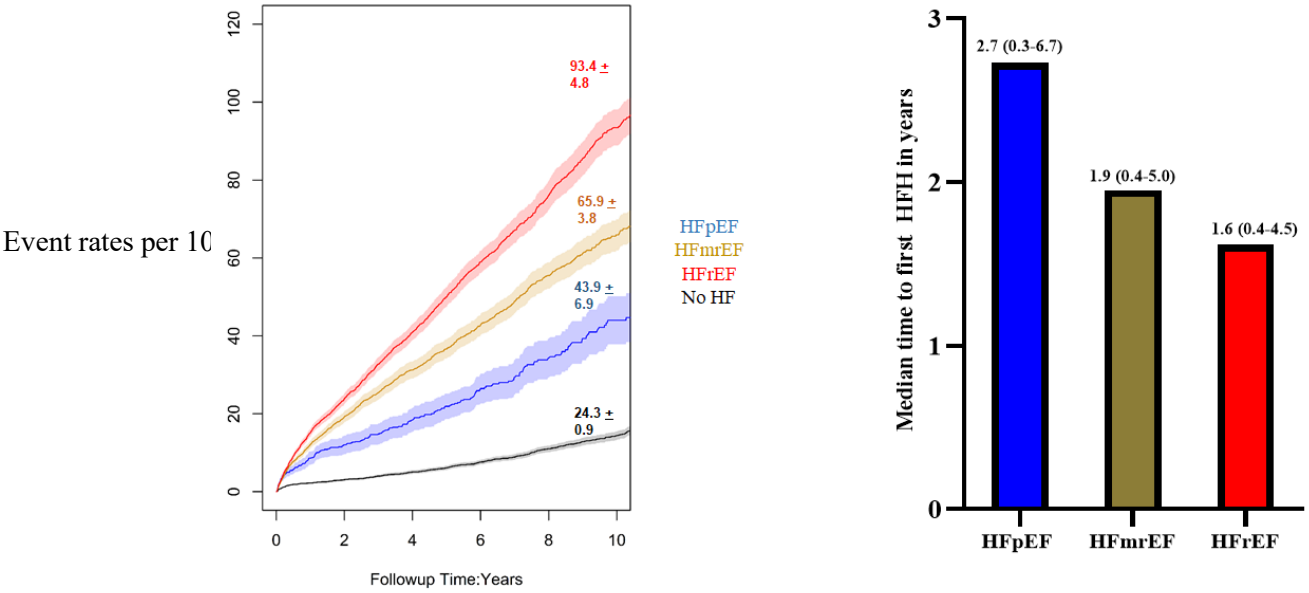
** Group with no heart failure was used as the reference*

** Model was adjusted for surgery, sex, race, prior history of myocardial infarction, prior percutaneous intervention, prior stroke, chronic kidney disease, prior heart surgery, prior atrial fibrillation, peripheral vascular disease, and preoperative dialysis dependence*

7.1.7 Heart failure hospitalisations following CABG stratified by heart failure phenotype

Overall, there were 3,344 heart failure hospitalisations in the whole cohort. At 5 years, the incidence of heart failure hospitalisations was 6.1 +/- 0.5, 21.9 +/- 3.4, 36.6 +/- 2.4 and 49.9 +/- 2.6 per 100 patient years of follow up in the no HF, HFpEF, HFmrEF and HFrEF groups. At 10 years, I observed 14.3 +/- 1.1, 43.9 +/- 6.9, 65.9 +/- 3.8 and 93.4 +/- 4.8 heart failure hospitalisations per 100 patient years of follow up in the no HF, HFpEF, HFmrEF and HFrEF groups respectively (Figure 7.6A). The median time to first heart failure hospitalisation post CABG was progressively shorter with a lower baseline EF (Figure 7.6 B). On adjusted analysis, HFpEF [HF 2.32(1.93 – 2.79); p < 0.001], HFmrEF [HF 3.49(3.09 – 3.93); p < 0.001] and HFrEF [HR 5.01 (4.46 – 5.63); p < 0.001] had higher risk for heart failure hospitalisations compared to the control group.

Figure 7.6 Heart Failure burden following CABG stratified by HF phenotypes;



A) Recurrent Heart Failure Hospitalisations **B) Median Time to First Heart Failure Hospitalisation**

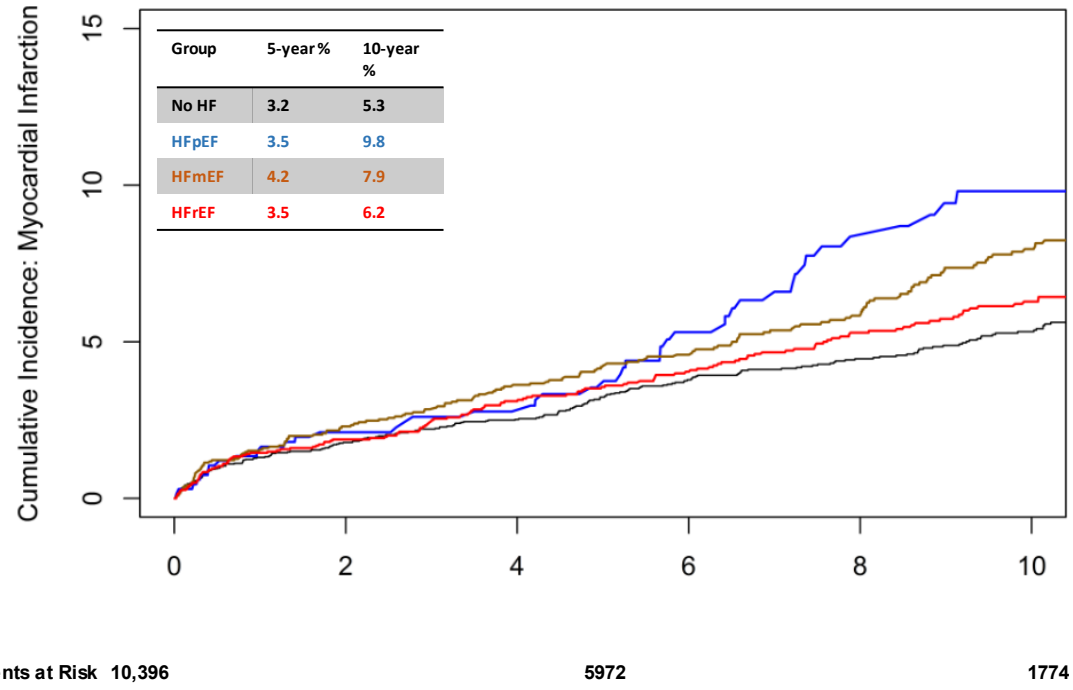
Heart failure hospitalisation is presented as median (25-75 IQR); HFH: heart failure hospitalisation; HF: heart failure; All HF phenotypes were compared with patients with no HF (reference group)

7.1.8 Myocardial infarction following CABG stratified by HF phenotype and its impact on overall survival

Figure 7.7 describes the cumulative estimate for MI following revascularisation for the entire cohort stratified HF phenotype. At 10 years, the cumulative incidence of MI was highest in the HFpEF group

(9.8%), followed by normal patients (7.9%), HFmrEF (6.2%), and HFrEF (5.3%). Compared to the normal group, the crude risk of myocardial infarction was higher in the HFpEF [HR 1.52(1.11 – 2.08); p = 0.007] and HFmrEF [HR 1.31(1.07 – 1.599); p = 0.008].

Figure 7.7 Cumulative incidence of Myocardial Infarction following CABG stratified by HF phenotypes



DISCUSSION

In this nationwide analysis of predominantly with CAD undergoing CABG in the VA health system, I carefully stratified patients by baseline HF phenotype (HFpEF, HFmrEF, HFrEF) and compared their future risk of death, HF hospitalisation and MI to a control group of patients without HF who underwent CABG

7.1.9 Major findings

The major findings of this study are as follows.

i) Despite increasing hazard in the first year following revascularisation, the long-term outcomes (composite of mortality and heart failure hospitalisation) of HFpEF post CABG were comparable to CABG patients with no heart failure.

ii) Heart failure hospitalisation burden, modelled as recurrent event, was higher in HFpEF patients following CABG when compared to those with no heart failure; however, the median time to first heart failure hospitalisation, though numerically higher in the HFpEF group was not statistically significant between HFpEF and those with no HF

iii) Following revascularisation, the cumulative incidence of myocardial infarction was highest in patients with HFpEF (9.8%).

iv) Among all the groups, composite outcome, and survival of patients with HFrEF following revascularisation was the lowest, followed by HFmrEF and HFpEF.

7.1.10 Revascularisation and its impact on different heart failure phenotypes

The role of coronary revascularisation in patients with CAD and systolic heart failure has been well established. The 10 year follow up results of the STITCH trial showed the rate of death from any cause and death from cardiovascular cause or cardiovascular hospitalisation to be lower among patients with systolic heart failure who underwent CABG compared to those receiving medical therapy alone (179). However, there is no concrete evidence on the impact of revascularisation in patients with CAD and diastolic heart failure. Borlaug et al demonstrated that, among patients with CAD and HFpEF, revascularisation was associated with a lesser decline in ejection fraction compared to those only receiving medical therapy (181). However, this study has inherent limitations, including patients from a single tertiary referral centre, a relatively short follow up period, and observational nature limiting causal inference. There are no randomised trials to date which determined the optimal management of CAD in patients with HFpEF. In this nationwide study from Veteran Affairs Health System, the primary outcome of HFpEF following revascularisation was comparable to the control group with no HF, indicating that revascularisation may have had a favourable impact in the prognosis of HFpEF. The results of my study were contrary to those observed in the analysis of nationwide cohort from Swedish population and from the CREDO-Kyoto CABG Registry were HFpEF patients post CABG had increased adjusted hazard for mortality compared to those with no HF(182,183). This could be due to a

myriad of reasons. Firstly, the median follow-up of our study was much higher compared to the other two studies. Secondly, while this analysis included a nationwide cohort of patients who underwent CABG, the veteran population is unique with a different set of risk factors compared to general population. Finally, it is plausible there are cross country differences in the patient selection for cardiac surgeries in patients with heart failure.

7.1.11 CAD-HFpEF: A distinct sub-phenotype?

Concomitant CAD has prognostic implications in patients with HFpEF and is associated with a higher risk of cardiovascular death and heart failure hospitalisation compared to HFpEF patients with no CAD (188,189). A retrospective single centre study of 376 patients with HFpEF showed that CAD was associated with a greater decline in left ventricular systolic function in patients with HFpEF compared to those without CAD (181). Lupon et al, provided convincing evidence of only a marginal decline in left ventricular ejection fraction (+0.5% annually) in a prospective study of HFpEF patients with 11 years follow up. However, the investigators observed a transition of HFpEF to HFrEF in patients with CAD(190). The findings of these two studies coupled with the results of my analysis suggest ischemic cardiomyopathy to be continuum characterised by a longitudinal decline in left ventricular systolic function (HFpEF to HFrEF). Early intervention with revascularisation may arrest the decline of progressive contractile dysfunction and improve survival as demonstrated by the long-term follow-up results of this study. I also believe that the definition of ischemic cardiomyopathy might need a rethink to include patients with significant ischemic heart disease and clinical heart failure regardless of left ventricular ejection fraction (191).

7.1.12 Strengths and limitations

Previous studies have shown a poor discriminative performance of clinical assessment and non-invasive stress testing strategies for identification of CAD among patients with HFpEF (181). Since this cohort included patients undergoing CABG, it is likely that these patients had angiographically proven CAD with significant ischemic burden. Unlike previous studies, I had included a rigorous definition of HFpEF which was well validated and excluded all potential alternative causes of cardiomyopathy (e.g., valvular cardiomyopathy, acute coronary syndromes, constrictive and restrictive cardiomyopathy). The baseline characteristics of HFpEF and HFrEF patients in this cohort were in line with the previous studies, with significantly higher prevalence of Caucasians, obesity and atrial fibrillation among patients with HFpEF and a higher prevalence of prior MI in patients with HFrEF (188,192,193). The 10-year event rates in the HFrEF population following CABG in this study was similar to the revascularisation arm of the STITCH trial, signifying reasonable validity to the results of the analysis (179).

While this study has several strengths there are some important limitations. The co-morbidity burden among the Veterans may be different from those in the general population. Less than 3% of the study

population were women. The external applicability of the study to the general population needs further evaluation. The classification of HFpEF in this study required a higher ejection fraction than defined in the European Society of Cardiology guidelines (55% instead of 50%). This is because EF was only available as a nominal variable in the VASQIP database. EF was categorised into six groups <20%, 20-30%, 30-35%, 35-40%, 41-45%, 46-55% and > 55%. Certain important information such as the cause of death and follow up echocardiogram were not available in this database. I was not able to create a true control group within the VASQIP database, i.e., patients with CAD and HFpEF with no revascularisation, as the database included only patients who underwent surgery.

CONCLUSION

This nationwide study from the Veteran Affairs Health System in the United States suggest that CAD might have a causal link in the pathogenesis of HFpEF, indicating a distinct sub-phenotype. Overall, the data supports the safety of CABG in HFpEF patients and suggests a possible continuum of mortality risk in ischemic HF when stratified by baseline EF. Early intervention with revascularisation may arrest the decline of progressive contractile dysfunction and improve survival in patients with CAD and HFpEF. Further randomised control trials are needed to confirm this hypothesis generating observation.

Chapter 8: **Conclusion – Future Research Directions**

TRANSCULTURAL LESSONS IN THE MANAGEMENT OF HEART FAILURE; NEED TO EVALUATE LONG TERM OUTCOMES?

The prognosis of patients with heart failure (HF) is reported to differ amongst health care systems. However, many such analyses come from clinical trials of highly selected patients that are unrepresentative of the general population with HF. Clinical trial protocols usually recruit patients with a definite diagnosis and heightened risk of events. Patients who agree to trials may have a specific psychological profile and disease severity (neither very well nor very ill) and, for various reasons, researchers often avoid enrolling the sickest, frailest patients. It is therefore imperative that post hoc analysis of clinical trials of geographic differences in patient characteristics, health care resource utilisation (HRU) and outcomes be interpreted with caution. While the external validity of registries is superior to that of clinical trials population, it is not necessarily the gold standard for real world evidence. Patients in registries are often recruited from tertiary medical centres, non-consecutively enrolled and treated differently than those in regular clinical practice.

The results of specific aims 1 and 2 using electronic healthcare records (EHR) from respective countries, indicate that there are marked cross country differences in patient characteristics, treatment patterns and health HRU among patients hospitalised for HF. However, these hypothesis generating findings raises multiple questions i) Firstly, while there are differences in short term outcomes, it is unclear if this observation is true for long term outcomes and requires further investigation. Future research focussing on long term outcomes could be used to create prognostic models within each data set (and in key subgroups of interest in each dataset). The model could be applied to clinical trials to determine whether similar patients drawn from the general population and from the trial population have similar outcomes ii) It is possible that the differences observed could be related to the variations in the threshold for HF hospitalisation across the countries. There are multiple factors including cultural differences and financial incentives which could affect the threshold for heart hospitalisation.

PHENOTYPING HEART FAILURE AT THE POPULATION LEVEL IN ELECTRONIC HEALTHCARE RECORDS

EHR provides an excellent resource for population science research in heart failure. However, identifying specific heart failure phenotypes in EHR is challenging due to the lack of availability of left

ventricular ejection fraction (LVEF) measurements. In my study using the Health Care Improvement Network (THIN), I was not able to identify an algorithm as an acceptable surrogate to LVEF measurements. While I was able to identify algorithms for identification of HFrEF with reasonable PPV and specificity, the study was not designed to investigate the negative predictive value and sensitivity. The results of my study iterate the fact that future HF validation studies should focus on building natural language processing (NLP) tools to capture LVEF from unstructured data such as text files etc. Furthermore, linkage of nationwide electronic health records (CPRD and THIN) with national audits such as National Heart Failure Audit (LVEF data is available), similar to CPRD linkages with cancer registries including the National Radiotherapy Dataset (RTDS) and Systemic Anti-Cancer Therapy (SACT) Dataset in the UK (194,195), might ensure phenotypic refinement of heart failure and facilitate phenotypic specific research at the population level, which is crucial given the heterogenous nature of the disease.

OBESE HEART FAILURE WITH PRESERVED EJECTION FRACTION (OBESE HFPEF): NEED FOR URGENT FOCUS ON PREVENTION AND TREATMENT

Obesity is a major public health issue, and the worldwide prevalence of obesity has increased substantially in the past four decades, across developed and developing economies. Although obesity is linked with incident HFpEF and has distinct pathophysiological features that support a causal relationship, it has been challenging to uncouple the effects of diabetes from obesity in HFpEF epidemiology (44,161,196,197). In chapter 6, I have attempted to delineate the independent contribution of diabetes versus obesity to the rising prevalence of HFpEF in the last decade. I observed that in the United States, there has been a substantial increase in the prevalence of obesity in HFpEF patients in the last decade which is far greater than the prevalence of diabetes. Obesity disproportionately affected younger patients contributing to a substantial national disease burden. These findings warrant further evaluation of the metabolic heterogeneity of obesity and the risk of HFpEF. Further evaluation of the impact of treating obesity (gastric bypass surgery, liraglutide/semgalutide, other weight loss programs etc.) in preventing incident HFpEF (primary prevention) and reducing heart failure burden (secondary prevention) among those with established HFpEF is urgently needed.

RANDOMISED TRIALS TO EVALUATE THE EFFECT OF REVASCULARISATION IN ISCHEMIC HFPEF

Coronary artery disease (CAD) is one of the commonest comorbidities in patients with HFpEF. In HFpEF the presence of CAD may contribute to a distinct HFpEF phenotype. Although, there is no approved treatment for HFpEF, revascularisation of obstructive CAD may have therapeutic implications. In my analysis, I observed that unlike non-ischemic HF (177,178), were there is U shaped relationship between LVEF and outcomes, ischemic HF probably exists on continuous spectrum with a stepwise increase in the risk of future HF hospitalisations and mortality with declining LVEF. This signifies the possible role of conventional neurohormonal antagonists across the spectrum of ischemic heart failure (including ischemic HFpEF), a hypothesis which requires confirmation with further studies. Finally, the role of revascularisation in patients with significant CAD and HFpEF needs to be systematically investigated in a randomised fashion.

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Page No.	Type of work:	Name of work	Source of work	Copyright holder and contact	permission requested on	I have permission yes /no	Permission note
10	Figure 1.1	Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF	2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC	RightsLink / Oxford University Press	MARCH 8, 2021	yes	Online permission
11	Figure 1.2	Figure 1. The Challenging Landscape of Heart Failure	The Emerging Epidemic of Heart Failure with Preserved Ejection Fraction. Curr Heart Fail Rep. 2013 Dec; 10(4): 10.1007/s11897-013-0155-7.	Springer Nature	MARCH 8, 2021	yes	Online permission

12	Figure 1.3 A,	Figure 1. Kaplan–Meier Plot of Time to the First Confirmed Primary-Outcome Event	Spironolactone for Heart Failure with Preserved Ejection Fraction. N Engl J Med 2014; 370:1383-1392	Massachusetts Medical Society			Out of copyright
12	Figure 1.3 B	Figure 2. Primary outcome	Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003 Sep 6;362(9386):777-81	Elselvier	MARCH 8, 2021	Yes	Yes
12	Figure 1.3 C	Figure 2. Time-to-Event Curves for Primary Composite Outcome and Its Components	Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. N Engl J Med 2019; 381:1609-1620	Massachusetts Medical Society			Out of Copyright
12	Figure 1.3 D	Figure 1. Kaplan–Meier Curves for the Primary Outcome	Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction. N Engl J Med 2008; 359:2456-2467	Massachusetts Medical Society			Out of Copyright
14	Figure 1.4	Figure 1. Mechanisms by which activation of the leptin-aldosterone-neprilysin axis may	Leptin-Aldosterone-Neprilysin Axis: Identification of Its Distinctive Role in the Pathogenesis of the Three Phenotypes of Heart	Wolters Kluwer Health, Inc.	MARCH 8, 2021	Yes	Yes

		exacerbate the pathophysiological abnormalities of heart failure	Failure in People With Obesity. Circulation. 2018 Apr 10;137(15):1614-1631				
14	Figure 1.5	Figure 1 Mechanisms by which metabolic disorders may simul-taneously cause atrial and ventricular myopathy, leading to atrial □brillation and to heart failure with preserved ejection fraction.	Do most patients with obesity or type 2 diabetes, and atrial fibrillation, also have undiagnosed heart failure? A critical conceptual framework for understanding mechanisms and improving diagnosis and treatment. Eur J Heart Fail. 2020 Feb;22(2):214-227	John Wiley and Sons	MARCH 8, 2021	Yes	Yes
21	Figure 2.1	Figure2 Example of Data structure	Data Resource Profile: Clinical Practice Research Datalink (CPRD): Int J Epidemiol. 2015 Jun; 44(3): 827–836	Creative commons			Unrestricted use; out of copyright
22	Table 2.2	Supplementary Table 2: Data files supplied by the Clinical Practice Research Datalink	Data Resource Profile: Clinical Practice Research Datalink (CPRD): Int J Epidemiol. 2015 Jun; 44(3): 827–836	Creative commons			Unrestricted use; out of copyright

23	Table 2.3	Table 1 Structure of hierarchies	What are Read codes? Health Libr Rev. 1994 Sep;11(3):177-82.	John Wiley and Sons	MARCH 8, 2021	Yes	Yes
23	Figure 2.2	Figure 1: Identifiable data	Approach to record linkage of primary care data from Clinical Practice Research Datalink to other health-related patient data: overview and implications. European Journal of Epidemiology volume 34, pages91–99(2019)	Creative commons			Unrestricted use; out of copyright
24	Table 2.4	Table 1 Selection of key data fields available for each finished consultant episode (FCE) in HES APC data22	Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). Int J Epidemiol. 2017 Aug 1;46(4):1093–1093i	Creative commons			Unrestricted use; out of copyright
26	Table 2.5	Table 1: Quality and Outcomes Framework (QOF) condition crude prevalence's in THIN compared with UK national QOF data	Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. Inform Prim Care. 2011;19(4):251–5		March 15th,2021	Not yet; awaiting	

27	Figure 2.3	Figure 1 Comparison of The Health Improvement Network (THIN) population and UK population in 2009 according to age and gender	Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. Inform Prim Care. 2011;19(4):251–5		March 15th,2021	Not yet; awaiting	

Supplementary Appendix

Supplementary Table 1: Codes for identification of heart failure in the UK, US, Taiwan and Japan

ICD-9-CM (United States and Taiwan)		ICD-10 (United Kingdom and Japan)	
Code	**Diagnosis**	**Code**	**Diagnosis**
39891	Rheumatic heart failure (congestive)	I09.81	Rheumatic heart failure
4280	Congestive heart failure, unspecified	I50.814	Right heart failure due to left heart failure
		I50.9	Heart failure, unspecified
4281	Left heart failure	I50.1	Left ventricular failure, unspecified
42820	Systolic heart failure, unspecified	I50.20	Unspecified systolic (congestive) heart failure
42821	Acute systolic heart failure	I50.21	Acute systolic (congestive) heart failure
42822	Chronic systolic heart failure	I50.22	Chronic systolic (congestive) heart failure
42823	Acute on chronic systolic heart failure	I50.23	Acute on chronic systolic (congestive) heart failure
42830	Diastolic heart failure, unspecified	I50.30	Unspecified diastolic (congestive) heart failure
42831	Acute diastolic heart failure	I50.31	Acute diastolic (congestive) heart failure
42832	Chronic diastolic heart failure	I50.32	Chronic diastolic (congestive) heart failure
42833	Acute on chronic diastolic heart failure	I50.33	Acute on chronic diastolic (congestive) heart failure
42840	Combined systolic and diastolic heart failure, unspecified	I50.40	Unspecified combined systolic (congestive) and diastolic (congestive) heart failure
42841	Acute combined systolic and diastolic heart failure	I50.41	Acute combined systolic (congestive) and diastolic (congestive) heart failure
42842	Chronic combined systolic and diastolic heart failure	I50.42	Chronic combined systolic (congestive) and diastolic (congestive) heart failure
42843	Acute on chronic combined systolic and diastolic heart failure	I50.43	Acute on chronic combined systolic (congestive) and diastolic (congestive) heart failure
4289	Heart failure, unspecified	I50.810	Right heart failure, unspecified
		I50.811	Acute right heart failure
		I50.812	Chronic right heart failure
		I50.813	Acute on chronic right heart failure
		I50.82	Biventricular heart failure
		I50.83	High output heart failure

	I50.84	End stage heart failure
	I50.89	Other heart failure
	I50.9	Heart failure, unspecified

Supplementary Table 2: Codes used for evaluation of co-morbidities in the UK, USA, Taiwan, and Japan

9.1.1 Coronary artery disease

9.1.2 Atrial fibrillation

9.1.3 Diabetes mellitus

9.1.4 Hypertension

9.1.5 Chronic lung disease

9.1.6 Chronic kidney disease

9.1.7 Chronic liver disease

9.1.8 Peripheral arterial disease

9.1.9 Obesity

9.1.10 Chronic anaemia

9.1.11 Pulmonary circulation disorders

9.1.12 Alcohol abuse

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
Coronary artery disease						
4110	Postmyocardial infarction syndrome	I241	Dressler's syndrome	241	G30..00	acute myocardial infarction
4111	Intermediate coronary syndrome	I200	Unstable angina	732	7928z00	Transluminal balloon angioplasty of coronary artery NOS
41181	Acute coronary occlusion without myocardial infarction	I240	Acute coronary thrombosis not resulting in myocardial infrc	733	7A54000	Percutaneous transluminal angioplasty of artery NEC
41189	Other acute and subacute forms of ischemic heart disease, other	I248	Other forms of acute ischemic heart disease	737	792..11	Coronary artery bypass graft operations
412	Old myocardial infarction	I252	Old myocardial infarction	1021	5543.00	Coronary arteriograph.abnormal
4130	Angina decubitus	I208	Other forms of angina pectoris	1204	G30..14	Heart attack
4131	Prinzmetal angina	I201	Angina pectoris with documented spasm	1344	G340.12	Coronary artery disease
4139	Other and unspecified angina pectoris	I209	Angina pectoris, unspecified	1430	G33..00	Angina pectoris
41400	Coronary atherosclerosis of unspecified type of vessel, native or graft	I2510	Athscl heart disease of native coronary artery w/o ang pctrs	1431	G311.13	Unstable angina
41401	Coronary atherosclerosis of native coronary artery	I25810	Atherosclerosis of CABG w/o angina pectoris	1655	G340.11	Triple vessel disease of the heart
41402	Coronary atherosclerosis of autologous vein bypass graft	I25811	thscl native cor art of transplanted heart w/o ang pctrs	1676	G3z..00	Ischaemic heart disease NOS
41403	Coronary atherosclerosis of non-autologous biological bypass graft	I2582	Chronic total occlusion of coronary artery	1677	G30..15	MI - acute myocardial infarction
41404	Coronary atherosclerosis of artery bypass graft	I2583	Coronary atherosclerosis due to lipid rich plaque	1678	G308.00	Inferior myocardial infarction NOS
41405	Coronary atherosclerosis of unspecified bypass graft	I2584	Coronary atherosclerosis due to calcified coronary lesion	1792	G3...13	IHD - Ischaemic heart disease
41406	Coronary atherosclerosis of native coronary artery of transplanted heart	I259	Chronic ischemic heart disease, unspecified	2155	G341000	Ventricular cardiac aneurysm
4142	Chronic total occlusion of coronary artery	I2589	Other forms of chronic ischemic heart disease	2491	G30..12	Coronary thrombosis
4143	Coronary atherosclerosis due to lipid rich plaque	I255	Ischemic cardiomyopathy	2901	7928.00	Transluminal balloon angioplasty of coronary artery
4144	Coronary atherosclerosis due to calcified coronary lesion	Z951	Presence of aortocoronary bypass graft	3704	G307.00	acute subendocardial infarction
4148	Other specified forms of chronic ischemic heart disease	Z9861	Coronary angioplasty status	3999	G340000	Single coronary vessel disease

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
4149	Chronic ischemic heart disease, unspecified	I2589	Other forms of chronic ischemic heart disease	4017	G32..00	Old myocardial infarction
V4581	Aortocoronary bypass status			5387	G301.00	other specified anterior myocardial infarction
V4582	Percutaneous transluminal coronary angioplasty status			5413	G340.00	Coronary atherosclerosis
4110	Postmyocardial infarction syndrome			5703	7928.11	Percutaneous balloon coronary angioplasty
4111	Intermediate coronary syndrome			5744	7927500	Open angioplasty of coronary artery
41181	Acute coronary occlusion without myocardial infarction			5904	792..00	Coronary artery operations
41189	Other acute and subacute forms of ischemic heart disease, other			6182	7929y00	Other therapeutic transluminal op on coronary artery OS
412	Old myocardial infarction			7134	7921.11	Other autograft bypass of coronary artery
4130	Angina decubitus			7137	7920y00	Saphenous vein graft replacement of coronary artery OS
				7320	G343.00	Ischaemic cardiomyopathy
				7347	G311100	Unstable angina
				7442	7920200	Saphenous vein graft replacement of three coronary arteries
				7609	7921z00	Other autograft replacement of coronary artery NOS
				7634	7920100	Saphenous vein graft replacement of two coronary arteries
				8312	7920.11	Saphenous vein graft bypass of coronary artery
				8679	7920000	Saphenous vein graft replacement of one coronary artery
				8935	G302.00	acute inferolateral infarction
				8942	7929400	Insertion of coronary artery stent
				9276	G31y000	Acute coronary insufficiency
				9413	G31y.00	Other acute and subacute ischaemic heart disease

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				9414	7921.00	Other autograft replacement of coronary artery
				9507	G307000	acute non-q wave infarction
				9555	G33z500	Post infarct angina
				10209	7921200	Autograft replacement of three coronary arteries NEC
				10260	6A4..00	Coronary heart disease review
				10562	G307100	acute non-st segment elevation myocardial infarction
				10603	792z.00	Coronary artery operations NOS
				11648	8B3k.00	Coronary heart disease medication review
				11983	G311500	Acute coronary syndrome
				12139	G300.00	acute anterolateral infarction
				12229	G30X000	Acute ST segment elevation myocardial infarction
				12734	SP07600	Coronary artery bypass graft occlusion
				12804	G33z700	stable angina
				13185	662K.00	angina control
				13566	G30..11	Attack - heart
				13571	G30..16	Thrombosis - coronary
				14658	G30z.00	Acute myocardial infarction NOS
				14782	662K200	Angina control - improving
				14897	G301z00	Anterior myocardial infarction NOS
				14898	G305.00	Lateral myocardial infarction NOS
				15349	662Kz00	Angina control NOS
				15373	662K100	angina control - poor
				15754	G34z.00	Other chronic ischaemic heart disease NOS
				16408	G32..11	healed myocardial infarction
				17133	G30A.00	mural thrombosis
				17464	G32..12	personal history of myocardial infarction

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				17689	G30..17	silent myocardial infarction
				17872	G301100	acute anteroseptal infarction
				18118	G311400	worsening angina
				18135	6A2..00	Coronary heart disease annual review
				18150	9Ob..00	Coronary heart disease monitoring administration
				18249	7920.00	Saphenous vein graft replacement of coronary artery
				18643	ZV45800	[V]Presence of coronary angioplasty implant and graft
				18670	7928000	Percut transluminal balloon angioplasty one coronary artery
				18842	G35..00	subsequent myocardial infarction
				18913	ZV45700	[V]Presence of aortocoronary bypass graft
				19046	7929300	Rotary blade coronary angioplasty
				19193	7923z00	Prosthetic replacement of coronary artery NOS
				19402	7923.00	Prosthetic replacement of coronary artery
				19413	7921100	Autograft replacement of two coronary arteries NEC
				19542	662K000	angina control - good
				19655	G311.14	angina at rest
				19744	8I37.00	Coronary heart disease monitoring refused
				20416	G3...12	Atherosclerotic heart disease
				20903	7A6G100	Peroperative angioplasty
				22020	792B000	Endarterectomy of coronary artery NEC
				22383	G3y..00	Other specified ischaemic heart disease
				22647	7925311	LIMA single anastomosis
				22828	7929000	Percutaneous transluminal laser coronary angioplasty

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				23078	G34y100	Chronic myocardial ischaemia
				23579	G310.00	Postmyocardial infarction syndrome
				23892	G304.00	posterior myocardial infarction nos
				24126	G360.00	Haemopericardium/current comp folow acut myocard infarct
				24540	G34y000	Chronic coronary insufficiency
				24783	G3...11	Arteriosclerotic heart disease
				24888	7929.00	Other therapeutic transluminal operations on coronary artery
				25814	9Ob3.00	Coronary heart disease monitoring 1st letter
				26318	G563.00	Left main stem bundle branch block
				26863	G33z600	New onset angina
				26966	32E3.00	ECG: S-T elevation
				27484	G341.11	Cardiac aneurysm
				27951	G31..00	Other acute and subacute ischaemic heart disease
				27977	G31yz00	Other acute and subacute ischaemic heart disease NOS
				28138	G34..00	Other chronic ischaemic heart disease
				28554	G33zz00	angina pectoris nos
				28736	G30y000	Acute atrial infarction
				28837	7925.11	Creation of bypass from mammary artery to coronary artery
				29300	662K300	angina control - worsening
				29421	G344.00	Silent myocardial ischaemia
				29553	G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
				29643	G303.00	Acute inferoposterior infarction
				29758	G30X.00	acute transmural myocardial infarction of unspecif site
				30330	G309.00	acute q-wave infarct
				30421	G30..13	Cardiac rupture following myocardial infarction (MI)

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				31519	7925100	Double implant of mammary arteries into coronary arteries
				31540	7924200	Revision of bypass for three coronary arteries
				31556	7922.00	Allograft replacement of coronary artery
				31571	792y.00	Other specified operations on coronary artery
				31679	7929z00	Other therapeutic transluminal op on coronary artery NOS
				32272	G38..00	postoperative myocardial infarction
				32651	7922.11	Allograft bypass of coronary artery
				32854	G30B.00	acute posterolateral myocardial infarction
				33461	7924.00	Revision of bypass for coronary artery
				33471	792Dz00	Other bypass of coronary artery NOS
				33620	792B.00	Repair of coronary artery NEC
				33650	7929100	percut transluminal coronary thrombolysis with streptokinase
				33718	7925000	Double anastomosis of mammary arteries to coronary arteries
				33735	7928100	Percut translum balloon angioplasty mult coronary arteries
				34207	9Ob4.00	Coronary heart disease monitoring 2nd letter
				34328	G311300	refractory angina
				34329	9Ob5.00	Coronary heart disease monitoring 3rd letter
				34803	G30y.00	other acute myocardial infarction
				34963	792D.00	Other bypass of coronary artery
				35277	9Ob1.00	Refuses coronary heart disease monitoring
				35373	9Ob0.00	Attends coronary heart disease monitoring

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				35713	G34yz00	Other specified chronic ischaemic heart disease NOS
				36011	7923.11	Prosthetic bypass of coronary artery
				36423	G36..00	Certain current complication follow acute myocardial infarct
				36609	G342.00	Atherosclerotic cardiovascular disease
				37657	G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
				37682	7925.00	Connection of mammary artery to coronary artery
				37719	7925y00	Connection of mammary artery to coronary artery OS
				37908	9Ob6.00	Coronary heart disease monitoring verbal invitation
				38609	G351.00	Subsequent myocardial infarction of inferior wall
				38813	7A54500	Rotary blade angioplasty
				39449	G312.00	Coronary thrombosis not resulting in myocardial infarction
				39500	9Ob8.00	Coronary heart disease monitoring check done
				39584	3889.00	euroscore for angina
				40429	G301000	acute anteroapical infarction
				40996	7929111	Percut translum coronary thrombolytic therapy- streptokinase
				41221	G30y200	Acute septal infarction
				41547	7928y00	Transluminal balloon angioplasty of coronary artery OS
				41677	G341z00	Aneurysm of heart NOS
				41757	7927z00	Other open operation on coronary artery NOS
				42304	7929500	Insertion of drug-eluting coronary artery stent
				42462	7928200	Percut translum balloon angioplasty bypass graft coronary a

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				42708	7921300	Autograft replacement of four of more coronary arteries NEC
				43939	793G.00	Perc translumin balloon angioplasty stenting coronary artery
				44561	7921000	Autograft replacement of one coronary artery NEC
				44585	792Bz00	Repair of coronary artery NOS
				44723	7925200	Single anast mammary art to left ant descend coronary art
				45370	7922300	Allograft replacement of four or more coronary arteries
				45809	G350.00	Subsequent myocardial infarction of anterior wall
				45886	7922200	Allograft replacement of three coronary arteries
				45960	8B27.00	antianginal therapy
				46017	G30yz00	other acute myocardial infarction nos
				46112	G380.00	postoperative transmural myocardial infarction anterior wall
				46166	G35X.00	Subsequent myocardial infarction of unspecified site
				46276	G381.00	Postoperative transmural myocardial infarction inferior wall
				47637	Gyu3300	Other forms of chronic ischaemic heart disease
				47788	7927.00	Other open operations on coronary artery
				47798	9Ob2.00	Coronary heart disease monitoring default
				48767	7922z00	Allograft replacement of coronary artery NOS
				48822	7925011	LIMA sequential anastomosis
				49735	G5y6.00	Rupture of papillary muscle
				50372	14AH.00	H/O: Myocardial infarction in last year

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				51507	7925300	Single anastomosis of mammary artery to coronary artery NEC
				51515	7920z00	Saphenous vein graft replacement coronary artery NOS
				52517	Gyu3.00	[X]Ischaemic heart diseases
				52637	388E.00	Canadian Cardiovascular Society classification of angina
				52938	7924000	Revision of bypass for one coronary artery
				53546	P6y4z00	Coronary artery anomaly NOS
				55092	792C000	Replacement of coronary arteries using multiple methods
				55598	792C.00	Other replacement of coronary artery
				55673	ZR3P.00	clasp angina score
				56990	7925z00	Connection of mammary artery to coronary artery NOS
				57241	7922100	Allograft replacement of two coronary arteries
				57634	7924z00	Revision of bypass for coronary artery NOS
				59189	G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
				59350	ZR37.00	Canadian Cardiovascular Society classification of angina
				59423	7922y00	Other specified allograft replacement of coronary artery
				59940	G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
				60067	793G000	Perc translum ball angio insert 1-2 drug elut stents cor art
				60753	7926300	Single implantation thoracic artery into coronary artery NEC
				61208	793Gz00	Perc translum balloon angioplasty stenting coronary art NOS

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				61310	7921y00	Other autograft replacement of coronary artery OS
				61670	889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
				62608	7926000	Double anastom thoracic arteries to coronary arteries NEC
				62626	G30y100	acute papillary muscle infarction
				63153	7924500	Revision of implantation of thoracic artery into heart
				63467	G306.00	true posterior myocardial infarction
				66236	7923200	Prosthetic replacement of three coronary arteries
				66583	7929200	Percut translum inject therap subst to coronary artery NEC
				66664	7923100	Prosthetic replacement of two coronary arteries
				67554	7924100	Revision of bypass for two coronary arteries
				67591	7926200	Single anastomosis of thoracic artery to coronary artery NEC
				67761	7923300	Prosthetic replacement of four or more coronary arteries
				68123	7925312	RIMA single anastomosis
				68139	7925400	Single implantation of mammary artery into coronary artery
				68401	Gyu3200	Other forms of acute ischaemic heart disease
				68748	G38z.00	postoperative myocardial infarction, unspecified
				69247	792By00	Other specified repair of coronary artery
				69474	G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
				69776	SP00300	Mechanical complication of coronary bypass

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				70111	7922000	Allograft replacement of one coronary artery
				70160	9Ob9.00	Coronary heart disease monitoring telephone invite
				70185	7A54800	Percutaneous transluminal atherectomy
				70755	792Cz00	Replacement of coronary artery NOS
				72562	G353.00	Subsequent myocardial infarction of other sites
				72780	7926z00	Connection of other thoracic artery to coronary artery NOS
				85947	793G200	Perc translum balloon angioplasty insert 1-2 stents cor art
				86071	7928300	Percut translum cutting balloon angioplasty coronary artery
				86773	7A56400	Percutaneous transluminal balloon angioplasty of artery
				87849	793G100	Perc tran ball angio ins 3 or more drug elut stents cor art
				92233	7925012	RIMA sequential anastomosis
				92267	G5yy200	Papillary muscle dysfunction
				92419	7923000	Prosthetic replacement of one coronary artery
				92927	793G300	Percutaneous cor balloon angiop 3 more stents cor art NEC
				93618	7929600	Percutaneous transluminal atherectomy of coronary artery
				93828	792Cy00	Other specified replacement of coronary artery
				95382	7927y00	Other specified other open operation on coronary artery
				95550	8H2V.00	Admit ischaemic heart disease emergency
				96537	793Gy00	OS perc translumina balloon angioplast stenting coronary art

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				96804	7926.00	Connection of other thoracic artery to coronary artery
				96838	Gyu3400	[x]acute transmural myocardial infarction of unspecif site
				97953	7924y00	Other specified revision of bypass for coronary artery
				98295	ZRB1.00	euroscore for angina
				99991	Gyu3600	[X]Subsequent myocardial infarction of unspecified site
				100139	14AT.00	history of myocardial infarction
				100437	9hM..00	exception reporting: myocardial infarction quality indicator
				100496	8CEJ.00	Coronary heart disease leaflet given
				101121	8L40.00	Coronary artery bypass graft operation planned
				101569	7924300	Revision of bypass for four or more coronary arteries
				103655	187..00	frequency of angina
				103932	8CMP.00	Coronary heart disease care plan
				105184	792E.00	Percutaneous coronary intervention
				106812	G383.00	postoperative transmural myocardial infarction unspec site
				107406	792E000	Emergency percutaneous coronary intervention
				107967	661M000	angina self-management plan agreed
				109035	Gyu3500	[x]subsequent myocardial infarction of other sites
				109391	661N000	angina self-management plan review
Atrial fibrillation						
42731	Atrial fibrillation	I4891	Unspecified atrial fibrillation	1268	G573200	Paroxysmal atrial fibrillation
42732	Atrial flutter	I4892	Unspecified atrial flutter	1664	G573000	Atrial fibrillation
				1757	G573100	Atrial flutter
				2212	G573.00	Atrial fibrillation and flutter

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
				3757	3272.00	ECG: atrial fibrillation
				6345	14AN.00	H/O: atrial fibrillation
				6771	3273.00	ECG: atrial flutter
				9479	7936A00	Implant intravenous pacemaker for atrial fibrillation
				18746	662S.00	Atrial fibrillation monitoring
				23437	G573z00	Atrial fibrillation and flutter NOS
				35127	G573300	Non-rheumatic atrial fibrillation
				39114	9hF1.00	Excepted from atrial fibrillation qual indic: Inform dissent
				45773	6A9..00	Atrial fibrillation annual review
				57832	9Os..00	Atrial fibrillation monitoring administration
				63350	9hF..00	Exception reporting: atrial fibrillation quality indicators
				90187	9Os0.00	Atrial fibrillation monitoring first letter
				90188	9Os1.00	Atrial fibrillation monitoring second letter
				90189	9Os2.00	Atrial fibrillation monitoring third letter
				90190	9Os3.00	Atrial fibrillation monitoring verbal invite
				90191	9Os4.00	Atrial fibrillation monitoring telephone invite
				92361	793M000	Perc translum ablat pulmon vein to lft atrium conduct system
				93460	14AR.00	History of atrial flutter
				96076	G573500	Persistent atrial fibrillation
				96277	G573400	Permanent atrial fibrillation
				105554	8CMW200	Atrial fibrillation care pathway
				107472	G573600	Paroxysmal atrial flutter
Diabetes mellitus						

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
25000	Diabetes mellitus without mention of complication, type II or unspecified type, not stated as uncontrolled	E11.9	Type 2 diabetes mellitus without complications	506	C100112	Diabetes mellitus with no mention of complication
25001	Diabetes mellitus without mention of complication, type I [juvenile type], not stated as uncontrolled	E10.9	Type 1 diabetes mellitus without complications	711	C10..00	Diabetes mellitus
25002	Diabetes mellitus without mention of complication, type II or unspecified type, uncontrolled	E11.65	Type 2 diabetes mellitus with hyperglycemia	758	C10F.00	Type 2 diabetes mellitus
25003	Diabetes mellitus without mention of complication, type I [juvenile type], uncontrolled	E10.65	Type 1 diabetes mellitus with hyperglycemia	1038	C100011	Diabetes mellitus with no mention of complication
25010	Diabetes with ketoacidosis, type II or unspecified type, not stated as uncontrolled	E11.10	Type 2 diabetes mellitus with ketoacidosis without coma	1323	F420.00	Diabetic retinopathy
		E11.69	Type 2 diabetes mellitus with other specified complication	1407	C10FJ00	Type 2 diabetes mellitus
		E13.10	Other specified diabetes mellitus with ketoacidosis without coma	1549	C10E.00	Type 1 diabetes mellitus
25011	Diabetes with ketoacidosis, type I [juvenile type], not stated as uncontrolled	E10.10	Type 1 diabetes mellitus with ketoacidosis without coma	1647	C108.00	Insulin dependent diabetes mellitus
25012	Diabetes with ketoacidosis, type II or unspecified type, uncontrolled	E11.10	Type 2 diabetes mellitus with ketoacidosis without coma	1682	C101.00	Diabetes mellitus with ketoacidosis
		E11.69	Type 2 diabetes mellitus with other specified complication	1684	66A4.00	Diabetic on oral treatment
		E13.10	Other specified diabetes mellitus with ketoacidosis without coma	2342	F372.12	Polyneuropathy in diabetes
		E11.65	Type 2 diabetes mellitus with hyperglycemia	2378	66AJ.00	Diabetic - poor control
25013	Diabetes with ketoacidosis, type I [juvenile type], uncontrolled	E10.10	Type 1 diabetes mellitus with ketoacidosis without coma	2475	C104.11	Diabetes mellitus with renal manifestation
		E10.65	Type 1 diabetes mellitus with hyperglycemia	2478	66AJ100	Diabetic - poor control
25020	Diabetes with hyperosmolarity, type II or unspecified type, not stated as uncontrolled	E11.00	Type 2 diabetes mellitus with hyperosmolarity without nonketotic hyperglycemic-hyperosmolar coma (NKHHC)	2986	F420200	Diabetic retinopathy

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
		E11.01	Type 2 diabetes mellitus with hyperosmolarity with coma	3286	F420100	Diabetic retinopathy
25021	Diabetes with hyperosmolarity, type I [juvenile type], not stated as uncontrolled	E10.69	Type 1 diabetes mellitus with other specified complication	3550	66A..00	Diabetic monitoring
25022	Diabetes with hyperosmolarity, type II or unspecified type, uncontrolled	E11.00	Type 2 diabetes mellitus with hyperosmolarity without nonketotic hyperglycemic-hyperosmolar coma (NKHHC)	3837	F420400	Diabetic retinopathy
		E11.65	Type 2 diabetes mellitus with hyperglycemia	4513	C109.00	Non-insulin dependent diabetes mellitus
25023	Diabetes with hyperosmolarity, type I [juvenile type], uncontrolled	E10.65	Type 1 diabetes mellitus with hyperglycemia	5002	F372.11	Polyneuropathy in diabetes
		E10.69	Type 1 diabetes mellitus with other specified complication	5717	42W..11	Hb. A1C - diabetic control
25030	Diabetes with other coma, type II or unspecified type, not stated as uncontrolled	E11.11	Type 2 diabetes mellitus with ketoacidosis with coma	5884	C109.11	Non-insulin dependent diabetes mellitus
		E11.641	Type 2 diabetes mellitus with hypoglycemia with coma	6125	66AS.00	Diabetic annual review
25031	Diabetes with other coma, type I [juvenile type], not stated as uncontrolled	E10.11	Type 1 diabetes mellitus with ketoacidosis with coma	6509	C108700	Insulin dependent diabetes mellitus
		E10.641	Type 1 diabetes mellitus with hypoglycemia with coma	6791	C108800	Insulin dependent diabetes mellitus
25032	Diabetes with other coma, type II or unspecified type, uncontrolled	E11.01	Type 2 diabetes mellitus with hyperosmolarity with coma	6813	1434	H/O: diabetes mellitus
		E11.65	Type 2 diabetes mellitus with hyperglycemia	7045	14F4.00	H/O: Admission in last year for diabetes foot problem
		E10.65	Type 1 diabetes mellitus with hyperglycemia	7069	F420000	Diabetic retinopathy
25040	Diabetes with renal manifestations, type II or unspecified type, not stated as uncontrolled	E11.29	Type 2 diabetes mellitus with other diabetic kidney complication	7563	66A3.00	Diabetic on diet only
25041	Diabetes with renal manifestations, type I [juvenile type], not stated as uncontrolled	E10.29	Type 1 diabetes mellitus with other diabetic kidney complication	7795	C106.12	Diabetes mellitus with neurological manifestation
25042	Diabetes with renal manifestations, type II or unspecified type, uncontrolled	E11.21	Type 2 diabetes mellitus with diabetic nephropathy	8403	C109700	Non-insulin dependent diabetes mellitus
		E11.65	Type 2 diabetes mellitus with hyperglycemia	8836	66AR.00	Diabetes management plan given

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
25043	Diabetes with renal manifestations, type I [juvenile type], uncontrolled	E10.21	Type 1 diabetes mellitus with diabetic nephropathy	8842	66A5.00	Diabetic on insulin
		E10.65	Type 1 diabetes mellitus with hyperglycemia	9013	66AJ.11	Diabetic - poor control
25050	Diabetes with ophthalmic manifestations, type II or unspecified type, not stated as uncontrolled	E11.311	Type 2 diabetes mellitus with unspecified diabetic retinopathy with macular edema	9897	9OL..00	Diabetes monitoring admin.
		E11.319	Type 2 diabetes mellitus with unspecified diabetic retinopathy without macular edema	9958	42W..00	Hb. A1C - diabetic control
		E11.36	Type 2 diabetes mellitus with diabetic cataract	10098	C10yy00	Diabetes mellitus with other specified manifestation
		E11.39	Type 2 diabetes mellitus with other diabetic ophthalmic complication	10099	F420300	Diabetic retinopathy
25051	Diabetes with ophthalmic manifestations, type I [juvenile type], not stated as uncontrolled	E10.311	Type 1 diabetes mellitus with unspecified diabetic retinopathy with macular edema	10418	C10ED00	Type 1 diabetes mellitus
		E10.319	Type 1 diabetes mellitus with unspecified diabetic retinopathy without macular edema	10692	C10EM00	Type 1 diabetes mellitus
		E10.36	Type 1 diabetes mellitus with diabetic cataract	10755	F420600	Diabetic retinopathy
		E10.37X1	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, right eye	10977	66Ac.00	Diabetic peripheral neuropathy screening
		E10.37X2	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, left eye	11018	8HBG.00	Diabetic retinopathy 12 month review
		E10.37X3	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, bilateral	11047	66AH000	Diabetic treatment changed
		E10.37X9	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, unspecified eye	11471	8B3l.00	Diabetes medication review
		E10.39	Type 1 diabetes mellitus with other diabetic ophthalmic complication	11551	C10B.00	Diabetes mellitus induced by steroids
25052	Diabetes with ophthalmic manifestations, type II or unspecified type, uncontrolled	E11.311	Type 2 diabetes mellitus with unspecified diabetic retinopathy with macular edema	11599	7276	Pan retinal photocoagulation for diabetes

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
		E11.319	Type 2 diabetes mellitus with unspecified diabetic retinopathy without macular edema	11626	F420z00	Diabetic retinopathy
		E11.36	Type 2 diabetes mellitus with diabetic cataract	11930	9NN9.00	Under care of diabetes specialist nurse
		E11.39	Type 2 diabetes mellitus with other diabetic ophthalmic complication	12030	9OL6.00	Diabetes monitoring 3rd letter
		E11.65	Type 2 diabetes mellitus with hyperglycemia	12213	8BL2.00	Patient on maximal tolerated therapy for diabetes
25053	Diabetes with ophthalmic manifestations, type I [juvenile type], uncontrolled	E10.311	Type 1 diabetes mellitus with unspecified diabetic retinopathy with macular edema	12307	66AU.00	Diabetes care by hospital only
		E10.319	Type 1 diabetes mellitus with unspecified diabetic retinopathy without macular edema	12455	C10E.11	Type 1 diabetes mellitus
		E10.36	Type 1 diabetes mellitus with diabetic cataract	12506	66AP.00	Diabetes: practice programme
		E10.39	Type 1 diabetes mellitus with other diabetic ophthalmic complication	12640	C10FC00	Type 2 diabetes mellitus
		E10.65	Type 1 diabetes mellitus with hyperglycemia	12675	66AQ.00	Diabetes: shared care programme
25060	Diabetes with neurological manifestations, type II or unspecified type, not stated as uncontrolled	E11.40	Type 2 diabetes mellitus with diabetic neuropathy, unspecified	12682	679R.00	Patient offered diabetes structured education programme
25061	Diabetes with neurological manifestations, type I [juvenile type], not stated as uncontrolled	E10.40	Type 1 diabetes mellitus with diabetic neuropathy, unspecified	12703	3881	Education score - diabetes
25062	Diabetes with neurological manifestations, type II or unspecified type, uncontrolled	E11.40	Type 2 diabetes mellitus with diabetic neuropathy, unspecified	12736	C10F500	Type 2 diabetes mellitus
		E11.65	Type 2 diabetes mellitus with hyperglycemia	13036	TJ23B00	Adverse reaction to insulins and antidiabetic agents
25063	Diabetes with neurological manifestations, type I [juvenile type], uncontrolled	E10.40	Type 1 diabetes mellitus with diabetic neuropathy, unspecified	13057	679L.00	Health education - diabetes
		E10.65	Type 1 diabetes mellitus with hyperglycemia	13067	66AZ.00	Diabetic monitoring NOS
25070	Diabetes with peripheral circulatory disorders, type II or unspecified type, not stated as uncontrolled	E11.51	Type 2 diabetes mellitus with diabetic peripheral angiopathy without gangrene	13069	66A8.00	Has seen dietician - diabetes

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
25071	Diabetes with peripheral circulatory disorders, type I [juvenile type], not stated as uncontrolled	E10.51	Type 1 diabetes mellitus with diabetic peripheral angiopathy without gangrene	13071	66AI.00	Diabetic - good control
25072	Diabetes with peripheral circulatory disorders, type II or unspecified type, uncontrolled	E11.51	Type 2 diabetes mellitus with diabetic peripheral angiopathy without gangrene	13191	9OL..11	Diabetes monitoring admin.
		E11.65	Type 2 diabetes mellitus with hyperglycemia	13192	9OLA.00	Diabetes monitor. check done
25073	Diabetes with peripheral circulatory disorders, type I [juvenile type], uncontrolled	E10.51	Type 1 diabetes mellitus with diabetic peripheral angiopathy without gangrene	13194	9OL4.00	Diabetes monitoring 1st letter
		E10.65	Type 1 diabetes mellitus with hyperglycemia	13195	9OL5.00	Diabetes monitoring 2nd letter
25080	Diabetes with other specified manifestations, type II or unspecified type, not stated as uncontrolled	E11.618	Type 2 diabetes mellitus with other diabetic arthropathy	13197	9OL1.00	Attends diabetes monitoring
		E11.620	Type 2 diabetes mellitus with diabetic dermatitis	13279	C104y00	Diabetes mellitus with renal manifestation
		E11.621	Type 2 diabetes mellitus with foot ulcer	13597	42W1.00	Hb. A1C < 7% - good control
		E11.622	Type 2 diabetes mellitus with other skin ulcer	13604	42W3.00	Hb. A1C > 10% - bad control
		E11.628	Type 2 diabetes mellitus with other skin complications	14049	42WZ.00	Hb. A1C - diabetic control NOS
		E11.630	Type 2 diabetes mellitus with periodontal disease	14050	42c..00	HbA1 - diabetic control
		E11.638	Type 2 diabetes mellitus with other oral complications	14052	42W..12	Hb. A1C - diabetic control
		E11.649	Type 2 diabetes mellitus with hypoglycemia without coma	14803	C100100	Diabetes mellitus with no mention of complication
		E11.65	Type 2 diabetes mellitus with hyperglycemia	14889	C100111	Diabetes mellitus with no mention of complication
		E11.69	Type 2 diabetes mellitus with other specified complication	15690	C103.00	Diabetes mellitus with ketoacidotic coma
25081	Diabetes with other specified manifestations, type I [juvenile type], not stated as uncontrolled	E10.618	Type 1 diabetes mellitus with other diabetic arthropathy	16230	C106.00	Diabetes mellitus with neurological manifestation
		E10.620	Type 1 diabetes mellitus with diabetic dermatitis	16490	66AH.00	Diabetic treatment changed

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
		E10.621	Type 1 diabetes mellitus with foot ulcer	16491	C106.13	Diabetes mellitus with neurological manifestation
		E10.622	Type 1 diabetes mellitus with other skin ulcer	16502	C104.00	Diabetes mellitus with renal manifestation
		E10.628	Type 1 diabetes mellitus with other skin complications	17236	14P3.00	H/O: insulin therapy
		E10.630	Type 1 diabetes mellitus with periodontal disease	17262	C109600	Non-insulin dependent diabetes mellitus
		E10.638	Type 1 diabetes mellitus with other oral complications	17545	C108F11	Insulin dependent diabetes mellitus
		E10.649	Type 1 diabetes mellitus with hypoglycemia without coma	17858	C108.12	Insulin dependent diabetes mellitus
		E10.65	Type 1 diabetes mellitus with hyperglycemia	17859	C109.12	Non-insulin dependent diabetes mellitus
		E10.69	Type 1 diabetes mellitus with other specified complication	17869	66AL.00	Diabetic-uncooperative patient
25082	Diabetes with other specified manifestations, type II or unspecified type, uncontrolled	E11.65	Type 2 diabetes mellitus with hyperglycemia	17886	66AM.00	Diabetic - follow-up default
		E11.69	Type 2 diabetes mellitus with other specified complication	18056	2G5C.00	Foot abnormality - diabetes related
25083	Diabetes with other specified manifestations, type I [juvenile type], uncontrolled	E10.65	Type 1 diabetes mellitus with hyperglycemia	18143	C109G11	Non-insulin dependent diabetes mellitus
		E10.69	Type 1 diabetes mellitus with other specified complication	18167	66AT.00	Annual diabetic blood test
25090	Diabetes with unspecified complication, type II or unspecified type, not stated as uncontrolled	E11.8	Type 2 diabetes mellitus with unspecified complications	18209	C109012	Non-insulin dependent diabetes mellitus
25091	Diabetes with unspecified complication, type I [juvenile type], not stated as uncontrolled	E10.8	Type 1 diabetes mellitus with unspecified complications	18219	C109.13	Non-insulin dependent diabetes mellitus
25092	Diabetes with unspecified complication, type II or unspecified type, uncontrolled	E11.65	Type 2 diabetes mellitus with hyperglycemia	18230	C108J12	Insulin dependent diabetes mellitus
		E11.8	Type 2 diabetes mellitus with unspecified complications	18264	C109J12	Non-insulin dependent diabetes mellitus

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
25093	Diabetes with unspecified complication, type I [juvenile type], uncontrolled	E10.65	Type 1 diabetes mellitus with hyperglycemia	18278	C109J00	Non-insulin dependent diabetes mellitus
		E10.8	Type 1 diabetes mellitus with unspecified complications	18387	C10E700	Type 1 diabetes mellitus
				18390	C10FM00	Type 2 diabetes mellitus
				18396	TJ23A00	Adverse reaction to insulins and antidiabetic agents
				18425	C10FB00	Type 2 diabetes mellitus
				18496	C10F600	Type 2 diabetes mellitus
				18505	C108.11	Insulin dependent diabetes mellitus
				18583	66Ad.00	Hypoglycaemic attack requiring 3rd party assistance
				18642	C10EH00	Type 1 diabetes mellitus
				18662	8HBH.00	Diabetic retinopathy 6 month review
				18683	C10E500	Type 1 diabetes mellitus
				18766	212H.00	Diabetes resolved
				18777	C10F000	Type 2 diabetes mellitus
				20900	9OLA.11	Diabetes monitor. check done
				21420	66AJ200	Diabetic - poor control
				21482	C102.00	Diabetes mellitus with hyperosmolar coma
				21983	C108012	Insulin dependent diabetes mellitus
				22023	66AJz00	Diabetic - poor control
				22130	9OL3.00	Diabetes monitoring default
				22305	TJ23400	Adverse reaction to insulins and antidiabetic agents
				22487	C10N.00	Secondary diabetes mellitus
				22573	C106z00	Diabetes mellitus with neurological manifestation
				22823	66Ab.00	Diabetic foot examination
				22871	C10EP00	Type 1 diabetes mellitus
				22884	C10F.11	Type 2 diabetes mellitus
				22959	66AJ000	Diabetic - poor control

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				22967	2BBF.00	Retinal abnormality - diabetes related
				23340	SL23400	Insulins and antidiabetic poisoning
				24363	8A13.00	Diabetic stabilisation
				24423	C108.13	Insulin dependent diabetes mellitus
				24458	C109711	Non-insulin dependent diabetes mellitus
				24490	C100000	Diabetes mellitus with no mention of complication
				24571	F372200	Polyneuropathy in diabetes
				24693	C109G00	Non-insulin dependent diabetes mellitus
				24694	C108B00	Insulin dependent diabetes mellitus
				24836	C109C12	Non-insulin dependent diabetes mellitus
				25591	C10FQ00	Type 2 diabetes mellitus
				25627	C10F700	Type 2 diabetes mellitus
				25636	66Aa.00	Diabetic diet - poor compliance
				26054	C10FL00	Type 2 diabetes mellitus
				26108	C10B000	Diabetes mellitus induced by steroids
				26604	66AY.00	Diabetic diet - good compliance
				26605	9OLB.00	Attended diabetes structured education programme
				26855	C108400	Insulin dependent diabetes mellitus
				28769	66AV.00	Diabetic on insulin and oral treatment
				28856	8CP2.00	Transition of diabetes care options discussed
				28873	66Ai.00	Diabetic 6 month review
				29041	66AN.00	Date diabetic treatment start
				29218	42W2.00	Hb. A1C 7-10% - borderline
				29979	C109900	Non-insulin dependent diabetes mellitus
				30247	TJ23000	Adverse reaction to insulins and antidiabetic agents

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				30294	C10EL00	Type 1 diabetes mellitus
				30323	C10EK00	Type 1 diabetes mellitus
				30477	F420700	Diabetic retinopathy
				31141	9OL8.00	Diabetes monitor.phone invite
				31240	9OL7.00	Diabetes monitor.verbal invite
				31241	9OLZ.00	Diabetes monitoring admin.NOS
				31310	C108900	Insulin dependent diabetes mellitus
				31790	F372.00	Polyneuropathy in diabetes
				32359	ZRbH.00	Perceived control of insulin-dependent diabetes
				32403	C107.11	Diabetes mellitus with peripheral circulatory disorder
				32556	C107.12	Diabetes mellitus with peripheral circulatory disorder
				32619	66Af.00	Patient diabetes education review
				32627	C10FN00	Type 2 diabetes mellitus
				33254	C105.00	Diabetes mellitus with ophthalmic manifestation
				33343	C10y.00	Diabetes mellitus with other specified manifestation
				33807	C107200	Diabetes mellitus with peripheral circulatory disorder
				33969	C10A100	Malnutrition-related diabetes mellitus
				34268	C10F200	Type 2 diabetes mellitus
				34283	C105z00	Diabetes mellitus with ophthalmic manifestation
				34450	C10FK00	Type 2 diabetes mellitus
				34528	3882	Diabetes well being questionnaire
				34912	C109400	Non-insulin dependent diabetes mellitus
				35105	C104100	Diabetes mellitus with renal manifestation
				35107	C104z00	Diabetes mellitus with renal manifestation

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				35288	C10E800	Type 1 diabetes mellitus
				35321	8H3O.00	Non-urgent diabetic admission
				35385	C10FH00	Type 2 diabetes mellitus
				35399	C107.00	Diabetes mellitus with peripheral circulatory disorder
				35785	F372100	Polyneuropathy in diabetes
				36633	C109K00	Non-insulin dependent diabetes mellitus
				36695	C10D.00	Diabetes mellitus autosomal dominant type 2
				37035	66Ae.00	HbA1c target
				37315	F3y0.00	Diabetic mononeuropathy
				37625	66AJ300	Diabetic - poor control
				37648	C109J11	Non-insulin dependent diabetes mellitus
				37806	C10FF00	Type 2 diabetes mellitus
				37957	C10K.00	Type A insulin resistance
				38078	66A9.00	Understands diet - diabetes
				38130	ZRB6.00	Diabetes wellbeing questionnaire
				38161	C108711	Insulin dependent diabetes mellitus
				38617	C101y00	Diabetes mellitus with ketoacidosis
				38986	C100.00	Diabetes mellitus with no mention of complication
				39070	C10EE00	Type 1 diabetes mellitus
				39317	C106100	Diabetes mellitus with neurological manifestation
				39406	C109800	Non-insulin dependent diabetes mellitus
				39481	C10F811	Type 2 diabetes mellitus
				39809	C108J00	Insulin dependent diabetes mellitus
				40023	C102000	Diabetes mellitus with hyperosmolar coma
				40401	C109500	Non-insulin dependent diabetes mellitus

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				40463	42c1.00	HbA1 7 - 10% - borderline control
				40682	C10E900	Type 1 diabetes mellitus
				40837	C10EN00	Type 1 diabetes mellitus
				40962	C109H00	Non-insulin dependent diabetes mellitus
				41049	C108712	Insulin dependent diabetes mellitus
				41389	C105100	Diabetes mellitus with ophthalmic manifestation
				41686	Cyu2000	[X]Diabetes mellitus
				41716	C108C00	Insulin dependent diabetes mellitus
				42360	42c0.00	HbA1 < 7% - good control
				42505	C101z00	Diabetes mellitus with ketoacidosis
				42567	C103000	Diabetes mellitus with ketoacidotic coma
				42729	C108E11	Insulin dependent diabetes mellitus
				42762	C109612	Non-insulin dependent diabetes mellitus
				42831	C10E200	Type 1 diabetes mellitus
				43139	C102100	Diabetes mellitus with hyperosmolar coma
				43227	C10F311	Type 2 diabetes mellitus
				43453	C10C.00	Diabetes mellitus autosomal dominant
				43785	C109D00	Non-insulin dependent diabetes mellitus
				43857	C10M.00	Lipoatrophic diabetes mellitus
				43921	C10E400	Type 1 diabetes mellitus
				43951	66AK.00	Diabetic - cooperative patient
				44260	C108F00	Insulin dependent diabetes mellitus
				44440	C108E00	Insulin dependent diabetes mellitus
				44443	C108500	Insulin dependent diabetes mellitus
				44779	C109E12	Non-insulin dependent diabetes mellitus
				44982	C10FE00	Type 2 diabetes mellitus

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				45276	C10E312	Type 1 diabetes mellitus
				45467	C109B00	Non-insulin dependent diabetes mellitus
				45491	C10z.00	Diabetes mellitus with unspecified complication
				45913	C109712	Non-insulin dependent diabetes mellitus
				45914	C108812	Insulin dependent diabetes mellitus
				45919	C109212	Non-insulin dependent diabetes mellitus
				46079	42c2.00	HbA1 > 10% - bad control
				46150	C109512	Non-insulin dependent diabetes mellitus
				46290	C108y00	Insulin dependent diabetes mellitus
				46301	C10EC00	Type 1 diabetes mellitus
				46577	66AX.00	Diabetes: shared care in pregnancy - diabetol and obstet
				46624	C10C.11	Diabetes mellitus autosomal dominant
				46850	C108811	Insulin dependent diabetes mellitus
				46917	C10FD00	Type 2 diabetes mellitus
				46963	C108000	Insulin dependent diabetes mellitus
				47011	8Hj0.00	Referral to diabetes structured education programme
				47032	8CS0.00	Diabetes care plan agreed
				47058	8Hg4.00	Discharged from care of diabetes specialist nurse
				47315	C10F711	Type 2 diabetes mellitus
				47321	C10F100	Type 2 diabetes mellitus
				47341	8A12.00	Diabetic crisis monitoring
				47377	C105y00	Diabetes mellitus with ophthalmic manifestation
				47409	C109B11	Non-insulin dependent diabetes mellitus
				47582	C10E000	Type 1 diabetes mellitus

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				47584	F420500	Diabetic retinopathy
				47649	C10E100	Type 1 diabetes mellitus
				47650	C10E300	Type 1 diabetes mellitus
				47816	C109H11	Non-insulin dependent diabetes mellitus
				47954	C10F900	Type 2 diabetes mellitus
				48078	F372000	Polyneuropathy in diabetes
				48192	C109E11	Non-insulin dependent diabetes mellitus
				49074	C10F400	Type 2 diabetes mellitus
				49146	C108211	Insulin dependent diabetes mellitus
				49276	C108100	Insulin dependent diabetes mellitus
				49554	C10EF00	Type 1 diabetes mellitus
				49655	C10F611	Type 2 diabetes mellitus
				49686	TJ23900	Adverse reaction to insulins and antidiabetic agents
				49869	C109G12	Non-insulin dependent diabetes mellitus
				49949	C10E411	Type 1 diabetes mellitus
				50175	66AW.00	Diabetic foot risk assessment
				50225	C109011	Non-insulin dependent diabetes mellitus
				50429	C109100	Non-insulin dependent diabetes mellitus
				50527	C10FB11	Type 2 diabetes mellitus
				50813	C109A11	Non-insulin dependent diabetes mellitus
				50972	C100z00	Diabetes mellitus with no mention of complication
				51066	9OLC.00	Family/carer attended diabetes structured education prog
				51261	C10E.12	Type 1 diabetes mellitus
				51697	C10G.00	Secondary pancreatic diabetes mellitus
				51756	C10FP00	Type 2 diabetes mellitus

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				51957	C108511	Insulin dependent diabetes mellitus
				52104	C108300	Insulin dependent diabetes mellitus
				52212	Cyu2.00	[X]Diabetes mellitus
				52236	C10A.00	Malnutrition-related diabetes mellitus
				52237	9360	Patient held diabetic record issued
				52283	C108200	Insulin dependent diabetes mellitus
				52303	C109000	Non-insulin dependent diabetes mellitus
				53200	C101000	Diabetes mellitus with ketoacidosis
				53238	66AG.00	Diabetic drug side effects
				53392	C10F911	Type 2 diabetes mellitus
				54008	C10EJ00	Type 1 diabetes mellitus
				54212	C109F00	Non-insulin dependent diabetes mellitus
				54600	C10E412	Type 1 diabetes mellitus
				54601	9NN8.00	Under care of diabetologist
				54773	C10F800	Type 2 diabetes mellitus
				54856	C101100	Diabetes mellitus with ketoacidosis
				54899	C109F11	Non-insulin dependent diabetes mellitus
				55075	C109411	Non-insulin dependent diabetes mellitus
				55123	66AO.00	Date diabetic treatment stopp.
				55239	C10EQ00	Type 1 diabetes mellitus
				55842	C109200	Non-insulin dependent diabetes mellitus
				56268	C109D11	Non-insulin dependent diabetes mellitus
				56448	C108A00	Insulin dependent diabetes mellitus
				56803	C107400	Diabetes mellitus with peripheral circulatory disorder
				56885	C10K000	Type A insulin resistance
				57278	C10F011	Type 2 diabetes mellitus

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				57356	TJ23300	Adverse reaction to insulins and antidiabetic agents
				57621	C108D00	Insulin dependent diabetes mellitus
				58604	C109611	Non-insulin dependent diabetes mellitus
				59253	C10FG00	Type 2 diabetes mellitus
				59288	C103y00	Diabetes mellitus with ketoacidotic coma
				59365	C109C00	Non-insulin dependent diabetes mellitus
				59725	C109111	Non-insulin dependent diabetes mellitus
				59903	C106.11	Diabetes mellitus with neurological manifestation
				59991	C10D.11	Diabetes mellitus autosomal dominant type 2
				60107	C108411	Insulin dependent diabetes mellitus
				60208	C108J11	Insulin dependent diabetes mellitus
				60499	C108600	Insulin dependent diabetes mellitus
				60699	C109F12	Non-insulin dependent diabetes mellitus
				60796	C10FL11	Type 2 diabetes mellitus
				61071	C109D12	Non-insulin dependent diabetes mellitus
				61122	C10H.00	Diabetes mellitus induced by non-steroid drugs
				61210	TJ23z00	Adverse reaction to insulins and antidiabetic agents
				61344	C108011	Insulin dependent diabetes mellitus
				61470	66Al.00	Diabetic monitoring - higher risk albumin excretion
				61523	C106y00	Diabetes mellitus with neurological manifestation
				61670	889A.00	Diab mellit insulin-glucose infus acute myocardial infarct

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				61829	C108212	Insulin dependent diabetes mellitus
				62107	C109511	Non-insulin dependent diabetes mellitus
				62146	C109300	Non-insulin dependent diabetes mellitus
				62209	C10EM11	Type 1 diabetes mellitus
				62352	C108H11	Insulin dependent diabetes mellitus
				62613	C10EA11	Type 1 diabetes mellitus
				62674	C10FA00	Type 2 diabetes mellitus
				63017	C108911	Insulin dependent diabetes mellitus
				63357	C107100	Diabetes mellitus with peripheral circulatory disorder
				63371	C10y100	Diabetes mellitus with other specified manifestation
				63412	8CR2.00	Diabetes clinical management plan
				63690	C10FR00	Type 2 diabetes mellitus
				63762	C10z100	Diabetes mellitus with unspecified complication
				64283	C10zy00	Diabetes mellitus with unspecified complication
				64357	C10zz00	Diabetes mellitus with unspecified complication
				64446	C108G00	Insulin dependent diabetes mellitus
				64449	C108z00	Insulin dependent diabetes mellitus
				64571	C109C11	Non-insulin dependent diabetes mellitus
				64668	C10FJ11	Type 2 diabetes mellitus
				64675	TA34100	Insulins and antidiabetic poisoning
				65025	C107z00	Diabetes mellitus with peripheral circulatory disorder
				65062	C103z00	Diabetes mellitus with ketoacidotic coma
				65267	C10F300	Type 2 diabetes mellitus
				65463	F420800	Diabetic retinopathy

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				65517	8BA4.00	Shock therapy - insulin
				65616	C108H00	Insulin dependent diabetes mellitus
				65704	C109412	Non-insulin dependent diabetes mellitus
				66145	C10EN11	Type 1 diabetes mellitus
				66274	66Ah.00	Insulin needles changed for each injection
				66475	66Ak.00	Diabetic monitoring - lower risk albumin excretion
				66675	C10A000	Malnutrition-related diabetes mellitus
				66872	C108D11	Insulin dependent diabetes mellitus
				66946	TJ23800	Adverse reaction to insulins and antidiabetic agents
				66965	C109H12	Non-insulin dependent diabetes mellitus
				67212	C10H000	Diabetes mellitus induced by non-steroid drugs
				67664	ZRBa.00	Education score - diabetes
				67853	C106000	Diabetes mellitus with neurological manifestation
				67905	C109211	Non-insulin dependent diabetes mellitus
				68105	C10EB00	Type 1 diabetes mellitus
				68390	C108512	Insulin dependent diabetes mellitus
				68517	C10J.00	Insulin autoimmune syndrome
				68714	SL23.00	Insulins and antidiabetic poisoning
				68792	C10z000	Diabetes mellitus with unspecified complication
				68818	ZRB5.11	Diabetes treatment satisfaction questionnaire
				68843	C103100	Diabetes mellitus with ketoacidotic coma
				68928	TJ23.00	Adverse reaction to insulins and antidiabetic agents

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				69124	C107300	Diabetes mellitus with peripheral circulatory disorder
				69152	66Aj.00	Insulin needles changed less than once a day
				69278	C109E00	Non-insulin dependent diabetes mellitus
				69676	C10EA00	Type 1 diabetes mellitus
				69748	C105000	Diabetes mellitus with ophthalmic manifestation
				69993	C10E600	Type 1 diabetes mellitus
				70316	C109112	Non-insulin dependent diabetes mellitus
				70448	C107000	Diabetes mellitus with peripheral circulatory disorder
				70766	C108E12	Insulin dependent diabetes mellitus
				70821	C10yz00	Diabetes mellitus with other specified manifestation
				71486	TJ23200	Adverse reaction to insulins and antidiabetic agents
				72320	C109A00	Non-insulin dependent diabetes mellitus
				72345	C102z00	Diabetes mellitus with hyperosmolar coma
				72702	C10E812	Type 1 diabetes mellitus
				82474	8Hl4.00	Referral to community diabetes specialist nurse
				83485	66Am.00	Insulin dose changed
				83532	66Ao.00	Diabetes type 2 review
				85660	66An.00	Diabetes type 1 review
				85991	C10FM11	Type 2 diabetes mellitus
				89737	TJ23500	Adverse reaction to insulins and antidiabetic agents
				90301	66Ag.00	Insulin needles changed daily
				91646	C10F411	Type 2 diabetes mellitus

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				91942	C10E311	Type 1 diabetes mellitus
				91943	C10EC11	Type 1 diabetes mellitus
				93380	C10N100	Secondary diabetes mellitus
				93390	9OLH.00	Attended DAFNE diabetes structured education programme
				93468	C10EG00	Type 1 diabetes mellitus
				93491	9OLJ.00	DAFNE diabetes structured education programme completed
				93529	9OLK.00	DESMOND diabetes structured education programme completed
				93530	9OLE.00	Attended DESMOND structured programme
				93631	9OLL.00	XPERT diabetes structured education programme completed
				93657	8Hj4.00	Referral to DESMOND diabetes structured education programme
				93704	8Hj3.00	Referral to DAFNE diabetes structured education programme
				93727	C10FE11	Type 2 diabetes mellitus
				93870	8Hj5.00	Referral to XPERT diabetes structured education programme
				93875	C10E712	Type 1 diabetes mellitus
				93878	C10E511	Type 1 diabetes mellitus
				93922	C104000	Diabetes mellitus with renal manifestation
				94011	9OLG.00	Attended XPERT diabetes structured education programme
				94186	9OLF.00	Diabetes structured education programme completed
				94383	C10N000	Secondary diabetes mellitus
				94699	ZRB5.00	Diabetes treatment satisfaction questionnaire
				95343	C10E711	Type 1 diabetes mellitus
				95351	C10FA11	Type 2 diabetes mellitus

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				95539	C10FS00	Type 2 diabetes mellitus
				95636	C10ER00	Type 1 diabetes mellitus
				95641	8Hj1.00	Family/carer referral to diabetes structured education prog
				95992	C108A11	Insulin dependent diabetes mellitus
				95994	66Aq.00	Diabetic foot screen
				96010	66Ap.00	Insulin treatment initiated
				96143	9kL..00	Insulin initiation - enhanced services administration
				96235	C10E911	Type 1 diabetes mellitus
				96506	C10G000	Secondary pancreatic diabetes mellitus
				97446	C108912	Insulin dependent diabetes mellitus
				97474	C108412	Insulin dependent diabetes mellitus
				97824	ZRB6.11	Diabetes wellbeing questionnaire
				97849	C10E912	Type 1 diabetes mellitus
				97894	C10EP11	Type 1 diabetes mellitus
				98071	C10E112	Type 1 diabetes mellitus
				98145	38DM.11	Age, BP, clinical feat, duration, diabetes 2 stroke rsk scre
				98392	C10C.12	Diabetes mellitus autosomal dominant
				98616	C10F211	Type 2 diabetes mellitus
				98704	C10E512	Type 1 diabetes mellitus
				98723	C10FD11	Type 2 diabetes mellitus
				98954	3883	Diabetes treatment satisfaction questionnaire
				98955	SL23100	Insulins and antidiabetic poisoning
				98978	38DM.00	Age, BP, clinical feat, duration, diabetes 2 stroke rsk scre
				99231	C108B11	Insulin dependent diabetes mellitus
				99311	C10E111	Type 1 diabetes mellitus
				99716	C10EE12	Type 1 diabetes mellitus
				99719	C10EA12	Type 1 diabetes mellitus
				99822	38DK.00	Finnish diabetes risk score

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				100292	Cyu2300	[X]Diabetes mellitus
				100347	C10A500	Malnutrition-related diabetes mellitus
				100422	8HgC.00	Discharged from diabetes shared care programme
				100436	679L000	Health education - diabetes
				100533	66AQ000	Diabetes: shared care programme
				100770	C10EF12	Type 1 diabetes mellitus
				100791	66Ar.00	Insulin treatment stopped
				100964	C10F111	Type 2 diabetes mellitus
				101177	66At.00	Diabetic dietary review
				101190	66AQ100	Diabetes: shared care programme
				101208	66Ae000	HbA1c target
				101311	C10EC12	Type 1 diabetes mellitus
				101455	9OLN.00	Diabetes monitor invitation by SMS (short message service)
				101728	66As.00	Diabetic on subcutaneous treatment
				101735	C10E212	Type 1 diabetes mellitus
				101801	66At100	Diabetic dietary review
				101872	SL23000	Insulins and antidiabetic poisoning
				101881	2BBr.00	Impaired vision due to diabetic retinopathy
				102112	C10E611	Type 1 diabetes mellitus
				102163	C10ED12	Type 1 diabetes mellitus
				102201	C10FC11	Type 2 diabetes mellitus
				102434	66Au.00	Diabetic erectile dysfunction review
				102549	66Aw.00	Insulin dose
				102611	66At111	Diabetic dietary review
				102620	C10EL11	Type 1 diabetes mellitus
				102704	66At000	Diabetic dietary review
				102740	C108112	Insulin dependent diabetes mellitus
				102946	C10E012	Type 1 diabetes mellitus
				103762	8BAi.00	Insulin passport completed

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				103902	C10FG11	Type 2 diabetes mellitus
				104287	8Hlc.00	Referral to community diabetes service
				104323	C10F511	Type 2 diabetes mellitus
				104374	67D8.00	Provision of diabetes clinical summary
				104453	66At011	Diabetic dietary review
				104639	C10FF11	Type 2 diabetes mellitus
				104858	8BAm.00	Insulin passport checked
				105337	C10E811	Type 1 diabetes mellitus
				105446	679c.00	Insulin administration education
				105784	C109912	Non-insulin dependent diabetes mellitus
				106061	C10FP11	Type 2 diabetes mellitus
				106358	679L100	Health education - diabetes
				106528	C10FN11	Type 2 diabetes mellitus
				106622	38Gj.00	QDiabetes risk calculator
				107331	66AH100	Diabetic treatment changed
				107361	679L200	Health education - diabetes
				107452	66o..00	Further diabetic monitoring
				107464	66AS000	Diabetic annual review
				107508	66AH200	Diabetic treatment changed
				107554	38Gv.00	Diabetes UK diabetes risk score
				107603	C10P.00	Diabetes mellitus in remission
				107701	C10FK11	Type 2 diabetes mellitus
				107739	679L211	Health education - diabetes
				107824	C10P100	Diabetes mellitus in remission
				108005	C109312	Non-insulin dependent diabetes mellitus
				108007	C108311	Insulin dependent diabetes mellitus
				108018	66o0.00	Incretin mimetic treatment started
				108218	66AJ400	Diabetic - poor control
				108360	C10P000	Diabetes mellitus in remission
				108724	C10EQ11	Type 1 diabetes mellitus

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
				108890	679L300	Health education - diabetes
				109051	C10E612	Type 1 diabetes mellitus
				109103	C109911	Non-insulin dependent diabetes mellitus
				109197	C10FH11	Type 2 diabetes mellitus
				109222	67HA.00	Lifestyle education for diabetes
				109628	C10P011	Diabetes mellitus in remission
				109700	66AH300	Diabetic treatment changed
				109760	1M8..00	Diabetic peripheral neuropathic pain
				109806	8Hgd.00	Discharge from secondary care diabetes service
				109837	C10E011	Type 1 diabetes mellitus
				109865	C109B12	Non-insulin dependent diabetes mellitus
				110344	66o2.00	Diabetic on non-insulin injectable medication
				110379	66o5.00	Diabetic on oral treatment and glucagon-like peptide 1
				110400	C108F12	Insulin dependent diabetes mellitus
				110409	679l.00	Diabetic injection administration education
				110511	67W1.00	Recommendation self-refer for diabetes structured education
				110611	C10P111	Diabetes mellitus in remission
				110978	TJ23100	Adverse reaction to insulins and antidiabetic agents
				110997	C10y000	Diabetes mellitus with other specified manifestation
				111106	C108A12	Insulin dependent diabetes mellitus
				111483	66o6.00	Diabetic on insulin and glucagon-like peptide 1
Hypertension						
4011	Benign essential hypertension	I10	Essential (primary) hypertension	2666	14A2.00	H/O: hypertension
4010	Malignant essential hypertension	I10	Essential (primary) hypertension	3269	2126100	Hypertension resolved

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
4019	Unspecified essential hypertension	I10	Essential (primary) hypertension	19342	212K.00	Hypertension resolved
		I16.9	Hypertensive crisis, unspecified	4444	662..12	Hypertension monitoring
40290	Unspecified hypertensive heart disease without heart failure	I11.9	Hypertensive heart disease without heart failure	30776	6629.00	Hypertension:follow-up default
40291	Unspecified hypertensive heart disease with heart failure	I11.0	Hypertensive heart disease with heart failure	12948	662H.00	Hypertension treatm.stopped
40300	Hypertensive chronic kidney disease, malignant, with chronic kidney disease stage I through stage IV, or unspecified	I12.9	Hypertensive chronic kidney disease with stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease	13186	662P.00	Hypertension monitoring
40301	Hypertensive chronic kidney disease, malignant, with chronic kidney disease stage V or end stage renal disease	I12.0	Hypertensive chronic kidney disease with stage 5 chronic kidney disease or end stage renal disease	12680	8CR4.00	Hypertension clinical management plan
40310	Hypertensive chronic kidney disease, benign, with chronic kidney disease stage I through stage IV, or unspecified	I12.9	Hypertensive chronic kidney disease with stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease	5215	9OI..00	Hypertension monitoring admin.
40311	Hypertensive chronic kidney disease, benign, with chronic kidney disease stage V or end stage renal disease	I12.0	Hypertensive chronic kidney disease with stage 5 chronic kidney disease or end stage renal disease	27525	9OI..11	Hypertension clinic admin.
40390	Hypertensive chronic kidney disease, unspecified, with chronic kidney disease stage I through stage IV, or unspecified	I12.9	Hypertensive chronic kidney disease with stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease	45149	9OI1.00	Attends hypertension monitor.
40391	Hypertensive chronic kidney disease, unspecified, with chronic kidney disease stage V or end stage renal disease	I12.0	Hypertensive chronic kidney disease with stage 5 chronic kidney disease or end stage renal disease	28828	9OI3.00	Hyperten.monitor offer default
40400	Hypertensive heart and chronic kidney disease, malignant, without heart failure and with chronic kidney disease stage I through stage IV, or unspecified	I13.10	Hypertensive heart and chronic kidney disease without heart failure, with stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease	31117	9OI4.00	Hypertens.monitor.1st letter
40401	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified	I13.0	Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease	31127	9OI5.00	Hypertens.monitor 2nd letter

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
40402	Hypertensive heart and chronic kidney disease, malignant, without heart failure and with chronic kidney disease stage V or end stage renal disease	I13.11	Hypertensive heart and chronic kidney disease without heart failure, with stage 5 chronic kidney disease, or end stage renal disease	31175	9OI6.00	Hypertens.monitor 3rd letter
40403	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end stage renal disease	I13.2	Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease	41634	9OI7.00	Hypertens.monitor verbal inv.
40410	Hypertensive heart and chronic kidney disease, benign, without heart failure and with chronic kidney disease stage I through stage IV, or unspecified	I13.10	Hypertensive heart and chronic kidney disease without heart failure, with stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease	28874	9OI8.00	Hypertens.monitor phone invite
40411	Hypertensive heart and chronic kidney disease, benign, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified	I13.0	Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease	36305	9OIA.00	Hypertension monitor.chck done
40412	Hypertensive heart and chronic kidney disease, benign, without heart failure and with chronic kidney disease stage V or end stage renal disease	I13.11	Hypertensive heart and chronic kidney disease without heart failure, with stage 5 chronic kidney disease, or end stage renal disease	24127	9OIA.11	Hypertension monitored
40413	Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end stage renal disease	I13.2	Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease	34192	9OIZ.00	Hypertens.monitoring admin.NOS
40490	Hypertensive heart and chronic kidney disease, unspecified, without heart failure and with chronic kidney disease stage I through stage IV, or unspecified	I13.10	Hypertensive heart and chronic kidney disease without heart failure, with stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease	16565	6627.00	Good hypertension control
40491	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified	I13.0	Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease	27511	6628.00	Poor hypertension control
40492	Hypertensive heart and chronic kidney disease, unspecified, without heart failure and with chronic kidney disease stage V or end stage renal disease	I13.11	Hypertensive heart and chronic kidney disease without heart failure, with stage 5 chronic kidney disease, or end stage renal disease	21826	662F.00	Hypertension treatm. started

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
40493	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease	I13.2	Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease	13188	662G.00	Hypertensive treatm.changed
40501	Malignant renovascular hypertension	I15.0	Renovascular hypertension	3425	662O.00	On treatment for hypertension
40509	Other malignant secondary hypertension	I15.8	Other secondary hypertension	18590	662b.00	Moderate hypertension control
40511	Benign renovascular hypertension	I15.0	Renovascular hypertension	18482	662c.00	Hypertension six month review
40599	Other unspecified secondary hypertension	I15.8	Other secondary hypertension	19070	662d.00	Hypertension annual review
40200	Malignant hypertensive heart disease without heart failure	I11.9	Hypertensive heart disease without heart failure	95359	662r.00	Trial withdrawal of antihypertensive therapy
40201	Malignant hypertensive heart disease with heart failure	I11.0	Hypertensive heart disease with heart failure	85944	7Q01.00	High cost hypertension drugs
64200	Benign essential hypertension complicating pregnancy, childbirth, and the puerperium, unspecified as to episode of care or not applicable	O10.019	Pre-existing essential hypertension complicating pregnancy, unspecified trimester	18057	8B26.00	Antihypertensive therapy
		O10.919	Unspecified pre-existing hypertension complicating pregnancy, unspecified trimester	11056	8BL0.00	Patient on maximal tolerated antihypertensive therapy
64201	Benign essential hypertension complicating pregnancy, childbirth, and the puerperium, delivered, with or without mention of antepartum condition	O10.011	Pre-existing essential hypertension complicating pregnancy, first trimester	37086	F404200	Blind hypertensive eye
		O10.012	Pre-existing essential hypertension complicating pregnancy, second trimester	6702	F421300	Hypertensive retinopathy
		O10.013	Pre-existing essential hypertension complicating pregnancy, third trimester	204	G2...00	Hypertensive disease
		O10.02	Pre-existing essential hypertension complicating childbirth	8732	G2...11	BP - hypertensive disease
		O10.911	Unspecified pre-existing hypertension complicating pregnancy, first trimester	799	G20..00	Essential hypertension
		O10.912	Unspecified pre-existing hypertension complicating pregnancy, second trimester	15377	G200.00	Malignant essential hypertension
		O10.913	Unspecified pre-existing hypertension complicating pregnancy, third trimester	1894	G201.00	Benign essential hypertension

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Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
		O10.92	Unspecified pre-existing hypertension complicating childbirth	4372	G202.00	Systolic hypertension
64202	Benign essential hypertension, complicating pregnancy, childbirth, and the puerperium, delivered, with mention of postpartum complication	O10.03	Pre-existing essential hypertension complicating the puerperium	83473	G203.00	Diastolic hypertension
64203	Benign essential hypertension complicating pregnancy, childbirth, and the puerperium, antepartum condition or complication	O10.011	Pre-existing essential hypertension complicating pregnancy, first trimester	10818	G20z.00	Essential hypertension NOS
		O10.012	Pre-existing essential hypertension complicating pregnancy, second trimester	3712	G20z.11	Hypertension NOS
		O10.013	Pre-existing essential hypertension complicating pregnancy, third trimester	16292	G21..00	Hypertensive heart disease
		O10.911	Unspecified pre-existing hypertension complicating pregnancy, first trimester	50157	G210.00	Malignant hypertensive heart disease
		O10.912	Unspecified pre-existing hypertension complicating pregnancy, second trimester	95334	G210000	Malignant hypertensive heart disease without CCF
		O10.913	Unspecified pre-existing hypertension complicating pregnancy, third trimester	72668	G210100	Malignant hypertensive heart disease with CCF
64204	Benign essential hypertension complicating pregnancy, childbirth, and the puerperium, postpartum condition or complication	O10.03	Pre-existing essential hypertension complicating the puerperium	52427	G211.00	Benign hypertensive heart disease
		O10.93	Unspecified pre-existing hypertension complicating the puerperium	61660	G211000	Benign hypertensive heart disease without CCF
64210	Hypertension secondary to renal disease, complicating pregnancy, childbirth, and the puerperium, unspecified as to episode of care or not applicable	O10.419	Pre-existing secondary hypertension complicating pregnancy, unspecified trimester	52127	G211100	Benign hypertensive heart disease with CCF
64211	Hypertension secondary to renal disease, complicating pregnancy, childbirth, and the puerperium, delivered, with or without mention of antepartum condition	O10.411	Pre-existing secondary hypertension complicating pregnancy, first trimester	31464	G21z.00	Hypertensive heart disease NOS
		O10.412	Pre-existing secondary hypertension complicating pregnancy, second trimester	61166	G21z000	Hypertensive heart disease NOS without CCF
		O10.413	Pre-existing secondary hypertension complicating pregnancy, third trimester	8857	G21z011	Cardiomegaly - hypertensive

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Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
		O10.42	Pre-existing secondary hypertension complicating childbirth	62718	G21z100	Hypertensive heart disease NOS with CCF
64212	Hypertension secondary to renal disease, complicating pregnancy, childbirth, and the puerperium, delivered, with mention of postpartum complication	O10.43	Pre-existing secondary hypertension complicating the puerperium	16173	G21zz00	Hypertensive heart disease NOS
64213	Hypertension secondary to renal disease, complicating pregnancy, childbirth, and the puerperium, antepartum condition or complication	O10.411	Pre-existing secondary hypertension complicating pregnancy, first trimester	4668	G22..00	Hypertensive renal disease
		O10.412	Pre-existing secondary hypertension complicating pregnancy, second trimester	39649	G220.00	Malignant hypertensive renal disease
		O10.413	Pre-existing secondary hypertension complicating pregnancy, third trimester	43935	G221.00	Benign hypertensive renal disease
64214	Hypertension secondary to renal disease, complicating pregnancy, childbirth, and the puerperium, postpartum condition or complication	O10.43	Pre-existing secondary hypertension complicating the puerperium	32423	G222.00	Hypertensive renal disease with renal failure
64220	Other pre-existing hypertension complicating pregnancy, childbirth, and the puerperium, unspecified as to episode of care or not applicable	O10.119	Pre-existing hypertensive heart disease complicating pregnancy, unspecified trimester	15106	G22z.00	Hypertensive renal disease NOS
		O10.219	Pre-existing hypertensive chronic kidney disease complicating pregnancy, unspecified trimester	29310	G22z.11	Renal hypertension
		O10.319	Pre-existing hypertensive heart and chronic kidney disease complicating pregnancy, unspecified trimester	63466	G23..00	Hypertensive heart and renal disease
		O11.9	Pre-existing hypertension with pre-eclampsia, unspecified trimester	67232	G230.00	Malignant hypertensive heart and renal disease
64221	Other pre-existing hypertension, complicating pregnancy, childbirth, and the puerperium, delivered, with or without mention of antepartum condition	O10.111	Pre-existing hypertensive heart disease complicating pregnancy, first trimester	63000	G231.00	Benign hypertensive heart and renal disease
		O10.112	Pre-existing hypertensive heart disease complicating pregnancy, second trimester	21837	G232.00	Hypertensive heart&renal dis wth (congestive) heart failure

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Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
		O10.113	Pre-existing hypertensive heart disease complicating pregnancy, third trimester	28684	G233.00	Hypertensive heart and renal disease with renal failure
		O10.12	Pre-existing hypertensive heart disease complicating childbirth	57987	G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail
		O10.211	Pre-existing hypertensive chronic kidney disease complicating pregnancy, first trimester	68659	G23z.00	Hypertensive heart and renal disease NOS
		O10.212	Pre-existing hypertensive chronic kidney disease complicating pregnancy, second trimester	18765	G2y..00	Other specified hypertensive disease
		O10.213	Pre-existing hypertensive chronic kidney disease complicating pregnancy, third trimester	7057	G2z..00	Hypertensive disease NOS
		O10.22	Pre-existing hypertensive chronic kidney disease complicating childbirth	3979	G672.00	Hypertensive encephalopathy
		O10.311	Pre-existing hypertensive heart and chronic kidney disease complicating pregnancy, first trimester	31816	G672.11	Hypertensive crisis
		O10.312	Pre-existing hypertensive heart and chronic kidney disease complicating pregnancy, second trimester	69753	Gyu2.00	[X]Hypertensive diseases
		O10.313	Pre-existing hypertensive heart and chronic kidney disease complicating pregnancy, third trimester	66567	L122.00	Other pre-existing hypertension in preg/childbirth/puerp
		O10.32	Pre-existing hypertensive heart and chronic kidney disease complicating childbirth	73586	L122000	Other pre-existing hypertension in preg/childb/puerp unspec
		O11.1	Pre-existing hypertension with pre-eclampsia, first trimester	72030	L122100	Other pre-existing hypertension in preg/childb/puerp - deliv
		O11.2	Pre-existing hypertension with pre-eclampsia, second trimester	96743	L122300	Other pre-exist hypertension in preg/childb/puerp-not deliv
		O11.3	Pre-existing hypertension with pre-eclampsia, third trimester	62432	L122z00	Other pre-existing hypertension in preg/childb/puerp NOS
64222	Other pre-existing hypertension, complicating pregnancy, childbirth, and the puerperium, delivered, with mention of postpartum complication	O10.13	Pre-existing hypertensive heart disease complicating the puerperium	43664	L127.00	Pre-eclampsia or eclampsia with pre-existing hypertension

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Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
64223	Other pre-existing hypertension, complicating pregnancy, childbirth, and the puerperium, antepartum condition or complication	O10.111	Pre-existing hypertensive heart disease complicating pregnancy, first trimester	93055	L127z00	Pre-eclampsia or eclampsia + pre-existing hypertension NOS
		O10.112	Pre-existing hypertensive heart disease complicating pregnancy, second trimester	44549	L128.00	Pre-exist hypertension compl preg childbirth and puerperium
		O10.113	Pre-existing hypertensive heart disease complicating pregnancy, third trimester	60655	L128000	Pre-exist hyperten heart dis compl preg childbth+puerperium
		O10.211	Pre-existing hypertensive chronic kidney disease complicating pregnancy, first trimester	52621	L128200	Pre-exist 2ndry hypertens comp preg childbth and puerperium
		O10.212	Pre-existing hypertensive chronic kidney disease complicating pregnancy, second trimester	21660	TJC7.00	Adverse reaction to other antihypertensives
		O10.213	Pre-existing hypertensive chronic kidney disease complicating pregnancy, third trimester	20497	TJC7z00	Adverse reaction to antihypertensives NOS
		O10.311	Pre-existing hypertensive heart and chronic kidney disease complicating pregnancy, first trimester	63164	U60C500	[X]Oth antihyperten drug caus advers eff in therap use, NEC
		O10.312	Pre-existing hypertensive heart and chronic kidney disease complicating pregnancy, second trimester	30770	U60C511	[X] Adverse reaction to other antihypertensives
		O10.313	Pre-existing hypertensive heart and chronic kidney disease complicating pregnancy, third trimester	44350	U60C51A	[X] Adverse reaction to antihypertensives NOS
		O11.1	Pre-existing hypertension with pre-eclampsia, first trimester	32976	6146200	Hypertension induced by oral contraceptive pill
		O11.2	Pre-existing hypertension with pre-eclampsia, second trimester	7329	G24..00	Secondary hypertension
		O11.3	Pre-existing hypertension with pre-eclampsia, third trimester	31755	G240.00	Secondary malignant hypertension
64224	Other pre-existing hypertension,complicating pregnancy, childbirth, and the puerperium, , postpartum condition or complication	O10.13	Pre-existing hypertensive heart disease complicating the puerperium	59383	G240000	Secondary malignant renovascular hypertension

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Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
		O10.23	Pre-existing hypertensive chronic kidney disease complicating the puerperium	73293	G240z00	Secondary malignant hypertension NOS
		O10.33	Pre-existing hypertensive heart and chronic kidney disease complicating the puerperium	57288	G241.00	Secondary benign hypertension
64270	Pre-eclampsia or eclampsia superimposed on pre-existing hypertension, unspecified as to episode of care or not applicable	O11.9	Pre-existing hypertension with pre-eclampsia, unspecified trimester	25371	G241000	Secondary benign renovascular hypertension
64271	Pre-eclampsia or eclampsia superimposed on pre-existing hypertension, delivered, with or without mention of antepartum condition	O11.1	Pre-existing hypertension with pre-eclampsia, first trimester	51635	G241z00	Secondary benign hypertension NOS
		O11.2	Pre-existing hypertension with pre-eclampsia, second trimester	34744	G244.00	Hypertension secondary to endocrine disorders
		O11.3	Pre-existing hypertension with pre-eclampsia, third trimester	16059	G24z.00	Secondary hypertension NOS
		O11.4	Pre-existing hypertension with pre-eclampsia, complicating childbirth	31387	G24z000	Secondary renovascular hypertension NOS
64272	Pre-eclampsia or eclampsia superimposed on pre-existing hypertension, delivered, with mention of postpartum complication	O11.4	Pre-existing hypertension with pre-eclampsia, complicating childbirth	31341	G24z100	Hypertension secondary to drug
64273	Pre-eclampsia or eclampsia superimposed on pre-existing hypertension, antepartum condition or complication	O11.1	Pre-existing hypertension with pre-eclampsia, first trimester	42229	G24zz00	Secondary hypertension NOS
		O11.2	Pre-existing hypertension with pre-eclampsia, second trimester	97533	Gyu2100	[X]Hypertension secondary to other renal disorders
		O11.3	Pre-existing hypertension with pre-eclampsia, third trimester			
64274	Pre-eclampsia or eclampsia superimposed on pre-existing hypertension, postpartum condition or complication	O11.5	Pre-existing hypertension with pre-eclampsia, complicating the puerperium			
64290	Unspecified hypertension complicating pregnancy, childbirth, or the puerperium, unspecified as to episode of care or not applicable	O16.9	Unspecified maternal hypertension, unspecified trimester			
64291	Unspecified hypertension complicating pregnancy, childbirth, or the puerperium,	O16.1	Unspecified maternal hypertension, first trimester			

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Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
	delivered, with or without mention of antepartum condition					
		O16.2	Unspecified maternal hypertension, second trimester			
		O16.3	Unspecified maternal hypertension, third trimester			
		O16.4	Unspecified maternal hypertension, complicating childbirth			
64292	Unspecified hypertension complicating pregnancy, childbirth, or the puerperium, delivered, with mention of postpartum complication	O16.5	Unspecified maternal hypertension, complicating the puerperium			
		O16.9	Unspecified maternal hypertension, unspecified trimester			
64293	Unspecified hypertension complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication	O16.1	Unspecified maternal hypertension, first trimester			
		O16.2	Unspecified maternal hypertension, second trimester			
		O16.3	Unspecified maternal hypertension, third trimester			
64294	Unspecified hypertension complicating pregnancy, childbirth, or the puerperium, postpartum condition or complication	O16.1	Unspecified maternal hypertension, first trimester			
		O16.2	Unspecified maternal hypertension, second trimester			
		O16.3	Unspecified maternal hypertension, third trimester			
		O16.5	Unspecified maternal hypertension, complicating the puerperium			
Chronic lung disease						
490	Bronchitis, not specified as acute or chronic	J40	Bronchitis, not specified as acute or chronic	78	H33..00	Asthma
4910	Simple chronic bronchitis	J41.0	Simple chronic bronchitis	81	663..11	Asthma monitoring
4911	Mucopurulent chronic bronchitis	J41.1	Mucopurulent chronic bronchitis	185	H333.00	Acute exacerbation of asthma

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Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
49120	Obstructive chronic bronchitis without exacerbation	J44.9	Chronic obstructive pulmonary disease, unspecified	232	H33z100	Asthma attack
49121	Obstructive chronic bronchitis with (acute) exacerbation	J44.1	Chronic obstructive pulmonary disease with (acute) exacerbation	233	H33z011	Severe asthma attack
49122	Obstructive chronic bronchitis with acute bronchitis	J44.0	Chronic obstructive pulmonary disease with acute lower respiratory infection	719	14B4.00	H/O: asthma
4918	Other chronic bronchitis	J41.8	Mixed simple and mucopurulent chronic bronchitis	998	H3...11	Chronic obstructive airways disease
4919	Unspecified chronic bronchitis	J42	Unspecified chronic bronchitis	1001	H3...00	Chronic obstructive pulmonary disease
4920	Emphysematous bleb	J43.9	Emphysema, unspecified	1446	H312200	Acute exacerbation of chronic obstructive airways disease
4928	Other emphysema	J43.9	Emphysema, unspecified	1555	H33..11	Bronchial asthma
49300	Extrinsic asthma, unspecified	J45.20	Mild intermittent asthma, uncomplicated	2195	H34..00	Bronchiectasis
49301	Extrinsic asthma with status asthmaticus	J45.22	Mild intermittent asthma with status asthmaticus	2290	H330.11	Allergic asthma
49302	Extrinsic asthma with (acute) exacerbation	J45.21	Mild intermittent asthma with (acute) exacerbation	3018	663V100	Mild asthma
49310	Intrinsic asthma, unspecified	J45.20	Mild intermittent asthma, uncomplicated	3366	663V300	Severe asthma
49311	Intrinsic asthma with status asthmaticus	J45.22	Mild intermittent asthma with status asthmaticus	3458	663V000	Occasional asthma
49312	Intrinsic asthma with (acute) exacerbation	J45.21	Mild intermittent asthma with (acute) exacerbation	3480	H30z.00	Bronchitis NOS
49320	Chronic obstructive asthma, unspecified	J44.9	Chronic obstructive pulmonary disease, unspecified	3665	H331.11	Late onset asthma
49321	Chronic obstructive asthma with status asthmaticus	J44.0	Chronic obstructive pulmonary disease with acute lower respiratory infection	4442	H33z.00	Asthma unspecified
49322	Chronic obstructive asthma with (acute) exacerbation	J44.1	Chronic obstructive pulmonary disease with (acute) exacerbation	4519	14B3.11	H/O: bronchitis
49381	Exercise induced bronchospasm	J45.990	Exercise induced bronchospasm	4606	H33zz11	Exercise induced asthma
49382	Cough variant asthma	J45.991	Cough variant asthma	5267	H331.00	Intrinsic asthma
49390	Asthma, unspecified type, unspecified	J45.909	Unspecified asthma, uncomplicated	5519	H563.12	Cryptogenic fibrosing alveolitis
		J45.998	Other asthma	5627	H330011	Hay fever with asthma
49391	Asthma, unspecified type, with status asthmaticus	J45.902	Unspecified asthma with status asthmaticus	5710	H3z..00	Chronic obstructive airways disease NOS

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Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
49392	Asthma, unspecified type, with (acute) exacerbation	J45.901	Unspecified asthma with (acute) exacerbation	5798	H312000	Chronic asthmatic bronchitis
4940	Bronchiectasis without acute exacerbation	J47.9	Bronchiectasis, uncomplicated	5867	173A.00	Exercise induced asthma
4941	Bronchiectasis with acute exacerbation	J47.1	Bronchiectasis with (acute) exacerbation	5909	H312011	Chronic wheezy bronchitis
4950	Farmers' lung	J67.0	Farmer's lung	6707	H330111	Extrinsic asthma with asthma attack
4951	Bagassosis	J67.1	Bagassosis	6837	H563.00	Idiopathic fibrosing alveolitis
4952	Bird-fanciers' lung	J67.2	Bird fancier's lung	7058	8H2P.00	Emergency admission, asthma
4953	Suberosis	J67.3	Suberosis	7092	H30..12	Recurrent wheezy bronchitis
4954	Malt workers' lung	J67.4	Maltworker's lung	7146	H330.00	Extrinsic (atopic) asthma
4955	Mushroom workers' lung	J67.5	Mushroom-worker's lung	7191	663P.00	Asthma limiting activities
4956	Maple bark-strippers' lung	J67.6	Maple-bark-stripper's lung	7229	663W.00	Asthma prophylactic medication used
4957	"Ventilation" pneumonitis	J67.7	Air conditioner and humidifier lung	7378	663U.00	Asthma management plan given
4958	Other specified allergic alveolitis and pneumonitis	J67.8	Hypersensitivity pneumonitis due to other organic dusts	7416	663N.00	Asthma disturbing sleep
4959	Unspecified allergic alveolitis and pneumonitis	J67.9	Hypersensitivity pneumonitis due to unspecified organic dust	7731	H330.14	Pollen asthma
496	Chronic airway obstruction, not elsewhere classified	J44.9	Chronic obstructive pulmonary disease, unspecified	8303	H41..00	Asbestosis
500	Coal workers' pneumoconiosis	J60	Coalworker's pneumoconiosis	8335	H33z111	Asthma attack NOS
501	Asbestosis	J61	Pneumoconiosis due to asbestos and other mineral fibers	8355	9OJA.11	Asthma monitored
502	Pneumoconiosis due to other silica or silicates	J62.8	Pneumoconiosis due to other dust containing silica	9520	66YB.00	Chronic obstructive pulmonary disease monitoring
503	Pneumoconiosis due to other inorganic dust	J63.0	Aluminosis (of lung)	9552	66Y5.00	Change in asthma management plan
		J63.1	Bauxite fibrosis (of lung)	9653	H5y1600	Bronchospasm
		J63.2	Berylliosis	9663	66Y9.00	Step up change in asthma management plan
		J63.3	Graphite fibrosis (of lung)	9876	H38..00	Severe chronic obstructive pulmonary disease
		J63.4	Siderosis	10043	66YJ.00	Asthma annual review
		J63.5	Stannosis	10274	8B3j.00	Asthma medication review
		J63.6	Pneumoconiosis due to other specified inorganic dusts	10487	663j.00	Asthma - currently active

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504	Pneumonopathy due to inhalation of other dust	J66.0	Byssinosis	10802	H37..00	Moderate chronic obstructive pulmonary disease
		J66.1	Flax-dressers' disease	10863	H36..00	Mild chronic obstructive pulmonary disease
		J66.2	Cannabinosis	10992	H47..11	Aspiration pneumonitis
		J66.8	Airway disease due to other specific organic dusts	11150	H311.00	Mucopurulent chronic bronchitis
505	Pneumoconiosis, unspecified	J64	Unspecified pneumoconiosis	11287	66YM.00	Chronic obstructive pulmonary disease annual review
5064	Chronic respiratory conditions due to fumes and vapors	J68.4	Chronic respiratory conditions due to chemicals, gases, fumes and vapors	11312	H35..00	Extrinsic allergic alveolitis
				11370	1O2..00	Asthma confirmed
				11833	H35z100	Hypersensitivity pneumonitis NOS
				12166	H3y..00	Other specified chronic obstructive airways disease
				12987	H33z200	Late-onset asthma
				13064	663V.00	Asthma severity
				13065	663V200	Moderate asthma
				13066	663h.00	Asthma - currently dormant
				13173	663O.00	Asthma not disturbing sleep
				13174	663Q.00	Asthma not limiting activities
				13175	663N200	Asthma disturbs sleep frequently
				13176	66YK.00	Asthma follow-up
				14777	H330000	Extrinsic asthma without status asthmaticus
				14798	H312100	Emphysematous bronchitis
				15157	H31z.00	Chronic bronchitis NOS
				15248	H330.13	Hay fever with asthma
				15588	H350.00	Farmers' lung
				15626	H310000	Chronic catarrhal bronchitis
				15693	A115.00	Tuberculous bronchiectasis
				16070	H33zz00	Asthma NOS
				16655	9OJ..00	Asthma monitoring admin.

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Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				16667	8795	Asthma control step 2
				16785	8794	Asthma control step 1
				17359	H30..11	Chest infection - unspecified bronchitis
				18141	66YE.00	Asthma monitoring due
				18207	H33zz13	Allergic bronchitis NEC
				18223	66YA.00	Step down change in asthma management plan
				18224	8796	Asthma control step 3
				18323	H331111	Intrinsic asthma with asthma attack
				18621	66YL.00	Chronic obstructive pulmonary disease follow-up
				18792	9Oi..00	Chronic obstructive pulmonary disease monitoring admin
				19167	66YQ.00	Asthma monitoring by nurse
				19492	H40..00	Coal workers' pneumoconiosis
				19519	663p.00	Asthma treatment compliance unsatisfactory
				19520	663n.00	Asthma treatment compliance satisfactory
				19539	9OJA.00	Asthma monitoring check done
				20364	H340.00	Recurrent bronchiectasis
				20422	9OJ..11	Asthma clinic administration
				20860	8798	Asthma control step 5
				20886	8797	Asthma control step 4
				21232	H33zz12	Allergic asthma NEC
				22752	173c.00	Occupational asthma
				23446	H42z.00	Silica pneumoconiosis NOS
				23461	H43z.00	Pneumoconiosis due to inorganic dust NOS
				24248	H313.00	Mixed simple and mucopurulent chronic bronchitis
				24479	663d.00	Emergency asthma admission since last appointment

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Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				24506	8791	Further asthma - drug prevent.
				24884	663u.00	Asthma causes daytime symptoms 1 to 2 times per week
				25181	663e.00	Asthma restricts exercise
				25462	A521.00	Varicella pneumonitis
				25603	H310.00	Simple chronic bronchitis
				25705	9OJ6.00	Asthma monitor 3rd letter
				25706	9OJ5.00	Asthma monitor 2nd letter
				25707	9OJ4.00	Asthma monitor 1st letter
				25791	8CR0.00	Asthma clinical management plan
				25796	H332.00	Mixed asthma
				26018	66YS.00	Chronic obstructive pulmonary disease monitoring by nurse
				26278	H357.00	'Ventilation' pneumonitis
				26496	679J.00	Health education - asthma
				26501	663s.00	Asthma never causes daytime symptoms
				26503	663v.00	Asthma causes daytime symptoms most days
				26504	663f.00	Asthma never restricts exercise
				26506	6.63E+102	Asthma severely restricts exercise
				26861	6.63E+02	Asthma sometimes restricts exercise
				27345	H352.00	Bird-fancier's lung
				27819	H312.00	Obstructive chronic bronchitis
				27926	H330100	Extrinsic asthma with status asthmaticus
				28229	H563z00	Idiopathic fibrosing alveolitis NOS
				28755	9Oi0.00	Chronic obstructive pulmonary disease monitoring 1st letter
				28853	N04y012	Fibrosing alveolitis associated with rheumatoid arthritis
				29325	H331000	Intrinsic asthma without status asthmaticus

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Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				29645	8793	Asthma control step 0
				30382	9OJZ.00	Asthma monitoring admin.NOS
				30458	66YR.00	Asthma monitoring by doctor
				30815	663N000	Asthma causing night waking
				31135	9OJ8.00	Asthma monitor phone invite
				31167	66YP.00	Asthma night-time symptoms
				31225	663t.00	Asthma causes daytime symptoms 1 to 2 times per month
				31423	H45..00	Pneumoconiosis NOS
				31722	H46..00	Respiratory disease due to chemical fumes and vapours
				32679	H34z.00	Bronchiectasis NOS
				33663	H46zz00	Respiratory conditions due to chemical fumes NOS
				34202	9Oi1.00	Chronic obstructive pulmonary disease monitoring 2nd letter
				34215	9Oi2.00	Chronic obstructive pulmonary disease monitoring 3rd letter
				37247	H3z..11	Chronic obstructive pulmonary disease NOS
				37371	66YD.00	Chronic obstructive pulmonary disease monitoring due
				37943	9OJ7.00	Asthma monitor verbal invite
				37959	H311100	Fetid chronic bronchitis
				38065	H263.00	Pneumonitis, unspecified
				38143	663O000	Asthma never disturbs sleep
				38144	663w.00	Asthma limits walking up hills or stairs
				38145	663x.00	Asthma limits walking on the flat
				38146	663N100	Asthma disturbs sleep weekly
				38639	H460.00	Bronchitis and pneumonitis due to chemical fumes
				39478	H35y700	Wood asthma
				39570	663r.00	Asthma causes night symptoms 1 to 2 times per month

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				40159	H311000	Purulent chronic bronchitis
				40823	H334.00	Brittle asthma
				40864	U60F615	[X] Adverse reaction to theophylline - asthma
				41020	66YC.00	Absent from work or school due to asthma
				41554	9OJ3.00	Asthma monitor offer default
				41694	H355.00	Mushroom workers' lung
				42313	679V.00	Health education - chronic obstructive pulmonary disease
				42824	663q.00	Asthma daytime symptoms
				44525	H312z00	Obstructive chronic bronchitis NOS
				45072	A785000	Cytomegaloviral pneumonitis
				45073	H331z00	Intrinsic asthma NOS
				45089	H31y100	Chronic tracheobronchitis
				45770	66Yg.00	Chronic obstructive pulmonary disease disturbs sleep
				45771	66Yh.00	Chronic obstructive pulmonary disease does not disturb sleep
				45777	8CR1.00	Chronic obstructive pulmonary disease clini management plan
				45782	H330z00	Extrinsic asthma NOS
				45998	66YT.00	Chronic obstructive pulmonary disease monitoring by doctor
				46460	H42..00	Silica and silicate pneumoconiosis
				46529	9OJ1.00	Attends asthma monitoring
				46977	H35z.00	Allergic alveolitis and pneumonitis NOS
				47142	H464.00	Chronic respiratory conditions due to chemical fumes
				47337	663m.00	Asthma accident and emergency attendance since last visit
				47782	H464200	Chronic pulmonary fibrosis due to chemical fumes

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				48591	TJF7300	Adverse reaction to theophylline (asthma)
				48647	H46z.00	Respiratory conditions due to chemical fumes NOS
				51116	U60F600	[X]Antiasthmats caus adverse effects in therapeut use, NEC
				51410	H41z.00	Asbestosis NOS
				51858	H35y.00	Other allergic alveolitis
				53095	H35zz00	Allergic alveolitis and pneumonitis NOS
				55552	H35yz00	Other allergic alveolitis NOS
				55758	H460z00	Bronchitis and pneumonitis due to chemical fumes NOS
				55816	TJF7.00	Adverse reaction to antiasthmatics
				56652	H356.00	Maple bark strippers' lung
				56762	AD04.00	Toxoplasma pneumonitis
				58196	H331100	Intrinsic asthma with status asthmaticus
				60805	H420.00	Talc pneumoconiosis
				61118	H310z00	Simple chronic bronchitis NOS
				61513	H311z00	Mucopurulent chronic bronchitis NOS
				62200	H351.00	Bagassosis
				62442	H35z000	Allergic extrinsic alveolitis NOS
				63172	H450.00	Pneumoconiosis associated with tuberculosis
				63233	TJF7z00	Adverse reaction to antiasthmatic NOS
				65117	A789900	HIV disease resulting in lymphoid interstitial pneumonitis
				65376	H43..00	Pneumoconiosis due to other inorganic dust
				65733	Hyu3100	[X]Other specified chronic obstructive pulmonary disease
				66043	H31y.00	Other chronic bronchitis

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				67040	H3y..11	Other specified chronic obstructive pulmonary disease
				67709	H354.00	Malt workers' lung
				68066	H31yz00	Other chronic bronchitis NOS
				70815	H464z00	Chronic respiratory conditions due to chemical fumes NOS
				73408	SLF7z00	Antiasthmatic poisoning NOS
				73522	173d.00	Work aggravated asthma
				92109	9NI8.00	Asthma outreach clinic
				93206	H353.00	Suberosis (cork-handlers' lung)
				93568	H39..00	Very severe chronic obstructive pulmonary disease
				98185	38DL.00	Asthma control test
				100107	679J000	Health education - asthma self management
				100509	9NNX.00	Under care of asthma specialist nurse
				100650	AB63600	Aspergillus bronchitis
				101133	U60F61A	[X] Adverse reaction to antiasthmatic NOS
				101775	H060100	Acute membranous bronchitis
				102301	1787	Asthma trigger - seasonal
				102341	1781	Asthma trigger - pollen
				102395	66Yr.00	Asthma causes symptoms most nights
				102400	66Yq.00	Asthma causes night time symptoms 1 to 2 times per week
				102449	1789	Asthma trigger - respiratory infection
				102685	66YB000	Chronic obstructive pulmonary disease 3 monthly review
				102713	663P000	Asthma limits activities 1 to 2 times per month
				102871	178B.00	Asthma trigger - exercise
				102888	663P100	Asthma limits activities 1 to 2 times per week
				102952	1783	Asthma trigger - warm air

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				103007	66YB100	Chronic obstructive pulmonary disease 6 monthly review
				103321	1786	Asthma trigger - animals
				103494	14B3.12	History of chronic obstructive pulmonary disease
				103559	H563300	Usual interstitial pneumonitis
				103612	66Ys.00	Asthma never causes night symptoms
				103637	H35..11	Hypersensitivity pneumonitis
				103813	1788	Asthma trigger - cold air
				103944	178A.00	Asthma trigger - airborne dust
				103945	1785	Asthma trigger - damp
				103952	1784	Asthma trigger - emotion
				103955	1782	Asthma trigger - tobacco smoke
				103998	663P200	Asthma limits activities most days
				104235	U60F611	[X] Adverse reaction to antiasthmatics
				104608	H3A..00	End stage chronic obstructive airways disease
				105420	661N100	Asthma self-management plan review
				105457	8CMW500	Chronic obstructive pulmonary disease care pathway
				105674	661M100	Asthma self-management plan agreed
				105939	Hyu4000	[X]Pneumoconiosis due to other dust containing silica
				106515	Hyu4300	[X]Hypersensitivity pneumonitis due to other organic dusts
				106650	H583200	Eosinophilic bronchitis
				106805	H335.00	Chronic asthma with fixed airflow obstruction
				108912	9OJB.00	Asthma monitorng invit SMS (short message servce) txt messge
				109683	2126F00	Chronic obstructive pulmonary disease resolved
				109816	14BA.00	H/O: bronchiectasis

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
				109958	H3B..00	Asthma-chronic obstructive pulmonary disease overlap syndrom
				109996	66Yz500	Telehealth asthma monitoring
				110339	9OJB000	Asthma monitoring SMS text message 1st invitation
				110533	9OJB100	Asthma monitoring SMS text message 2nd invitation
				111669	9OJB200	Asthma monitoring SMS text message 3rd invitation
Chronic kidney disease						
40301	Hypertensive chronic kidney disease, malignant, with chronic kidney disease stage V or end stage renal disease	I12.0	Hypertensive chronic kidney disease with stage 5 chronic kidney disease or end stage renal disease	2996	7L1A200	Haemodialysis NEC
40311	Hypertensive chronic kidney disease, benign, with chronic kidney disease stage V or end stage renal disease	I12.0	Hypertensive chronic kidney disease with stage 5 chronic kidney disease or end stage renal disease	2997	7B00.00	Transplantation of kidney
40391	Hypertensive chronic kidney disease, unspecified, with chronic kidney disease stage V or end stage renal disease	I12.0	Hypertensive chronic kidney disease with stage 5 chronic kidney disease or end stage renal disease	4503	PD11.00	Polycystic kidney disease
40402	Hypertensive heart and chronic kidney disease, malignant, without heart failure and with chronic kidney disease stage V or end stage renal disease	I13.11	Hypertensive heart and chronic kidney disease without heart failure, with stage 5 chronic kidney disease, or end stage renal disease	4504	PD1..13	Polycystic kidney
40403	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end stage renal disease	I13.2	Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease	4505	PD11100	Polycystic kidneys, adult type
40412	Hypertensive heart and chronic kidney disease, benign, without heart failure and with chronic kidney disease stage V or end stage renal disease	I13.11	Hypertensive heart and chronic kidney disease without heart failure, with stage 5 chronic kidney disease, or end stage renal disease	5504	7B00z00	Transplantation of kidney NOS
40492	Hypertensive heart and chronic kidney disease, unspecified, without heart failure and with chronic kidney disease stage V or end stage renal disease	I13.11	Hypertensive heart and chronic kidney disease without heart failure, with stage 5 chronic kidney disease, or end stage renal disease	5911	ZV42000	[V]Kidney transplanted

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
40493	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease	I13.2	Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease	11436	K13z000	Non-functioning kidney
5855	Chronic kidney disease, Stage V	N18.5	Chronic kidney disease, stage 5	11553	SP08300	Kidney transplant failure and rejection
5856	End stage renal disease	N18.6	End stage renal disease	11554	SP15400	Renal failure as a complication of care
V420	Kidney replaced by transplant	Z94.0	Kidney transplant status	11745	7B00100	Transplantation of kidney from live donor
V4511	Renal dialysis status	Z99.2	Dependence on renal dialysis	12479	1Z13.00	Chronic kidney disease stage 4
V560	Encounter for extracorporeal dialysis	Z49.31	Encounter for adequacy testing for hemodialysis	12566	1Z12.00	Chronic kidney disease stage 3
V561	Fitting and adjustment of extracorporeal dialysis catheter	Z49.01	Encounter for fitting and adjustment of extracorporeal dialysis catheter	12585	1Z14.00	Chronic kidney disease stage 5
V562	Fitting and adjustment of peritoneal dialysis catheter	Z49.02	Encounter for fitting and adjustment of peritoneal dialysis catheter	12586	1Z11.00	Chronic kidney disease stage 2
V568	Encounter for other dialysis	Z49.32	Encounter for adequacy testing for peritoneal dialysis	15917	PD1..00	Congenital cystic kidney disease
				19473	66i..00	Chronic kidney disease monitoring
				21381	PD11000	Polycystic kidneys, infantile type
				24361	7B00200	Transplantation of kidney from cadaver
				28158	TB11.00	Kidney dialysis with complication, without blame
				29013	1Z10.00	Chronic kidney disease stage 1
				30735	6AA..00	Chronic kidney disease annual review
				30739	9Ot0.00	Chronic kidney disease monitoring first letter
				39598	SP15411	Kidney failure as a complication of care
				46626	9hE..00	Exception reporting: chronic kidney disease quality indicato
				50331	PD1z.00	Congenital cystic kidney disease NOS
				54990	TB00100	Kidney transplant with complication, without blame

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				56852	PD11z00	Polycystic kidney disease NOS
				59031	PD1yz00	Other congenital cystic kidney disease NOS
				66705	7B00111	Allotransplantation of kidney from live donor
				69266	TA22000	Failure of sterile precautions during kidney dialysis
				69679	9Ot4.00	Chronic kidney disease monitoring telephone invite
				70874	7B00y00	Other specified transplantation of kidney
				71271	9Ot..00	Chronic kidney disease monitoring administration
				72004	7B01511	Excision of rejected transplanted kidney
				72878	7827200	Sphincteroplasty pancreatic duct using duodenal approach NEC
				72962	9Ot1.00	Chronic kidney disease monitoring second letter
				72964	9Ot2.00	Chronic kidney disease monitoring third letter
				88494	9Ot3.00	Chronic kidney disease monitoring verbal invite
				89332	9Ot5.00	Predicted stage chronic kidney disease
				89924	7B00300	Allotransplantation of kidney from cadaver, heart-beating
				93366	7B0F.00	Interventions associated with transplantation of kidney
				94373	K01y.00	Nephrotic syndrome with other pathological kidney lesions
				94789	1Z17.00	Chronic kidney disease stage 1 with proteinuria

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				94793	1Z1B.00	Chronic kidney disease stage 3 with proteinuria
				94964	7B0F400	Post-transplantation of kidney examination, live donor
				94965	1Z15.00	Chronic kidney disease stage 3A
				95121	1Z1A.00	Chronic kidney disease stage 2 without proteinuria
				95122	1Z1H.00	Chronic kidney disease stage 4 with proteinuria
				95123	1Z1C.00	Chronic kidney disease stage 3 without proteinuria
				95145	1Z1B.11	CKD stage 3 with proteinuria
				95146	1Z19.00	Chronic kidney disease stage 2 with proteinuria
				95175	1Z1E.00	Chronic kidney disease stage 3A without proteinuria
				95178	1Z1F.00	Chronic kidney disease stage 3B with proteinuria
				95179	1Z16.00	Chronic kidney disease stage 3B
				95180	1Z1F.11	CKD stage 3B with proteinuria
				95405	1Z1L.00	Chronic kidney disease stage 5 without proteinuria
				95406	1Z1J.00	Chronic kidney disease stage 4 without proteinuria
				95408	1Z1D.00	Chronic kidney disease stage 3A with proteinuria
				95422	9Ni9.00	Did not attend chronic kidney disease monitoring clinic
				95508	1Z1K.00	Chronic kidney disease stage 5 with proteinuria
				95571	1Z1D.11	CKD stage 3A with proteinuria
				95572	1Z18.00	Chronic kidney disease stage 1 without proteinuria
				96095	7B0F200	Pre-transplantation of kidney work-up, live donor

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				96133	7B00400	Allotransplantation kidney from cadaver, heart non-beating
				98364	7B00211	Allotransplantation of kidney from cadaver
				104049	7B0Fz00	Interventions associated with transplantation of kidney NOS
				104050	7B0Fy00	OS interventions associated with transplantation of kidney
				104619	K053.00	Chronic kidney disease stage 3
				104963	K054.00	Chronic kidney disease stage 4
				104981	K05..13	Chronic kidney disease
				105143	PD11111	Autosomal dominant polycystic kidney disease
				105151	K055.00	Chronic kidney disease stage 5
				105383	K052.00	Chronic kidney disease stage 2
				105392	K051.00	Chronic kidney disease stage 1
				105919	PD11011	Autosomal recessive polycystic kidney disease
				107771	K06..12	Kidney failure unspecified
				108766	661M200	Chronic kidney disease self-management plan agreed
				109455	7B00500	Allotransplantation of kidney from cadaver NEC
				111637	TA42000	Mechanical failure of apparatus during kidney dialysis
				111022	1Z18.11	CKD stage 1 without proteinuria
				110626	1Z1c.00	CKD with GFR category G4 & albuminuria category A3
				110484	1Z1P.00	CKD with GFR category G1 & albuminuria category A3
				110467	1Z1f.00	CKD with GFR category G5 & albuminuria category A3
				110269	1Z1Q.00	CKD with GFR category G2 & albuminuria category A1

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				110251	1Z1S.00	CKD with GFR category G2 & albuminuria category A3
				110133	1Z1d.00	CKD with GFR category G5 & albuminuria category A1
				110108	1Z1R.00	CKD with GFR category G2 & albuminuria category A2
				110033	1Z1M.00	CKD with GFR category G1 & albuminuria category A1
				110003	1Z1N.00	CKD with GFR category G1 & albuminuria category A2
				109990	1Z1Z.00	CKD with GFR category G3b & albuminuria category A3
				109981	1Z1e.00	CKD with GFR category G5 & albuminuria category A2
				109980	1Z1a.00	CKD with GFR category G4 & albuminuria category A1
				109963	1Z1X.00	CKD with GFR category G3b & albuminuria category A1
				109905	1Z1W.00	CKD with GFR category G3a & albuminuria category A3
				109904	1Z1b.00	CKD with GFR category G4 & albuminuria category A2
				109804	1Z1T.00	CKD with GFR category G3a & albuminuria category A1
				109805	1Z1V.00	CKD with GFR category G3a & albuminuria category A2
				109657	1Z1Y.00	CKD with GFR category G3b & albuminuria category A2
				100633	1Z1G.11	CKD stage 3B without proteinuria
				99312	1Z1H.11	CKD stage 4 with proteinuria
				99160	1Z1K.11	CKD stage 5 with proteinuria
				97980	1Z17.11	CKD stage 1 with proteinuria
				97978	1Z1A.11	CKD stage 2 without proteinuria
				97979	1Z19.11	CKD stage 2 with proteinuria
				97587	1Z1J.11	CKD stage 4 without proteinuria

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				95188	1Z1C.11	CKD stage 3 without proteinuria
				95180	1Z1F.11	CKD stage 3B with proteinuria
				95145	1Z1B.11	CKD stage 3 with proteinuria
				350	K06..00	Renal failure unspecified
				512	K05..00	Chronic renal failure
				4668	G22..00	Hypertensive renal disease
				6712	K050.00	End stage renal failure
				6842	K060.11	Impaired renal function
				8330	K0D..00	End-stage renal disease
				8919	K08..00	Impaired renal function disorder
				11773	7L1A.11	Dialysis for renal failure
				11787	K060.00	Renal impairment
				12720	1Z1..00	Chronic renal impairment
				15106	G22z.00	Hypertensive renal disease NOS
				16929	D215.00	Anaemia secondary to renal failure
				17253	8L50.00	Renal transplant planned
				20073	7L1A000	Renal dialysis
				22252	ZV45100	[V]Renal dialysis status
				25394	D215000	Anaemia secondary to chronic renal failure
				25980	K08z.00	Impaired renal function disorder NOS
				26001	4519	Deteriorating renal function
				29310	G22z.11	Renal hypertension
				31549	7L1A.00	Compensation for renal failure
				32423	G222.00	Hypertensive renal disease with renal failure
				34637	K080z00	Renal osteodystrophy NOS
				41013	K08y300	Renal function impairment with growth failure
				41148	K0B4000	Renal tubulo-interstitial disorder in SLE
				43935	G221.00	Benign hypertensive renal disease

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				47342	Q48y000	Congenital renal failure
				48022	7L1Ay00	Other specified compensation for renal failure
				53852	K05..12	End stage renal failure
				53940	Kyu2100	[X]Other chronic renal failure
				56760	7L1B.00	Placement ambulatory apparatus compensation renal failure
				59194	7L1By00	Placement ambulatory apparatus-compensate renal failure OS
				61930	Kyu2.00	[X]Renal failure
				64636	7L1Az00	Compensation for renal failure NOS
				66714	TB11.11	Renal dialysis with complication, without blame
				83513	7L1C.00	Placement other apparatus for compensation for renal failure
				100205	K0E..00	Acute-on-chronic renal failure
				104201	SP08H00	Acute rejection of renal transplant
				104630	SP08G00	Acute rejection of renal transplant - grade III
				104905	SP08D00	Acute-on-chronic rejection of renal transplant
				104960	SP08E00	Acute rejection of renal transplant - grade I
				105328	7B00212	Cadaveric renal transplant
				105787	7B00600	Xenograft renal transplant
				105811	SP08R00	Renal transplant rejection
				106620	SP08J00	Chronic rejection of renal transplant
				106860	C353600	Renal failure-associated hyperphosphataemia
				107000	SP08F00	Acute rejection of renal transplant - grade II
				107382	K0J0.00	Renal involvement in scleroderma
				107647	9mG0.00	Renal function monitoring invitation first letter

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
Chronic liver disease						
07022	Chronic viral hepatitis B with hepatic coma without hepatitis delta	B18.1	Chronic viral hepatitis B without delta-agent	1638	J615z13	Cirrhosis of liver NOS
07023	Chronic viral hepatitis B with hepatic coma with hepatitis delta	B18.0	Chronic viral hepatitis B with delta-agent	1641	G85..11	Oesophageal varices
07032	Chronic viral hepatitis B without mention of hepatic coma without mention of hepatitis delta	B18.1	Chronic viral hepatitis B without delta-agent	1754	J614.00	Chronic hepatitis
07033	Chronic viral hepatitis B without mention of hepatic coma with hepatitis delta	B18.0	Chronic viral hepatitis B with delta-agent	1755	J614200	Chronic aggressive hepatitis
07044	Chronic hepatitis C with hepatic coma	B18.2	Chronic viral hepatitis C	2243	43B6.00	Hepatitis B non immune
07054	Chronic hepatitis C without mention of hepatic coma	B18.2	Chronic viral hepatitis C	2413	A70z000	Hepatitis C
4560	Esophageal varices with bleeding	I85.01	Esophageal varices with bleeding	2834	A705000	Viral hepatitis C without mention of hepatic coma
4561	Esophageal varices without mention of bleeding	I85.00	Esophageal varices without bleeding	2860	A703.00	Viral (serum) hepatitis B
45620	Esophageal varices in diseases classified elsewhere, with bleeding	I85.11	Secondary esophageal varices with bleeding	3248	43B2.00	Hepatitis B immune
45621	Esophageal varices in diseases classified elsewhere, without mention of bleeding	I85.10	Secondary esophageal varices without bleeding	4405	7800	Transplantation of liver
5710	Alcoholic fatty liver	K70.0	Alcoholic fatty liver	4406	J631100	Hepatitis in cytomegalic inclusion virus
5712	Alcoholic cirrhosis of liver	K70.30	Alcoholic cirrhosis of liver without ascites	4743	J612.00	Alcoholic cirrhosis of liver
5713	Alcoholic liver damage, unspecified	K70.9	Alcoholic liver disease, unspecified	5129	J623.00	Portal hypertension
57140	Chronic hepatitis, unspecified	K73.9	Chronic hepatitis, unspecified	5638	J616000	Primary biliary cirrhosis
57141	Chronic persistent hepatitis	K73.0	Chronic persistent hepatitis, not elsewhere classified	6015	Jyu7100	[X]Other and unspecified cirrhosis of liver
57142	Autoimmune hepatitis	K75.4	Autoimmune hepatitis	6863	J61..00	Cirrhosis and chronic liver disease
57149	Other chronic hepatitis	K73.2	Chronic active hepatitis, not elsewhere classified	7602	J617000	Chronic alcoholic hepatitis
		K73.8	Other chronic hepatitis, not elsewhere classified	7943	J617.00	Alcoholic hepatitis
5715	Cirrhosis of liver without mention of alcohol	K74.0	Hepatic fibrosis	7957	J614111	Autoimmune chronic active hepatitis

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
		K74.60	Unspecified cirrhosis of liver	8206	C350012	Pigmentary cirrhosis of liver
		K74.69	Other cirrhosis of liver	8363	G852300	Oesophageal varices in alcoholic cirrhosis of the liver
5716	Biliary cirrhosis	K74.3	Primary biliary cirrhosis	9026	ZV42700	[V]Liver transplanted
		K74.4	Secondary biliary cirrhosis	9029	J614100	Chronic active hepatitis
		K74.5	Biliary cirrhosis, unspecified	9494	J616.00	Biliary cirrhosis
5718	Other chronic nonalcoholic liver disease	K76.0	Fatty (change of) liver, not elsewhere classified	10234	J61y100	Non-alcoholic fatty liver
		K76.89	Other specified diseases of liver	10539	J61z.00	Chronic liver disease NOS
5719	Unspecified chronic liver disease without mention of alcohol	K74.1	Hepatic sclerosis	10691	J610.00	Alcoholic fatty liver
5723	Portal hypertension	K76.6	Portal hypertension	11960	760C300	Fibreoptic endoscopic injection sclerotherapy oesoph varices
5728	Other sequelae of chronic liver disease	K72.10	Chronic hepatic failure without coma	15424	J616100	Secondary biliary cirrhosis
		K72.90	Hepatic failure, unspecified without coma	15489	J614z00	Chronic hepatitis NOS
V427	Liver replaced by transplant	Z94.4	Liver transplant status	16455	J615z00	Non-alcoholic cirrhosis NOS
				16725	J615.00	Cirrhosis - non alcoholic
				16759	760C500	Fibreoptic endoscopic banding of oesophageal varices
				17219	J635300	Toxic liver disease with chronic persistent hepatitis
				18652	J63B.00	Autoimmune hepatitis
				18739	J615z12	Cryptogenic cirrhosis of liver
				19512	C310400	Glycogenosis with hepatic cirrhosis
				20233	7609z00	Open operation on oesophageal varices NOS
				20912	7609400	Open injection sclerotherapy to oesophageal varices
				22841	J615z11	Macronodular cirrhosis of liver
				23578	J614000	Chronic persistent hepatitis
				24220	7609	Open operations on oesophageal varices

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				24813	A707000	Chronic viral hepatitis B with delta-agent
				24912	2J12.00	Hepatitis C non immune
				24989	G850.00	Oesophageal varices with bleeding
				26319	G852200	Oesophageal varices in cirrhosis of the liver
				26367	A707.00	Chronic viral hepatitis
				27174	43B5.00	Hepatitis e antigen present
				27176	43B7.00	Hepatitis C non-immune
				27319	7800z00	Transplantation of liver NOS
				30586	A707200	Chronic viral hepatitis C
				30655	G851.00	Oesophageal varices without bleeding
				30729	141E.00	History of hepatitis B
				31897	J62..00	Liver abscess and sequelae of chronic liver disease
				31997	TB00200	Liver transplant with complication, without blame
				32025	7800000	Orthotopic transplantation of liver
				32277	A707X00	Chronic viral hepatitis, unspecified
				33597	J61yz00	Other non-alcoholic chronic liver disease NOS
				34087	A785200	Cytomegaloviral hepatitis
				40567	J615600	Capsular portal cirrhosis
				41096	A707100	Chronic viral hepatitis B without delta-agent
				42843	J61y.00	Other non-alcoholic chronic liver disease
				43404	7609300	Local ligation of oesophageal varices
				44120	J635600	Toxic liver disease with fibrosis and cirrhosis of liver
				44424	G852.00	Oesophageal varices in diseases EC
				44676	J615400	Fatty portal cirrhosis
				46647	760F400	Rigid oesophagoscopic banding of oesophageal varices

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
				47214	760F300	Rigid oesophagoscopic injection sclerotherapy oesoph varices
				47257	J615.11	Portal cirrhosis
				48102	J62y.00	Other sequelae of chronic liver disease
				48928	J615H00	Infectious cirrhosis NOS
				53877	J614y00	Chronic hepatitis unspecified
				55454	J615y00	Portal cirrhosis unspecified
				58630	J616z00	Biliary cirrhosis NOS
				62582	G852z00	Oesophageal varices in diseases EC NOS
				64750	J635400	Toxic liver disease with chronic lobular hepatitis
				65050	A704000	Viral hepatitis C with coma
				66185	AD05.00	Toxoplasma hepatitis
				66534	J614400	Chronic lobular hepatitis
				69194	7800200	Replacement of previous liver transplant
				69204	J615100	Multilobular portal cirrhosis
				71422	7800100	Heterotopic transplantation of liver
				73139	G852100	Oesophageal varices without bleeding in diseases EC
				73482	J615D00	Bacterial portal cirrhosis
				89445	7800111	Auxillary liver transplant
				92909	J615500	Hypertrophic portal cirrhosis
				96756	G852000	Oesophageal varices with bleeding in diseases EC
				97157	7800500	Orthotopic transplantation of liver NEC
				98148	J61y800	Nonalcoholic steatohepatitis
				99250	7800y00	Other specified transplantation of liver
				99898	9kR..00	Chronic hepatitis annual review - enhanced services admin
				102372	2126700	Hepatitis C resolved

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
				102922	C370800	Cystic fibrosis related cirrhosis
				103706	J61y911	Fatty liver
				105611	Gyu9400	[X]Oesophageal varices in diseases classified elsewhere
				106642	A707300	Chronic viral hepatitis B
				107896	AyuB200	[X]Chronic viral hepatitis, unspecified
				107975	7609y00	Other specified open operation on oesophageal varices
				108343	AyuB100	[X]Other chronic viral hepatitis
				108800	J62z.00	Liver abscess and chronic liver disease causing sequelae NOS
				109540	J615G00	Zooparasitic portal cirrhosis
				111969	9kR..11	Chronic hepatitis annual review
Peripheral arterial disease						
4400	Atherosclerosis of aorta	I70.0	Atherosclerosis of aorta			
4401	Atherosclerosis of renal artery	I70.1	Atherosclerosis of renal artery			
44020	Atherosclerosis of native arteries of the extremities, unspecified	I70.209	Unspecified atherosclerosis of native arteries of extremities, unspecified extremity			
44021	Atherosclerosis of native arteries of the extremities with intermittent claudication	I70.219	Atherosclerosis of native arteries of extremities with intermittent claudication, unspecified extremity			
44022	Atherosclerosis of native arteries of the extremities with rest pain	I70.229	Atherosclerosis of native arteries of extremities with rest pain, unspecified extremity			
44023	Atherosclerosis of native arteries of the extremities with ulceration	I70.25	Atherosclerosis of native arteries of other extremities with ulceration			
44024	Atherosclerosis of native arteries of the extremities with gangrene	I70.269	Atherosclerosis of native arteries of extremities with gangrene, unspecified extremity			
44029	Other atherosclerosis of native arteries of the extremities	I70.299	Other atherosclerosis of native arteries of extremities, unspecified extremity			
44030	Atherosclerosis of unspecified bypass graft of the extremities	I70.399	Other atherosclerosis of unspecified type of bypass graft(s) of the extremities, unspecified extremity			

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
44031	Atherosclerosis of autologous vein bypass graft of the extremities	I70.499	Other atherosclerosis of autologous vein bypass graft(s) of the extremities, unspecified extremity			
44032	Atherosclerosis of nonautologous biological bypass graft of the extremities	I70.599	Other atherosclerosis of nonautologous biological bypass graft(s) of the extremities, unspecified extremity			
4404	Chronic total occlusion of artery of the extremities	I70.92	Chronic total occlusion of artery of the extremities			
4408	Atherosclerosis of other specified arteries	I70.8	Atherosclerosis of other arteries			
4409	Generalized and unspecified atherosclerosis	I70.90	Unspecified atherosclerosis			
44100	Dissection of aorta, unspecified site	I71.00	Dissection of unspecified site of aorta			
44101	Dissection of aorta, thoracic	I71.01	Dissection of thoracic aorta			
44102	Dissection of aorta, abdominal	I71.02	Dissection of abdominal aorta			
44103	Dissection of aorta, thoracoabdominal	I71.03	Dissection of thoracoabdominal aorta			
4411	Thoracic aneurysm, ruptured	I71.1	Thoracic aortic aneurysm, ruptured			
4412	Thoracic aneurysm without mention of rupture	I71.2	Thoracic aortic aneurysm, without rupture			
4413	Abdominal aneurysm, ruptured	I71.3	Abdominal aortic aneurysm, ruptured			
4414	Abdominal aneurysm without mention of rupture	I71.4	Abdominal aortic aneurysm, without rupture			
4415	Aortic aneurysm of unspecified site, ruptured	I71.8	Aortic aneurysm of unspecified site, ruptured			
4416	Thoracoabdominal aneurysm, ruptured	I71.5	Thoracoabdominal aortic aneurysm, ruptured			
4417	Thoracoabdominal aneurysm, without mention of rupture	I71.6	Thoracoabdominal aortic aneurysm, without rupture			
4419	Aortic aneurysm of unspecified site without mention of rupture	I71.9	Aortic aneurysm of unspecified site, without rupture			
4420	Aneurysm of artery of upper extremity	I72.1	Aneurysm of artery of upper extremity			
4421	Aneurysm of renal artery	I72.2	Aneurysm of renal artery			
4422	Aneurysm of iliac artery	I72.3	Aneurysm of iliac artery			
4423	Aneurysm of artery of lower extremity	I72.4	Aneurysm of artery of lower extremity			
44281	Aneurysm of artery of neck	I72.0	Aneurysm of carotid artery			

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
		I72.5	Aneurysm of other precerebral arteries			
		I72.6	Aneurysm of vertebral artery			
44282	Aneurysm of subclavian artery	I72.8	Aneurysm of other specified arteries			
44283	Aneurysm of splenic artery	I72.8	Aneurysm of other specified arteries			
44284	Aneurysm of other visceral artery	I72.8	Aneurysm of other specified arteries			
44289	Aneurysm of other specified artery	I72.8	Aneurysm of other specified arteries			
4429	Aneurysm of unspecified site	I72.9	Aneurysm of unspecified site			
4430	Raynaud's syndrome	I73.00	Raynaud's syndrome without gangrene			
4431	Thromboangiitis obliterans [Buerger's disease]	I73.1	Thromboangiitis obliterans [Buerger's disease]			
44321	Dissection of carotid artery	I77.71	Dissection of carotid artery			
44322	Dissection of iliac artery	I77.72	Dissection of iliac artery			
44323	Dissection of renal artery	I77.73	Dissection of renal artery			
44324	Dissection of vertebral artery	I77.74	Dissection of vertebral artery			
44329	Dissection of other artery	I77.75	Dissection of other precerebral arteries			
		I77.76	Dissection of artery of upper extremity			
		I77.77	Dissection of artery of lower extremity			
		I77.79	Dissection of other specified artery			
44381	Peripheral angiopathy in diseases classified elsewhere	I79.8	Other disorders of arteries, arterioles and capillaries in diseases classified elsewhere			
44382	Erythromelalgia	I73.81	Erythromelalgia			
44389	Other specified peripheral vascular diseases	I73.89	Other specified peripheral vascular diseases			
4439	Peripheral vascular disease, unspecified	I73.9	Peripheral vascular disease, unspecified			
4471	Stricture of artery	I77.1	Stricture of artery			
5571	Chronic vascular insufficiency of intestine	K55.1	Chronic vascular disorders of intestine			
5579	Unspecified vascular insufficiency of intestine	K55.9	Vascular disorder of intestine, unspecified			
V434	Blood vessel replaced by other means	Z95.828	Presence of other vascular implants and grafts			
Obesity						
27800	Obesity, unspecified	E66.9	Obesity, unspecified	430	C380.00	Obesity

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
27801	Morbid obesity	E66.01	Morbid (severe) obesity due to excess calories	854	C380300	Morbid obesity
				10728	ZC2CM00	Dietary advice for obesity
				11461	66C..00	Obesity monitoring
				13278	22K5.00	Body mass index 30+ - obesity
				17477	ZV65319	[V]Dietary counselling in obesity
				21744	9OK..11	Obesity clinic administration
				25968	C380500	Generalised obesity
				32843	9OK..00	Obesity monitoring admin.
				38799	C380000	Obesity due to excess calories
				40153	66CZ.00	Obesity monitoring NOS
				49409	9OK4.00	Obesity monitoring 1st letter
				52034	9OK1.00	Attends obesity monitoring
				55585	9OK6.00	Obesity monitoring 3rd letter
				55586	9OK5.00	Obesity monitoring 2nd letter
				7516	9OK2.00	Refuses obesity monitoring
				67517	9OK8.00	Obesity monitor phone invite
				70950	9OK7.00	Obesity monitoring verbal inv.
				104129	C380600	Adult-onset obesity
				104421	C380700	Lifelong obesity
				108147	8T11.00	Referral to multidisciplinary obesity clinic
				108355	8CV7.00	Anti-obesity drug therapy commenced
				110196	66Ce.00	Telehealth obesity monitoring
				110415	66CX.00	Obesity multidisciplinary case review
				110415	66CX.00	Obesity multidisciplinary case review
				10728	ZC2CM00	Dietary advice for obesity
				11461	66C..00	Obesity monitoring
Chronic anaemia						
2800	Iron deficiency anaemia secondary to blood loss (chronic)	D50.0	Iron deficiency anaemia secondary to blood loss (chronic)			

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
2801	Iron deficiency anaemia secondary to inadequate dietary iron intake	D50.8	Other iron deficiency anaemias			
2808	Other specified iron deficiency anaemias	D50.1	Sideropenic dysphagia			
		D50.8	Other iron deficiency anaemias			
2809	Iron deficiency anaemia, unspecified	D50.9	Iron deficiency anaemia, unspecified			
2810	Pernicious anaemia	D51.0	Vitamin B12 deficiency anaemia due to intrinsic factor deficiency			
2811	Other vitamin B12 deficiency anaemia	D51.1	Vitamin B12 deficiency anaemia due to selective vitamin B12 malabsorption with proteinuria			
		D51.3	Other dietary vitamin B12 deficiency anaemia			
		D51.8	Other vitamin B12 deficiency anaemias			
2812	Folate-deficiency anaemia	D52.0	Dietary folate deficiency anaemia			
		D52.1	Drug-induced folate deficiency anaemia			
		D52.8	Other folate deficiency anaemias			
		D52.9	Folate deficiency anaemia, unspecified			
2813	Other specified megaloblastic anaemias not elsewhere classified	D53.1	Other megaloblastic anaemias, not elsewhere classified			
2814	Protein-deficiency anaemia	D53.0	Protein deficiency anaemia			
2818	Anaemia associated with other specified nutritional deficiency	D53.2	Scorbutic anaemia			
		D53.8	Other specified nutritional anaemias			
2819	Unspecified deficiency anaemia	D53.9	Nutritional anaemia, unspecified			
28521	Anaemia in chronic kidney disease	D63.1	Anaemia in chronic kidney disease			
28522	Anaemia in neoplastic disease	D63.0	Anaemia in neoplastic disease			
28529	Anaemia of other chronic disease	D63.8	Anaemia in other chronic diseases classified elsewhere			
2859	Anaemia, unspecified	D64.9	Anaemia, unspecified			
64820	Anaemia of mother, unspecified as to episode of care or not applicable	O99.019	Anaemia complicating pregnancy, unspecified trimester			
64821	Anaemia of mother, delivered, with or without mention of antepartum condition	O99.011	Anaemia complicating pregnancy, first trimester			

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
		O99.012	Anaemia complicating pregnancy, second trimester			
		O99.013	Anaemia complicating pregnancy, third trimester			
		O99.02	Anaemia complicating childbirth			
64822	Anaemia of mother, delivered, with mention of postpartum complication	O99.03	Anaemia complicating the puerperium			
64823	Anaemia of mother, antepartum condition or complication	O99.011	Anaemia complicating pregnancy, first trimester			
		O99.012	Anaemia complicating pregnancy, second trimester			
		O99.013	Anaemia complicating pregnancy, third trimester			
64824	Anaemia of mother, postpartum condition or complication	O90.81	Anaemia of the puerperium			
		O99.03	Anaemia complicating the puerperium			
Pulmonary circulation disorders						
4160	Primary pulmonary hypertension	I27.0	Primary pulmonary hypertension	245	G410.00	Primary pulmonary hypertension
4161	Kyphoscoliotic heart disease	I27.1	Kyphoscoliotic heart disease	55603	7Q01000	Primary pulmonary hypertension drugs Band 1
4162	Chronic pulmonary embolism	I27.82	Chronic pulmonary embolism	63946	7Q01100	Primary pulmonary hypertension drugs Band 2
4168	Other chronic pulmonary heart diseases	I27.20	Pulmonary hypertension, unspecified	65081	7Q01200	Primary pulmonary hypertension drugs Band 3
		I27.21	Secondary pulmonary arterial hypertension	90875	7Q01300	Primary pulmonary hypertension drugs Band 4
		I27.22	Pulmonary hypertension due to left heart disease	42901	G411.00	Kyphoscoliotic heart disease
		I27.23	Pulmonary hypertension due to lung diseases and hypoxia	15782	G41z.00	Chronic pulmonary heart disease NOS

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
		I27.24	Chronic thromboembolic pulmonary hypertension	46294	G41..00	Chronic pulmonary heart disease
		I27.29	Other secondary pulmonary hypertension	54113	G41y.00	Other chronic pulmonary heart disease
		I27.89	Other specified pulmonary heart diseases	71046	G41yz00	Other chronic pulmonary heart disease NOS
4169	Chronic pulmonary heart disease, unspecified	I27.81	Cor pulmonale (chronic)	95488	Gyu4.00	[X]Pulmon heart disease & diseases of pulmonary circulation
		I27.9	Pulmonary heart disease, unspecified	73599	G42z.00	Other pulmonary circulation disease NOS
4179	Unspecified disease of pulmonary circulation	I28.9	Disease of pulmonary vessels, unspecified	61138	G4y..00	Other specified pulmonary circulation disease
				41728	G42yz00	Other specified pulmonary circulation disease NOS
				24549	G42..00	Other pulmonary circulation disease
				16084	G4z..00	Pulmonary circulation disease NOS
				7180	G4...00	Pulmonary circulation diseases
Alcohol abuse						
2910	Alcohol withdrawal delirium	F10.231	Alcohol dependence with withdrawal delirium			
2911	Alcohol-induced persisting amnestic disorder	F10.96	Alcohol use, unspecified with alcohol-induced persisting amnestic disorder			
2912	Alcohol-induced persisting dementia	F10.27	Alcohol dependence with alcohol-induced persisting dementia			
2913	Alcohol-induced psychotic disorder with hallucinations	F10.951	Alcohol use, unspecified with alcohol-induced psychotic disorder with hallucinations			
2915	Alcohol-induced psychotic disorder with delusions	F10.950	Alcohol use, unspecified with alcohol-induced psychotic disorder with delusions			
29181						Alcoh

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	Diagnosis	Code	Diagnosis	Medcode	Readcode	Diagnosis
29182	Alcohol induced sleep disorders	F10.182	Alcohol abuse with alcohol-induced sleep disorder			
		F10.282	Alcohol dependence with alcohol-induced sleep disorder			
		F10.982	Alcohol use, unspecified with alcohol-induced sleep disorder			
29189	Other alcohol-induced mental disorders	F10.159	Alcohol abuse with alcohol-induced psychotic disorder, unspecified			
		F10.180	Alcohol abuse with alcohol-induced anxiety disorder			
		F10.181	Alcohol abuse with alcohol-induced sexual dysfunction			
		F10.188	Alcohol abuse with other alcohol-induced disorder			
		F10.259	Alcohol dependence with alcohol-induced psychotic disorder, unspecified			
		F10.280	Alcohol dependence with alcohol-induced anxiety disorder			
		F10.281	Alcohol dependence with alcohol-induced sexual dysfunction			
		F10.288	Alcohol dependence with other alcohol-induced disorder			
		F10.959	Alcohol use, unspecified with alcohol-induced psychotic disorder, unspecified			
		F10.980	Alcohol use, unspecified with alcohol-induced anxiety disorder			
2919	Unspecified alcohol-induced mental disorders	F10.99	Alcohol use, unspecified with unspecified alcohol-induced disorder			
30300	Acute alcoholic intoxication in alcoholism, unspecified	F10.229	Alcohol dependence with intoxication, unspecified			
30301	Acute alcoholic intoxication in alcoholism, continuous	F10.229	Alcohol dependence with intoxication, unspecified			
30302	Acute alcoholic intoxication in alcoholism, episodic	F10.229	Alcohol dependence with intoxication, unspecified			
30303	Acute alcoholic intoxication in alcoholism, in remission	F10.229	Alcohol dependence with intoxication, unspecified			

ICD-9-CM (United States and Taiwan)		ICD-10 (Japan)		Read codes (United Kingdom)		
Code	**Diagnosis**	**Code**	**Diagnosis**	**Medcode**	**Readcode**	**Diagnosis**
30390	Other and unspecified alcohol dependence, unspecified	F10.20	Alcohol dependence, uncomplicated			
30391	Other and unspecified alcohol dependence, continuous	F10.20	Alcohol dependence, uncomplicated			
30392	Other and unspecified alcohol dependence, episodic	F10.20	Alcohol dependence, uncomplicated			
30393	Other and unspecified alcohol dependence, in remission	F10.21	Alcohol dependence, in remission			
30500	Alcohol abuse, unspecified	F10.10	Alcohol abuse, uncomplicated			
30501	Alcohol abuse, continuous	F10.10	Alcohol abuse, uncomplicated			
30502	Alcohol abuse, episodic	F10.10	Alcohol abuse, uncomplicated			
30503	Alcohol abuse, in remission	F10.11	Alcohol abuse, in remission			
V113	Personal history of alcoholism	Z65.8	Other specified problems related to psychosocial circumstances			

SUPPLEMENTARY TABLE 3: CODES USED FOR IDENTIFICATION OF PROCEDURES IN THE UK, US, TAIWAN AND JAPAN

9.1.13 Coronary angiogram

9.1.14 Right heart catheterisation

9.1.15 Mechanical ventilation

9.1.16 Device implantation

9.1.17 Percutaneous coronary intervention

9.1.18 Coronary artery bypass grafting

9.1.19 Cardioversion

9.1.20 Ablations

9.1.21 Mechanical hemodynamic support

ICD-9-CM (United States and Taiwan)		OPCS4.6 (United Kingdom)		ICD-9-CM (Japan)		
Code	**Description**	**Code**	**Description**	**Procedure ID**	**ICD-9-CM**	**Description**
Coronary angiogram						
3722	Left heart cardiac catheterisation	K634	Coronary arteriography using two catheters	12342	3722	left cardiac catheterisation
3723	Combined right and left heart cardiac catheterisation	K635	Coronary arteriography using single catheter	15220	8853	cardioangiography
8853	Angiocardiography of left heart structures	K636	Coronary arteriography NEC	14893	8857	coronary angiography
8854	Combined right and left heart angiocardiography			14894	8857	coronary angiography
8855	Coronary arteriography using a single catheter					
8856	Coronary arteriography using two catheters					
8857	Other and unspecified coronary arteriography					
Right heart catheterisation						
3721	Right heart cardiac catheterisation	K654	Catheterisation of left side of heart via atrial transeptal puncture	12340	3721	right cardiac catheterisation
3723	Combined right and left heart cardiac catheterisation	K651	Catheterisation of combination of right and left side of heart NEC	15219	8852	cardioangiography; angiocardiography of right heart structures
8852	Angiocardiography of right heart structures	K652	Catheterisation of right side of heart NEC			
8854	Combined right and left heart angiocardiography					
8963	Pulmonary artery pressure monitoring					
8964	Pulmonary artery wedge monitoring					
Mechanical ventilation						
9604	Insertion of endotracheal tube	X561	Nasotracheal intubation	14982	9604	trachial intubation
9605	Other intubation of respiratory tract	X562	Endotracheal intubation	33805	9604	insertion of endotracheal tube and lavage of trachea
9670	Continuous invasive mechanical ventilation of unspecified duration	X563	Tracheal intubation using laryngeal mask airway	33806	9604	intubation of trachea
9671	Continuous invasive mechanical ventilation for less than 96 consecutive hours	X568	Other specified intubation of trachea	14987	9605	intratracheal intubation
9672	Continuous invasive mechanical ventilation for 96 consecutive hours or more	X569	Unspecified intubation of trachea	14988	9605	respiratory tract intubation

ICD-9-CM (United States and Taiwan)		OPCS4.6 (United Kingdom)		ICD-9-CM (Japan)		
Code	**Description**	**Code**	**Description**	**Procedure ID**	**ICD-9-CM**	**Description**
		E851	Invasive ventilation	33843	9671	intermittent mandatory ventilation (for less than 96 concecutive hours)
		E852	Non-invasive ventilation NEC	33842	9671	intermittent mandatory ventilation(for less than 96 concecutive hours)
		E858	Other specified ventilation support	33844	9672	intermittent mandatory ventilation (for 96 concecutive hours and more)
		E859	Unspecified ventilation support			
Device implantation						
0050	Implantation of cardiac resynchronization pacemaker without mention of defibrillation, total system [CRT-P]	K591	Implantation of cardioverter defibrillator using one electrode lead	35748	50	Implantation of cardiac resynchronization pacemaker without mention of defibrillation, total system [CRT-P]
0051	Implantation of cardiac resynchronization defibrillator, total system [CRT-D]	K592	Implantation of cardioverter defibrillator using two electrode leads	35747	51	Implantation of cardiac resynchronization defibrillator, total system [CRT-D]
0052	Implantation or replacement of transvenous lead [electrode] into left ventricular coronary venous system	K596	Implantation of cardioverter defibrillator using three electrode leads	10508	3774	insertion of epicardial electrode into epicardium
0053	Implantation or replacement of cardiac resynchronization pacemaker pulse generator only [CRT-P]	K601	Implantation of intravenous cardiac pacemaker system NEC	10509	3778	insertion of temporary transvenous pacemaker system
0054	Implantation or replacement of cardiac resynchronization defibrillator pulse generator only [CRT-D]	K605	Implantation of intravenous single chamber cardiac pacemaker system	15770	3780	implant of cardiac pacemaker and cardiac electrode
3770	Initial insertion of lead [electrode], not otherwise specified	K606	Implantation of intravenous dual chamber cardiac pacemaker system	15771	3780	implant of cardiac pacemaker and cardiac electrode
3771	Initial insertion of transvenous lead [electrode] into ventricle	K607	Implantation of intravenous biventricular cardiac pacemaker system	15772	3780	implant of cardiac pacemaker and epicardial electrode
3772	Initial insertion of transvenous leads [electrodes] into atrium and ventricle	K611	Implantation of cardiac pacemaker system NEC	30938	3780	implant of cardiac pacemaker and insertion of epicardial electrode
3773	Initial insertion of transvenous lead [electrode] into atrium	K615	Implantation of single chamber cardiac pacemaker system	30939	3780	implant of cardiac pacemaker and insertion of electrode
3774	Insertion or replacement of epicardial lead [electrode] into epicardium	K616	Implantation of dual chamber cardiac pacemaker system	30941	3794	implant of cardioverter

ICD-9-CM (United States and Taiwan)		OPCS4.6 (United Kingdom)		ICD-9-CM (Japan)		
Code	**Description**	**Code**	**Description**	**Procedure ID**	**ICD-9-CM**	**Description**
3778	Insertion of temporary transvenous pacemaker system	K617	Implantation of biventricular cardiac pacemaker system	36199	3794	implant of cardioverter
3780	Insertion of permanent pacemaker, initial or replacement, type of device not specified	K618	Other specified other cardiac pacemaker system	36200	3794	implant of cardioverter
3781	Initial insertion of single-chamber device, not specified as rate responsive	K619	Unspecified other cardiac pacemaker system	36583	3794	implant of cardioverter
3782	Initial insertion of single-chamber device, rate responsive	K611	Implantation of subcutaneous cardioverter defibrillator			
3783	Initial insertion of dual-chamber device					
3794	Implantation or replacement of automatic cardioverter/defibrillator, total system [AICD]					
3795	Implantation of automatic cardioverter/defibrillator lead(s) only					
3796	Implantation of automatic cardioverter/defibrillator pulse generator only					
Percutaneous coronary intervention						
0066	Percutaneous transluminal coronary angioplasty [PTCA]	K491	Percutaneous transluminal balloon angioplasty of one coronary artery	12290	3601	percutaneous transluminal coronary angioplasty(PTCA)
3601	Percutaneous transluminal coronary angioplasty [PTCA] one vessel	K492	Percutaneous transluminal balloon angioplasty of multiple coronary arteries	12291	3601	percutaneous transluminal coronary angioplasty(PTCA)
3602	Percutaneous transluminal coronary angioplasty [PTCA] one vessel	K493	Percutaneous transluminal balloon angioplasty of bypass graft of coronary artery	30891	3601	percutaneous transluminal coronary angioplasty(PTCA)
3605	Percutaneous transluminal coronary angioplasty [PTCA] multi vessel	K494	Percutaneous transluminal cutting balloon angioplasty of coronary artery	35430	3601	percutaneous transluminal coronary angioplasty(PTCA)
3604	Intracoronary artery thrombolytic infusion	K498	Other specified transluminal balloon angioplasty of coronary artery	36457	3601	percutaneous transluminal coronary angioplasty(PTCA)
3606	Insertion of non-drug-eluting coronary artery stent(s)	K499	Unspecified transluminal balloon angioplasty of coronary artery	36625	3601	percutaneous transluminal coronary angioplasty(PTCA)
3607	Insertion of drug-eluting coronary artery stent(s)	K501	Percutaneous transluminal laser coronary angioplasty	36626	3601	percutaneous transluminal coronary angioplasty(PTCA)
		K751	Percutaneous transluminal balloon angioplasty and insertion of 1-2 drug-eluting stents into coronary artery	36627	3601	percutaneous transluminal coronary angioplasty(PTCA)

ICD-9-CM (United States and Taiwan)		OPCS4.6 (United Kingdom)		ICD-9-CM (Japan)		
Code	**Description**	**Code**	**Description**	**Procedure ID**	**ICD-9-CM**	**Description**
		K752	Percutaneous transluminal balloon angioplasty and insertion of 3 or more drug-eluting stents into coronary artery	36324	3601	percutaneous transluminal coronary angioplasty(PTCA)
		K753	Percutaneous transluminal balloon angioplasty and insertion of 1-2 stents into coronary artery	36192	3604	percutaneous transluminal coronary recanalization
		K754	Percutaneous transluminal balloon angioplasty and insertion of 3 or more stents into coronary artery NEC	35431	3605	coronary artherectomy
		K758	Other specified percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery	36628	3606	percutaneous coronary stent implantation
		K759	Unspecified percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery	36629	3606	percutaneous coronary stent implantation
				36630	3606	percutaneous coronary stent implantation
Coronary artery bypass grafting						
3610	Aortocoronary bypass for heart revascularisation, not otherwise specified	K401	Saphenous vein graft replacement of one coronary artery	12294	3610	aortocoronary sequential bypass graft
3611	(Aorto)coronary bypass of one coronary artery	K402	Saphenous vein graft replacement of two coronary arteries	12295	3610	bypass anastomosis for heart revascularisation
3612	(Aorto)coronary bypass of two coronary arteries	K403	Saphenous vein graft replacement of three coronary arteries	12296	3610	myocardial revascularisation
3613	(Aorto)coronary bypass of three coronary arteries	K404	Saphenous vein graft replacement of four or more coronary arteries	12297	3610	aortocoronary bypass with synthetic graft
3614	(Aorto)coronary bypass of four or more coronary arteries	K408	Other specified saphenous vein graft replacement of coronary artery	12298	3610	aortocoronary bypass with other vein graft
3615	Single internal mammary-coronary artery bypass	K409	Unspecified saphenous vein graft replacement of coronary artery	12299	3610	aortocoronry bypass
3616	Double internal mammary-coronary artery bypass	K411	Autograft replacement of one coronary artery NEC	12300	3610	aortocoronary artery bypass
3617	Abdominal-coronary artery bypass	K412	Autograft replacement of two coronary arteries NEC	12301	3610	aortocoronary bypass with saphenous vein graft

ICD-9-CM (United States and Taiwan)		OPCS4.6 (United Kingdom)		ICD-9-CM (Japan)		
Code	**Description**	**Code**	**Description**	**Procedure ID**	**ICD-9-CM**	**Description**
3619	Other bypass anastomosis for heart revascularisation	K413	Autograft replacement of three coronary arteries NEC	12302	3611	aortocoronary bypass with saphenous vein graft(single)
362	Heart revascularisation by arterial implant	K414	Autograft replacement of four or more coronary arteries NEC	12303	3612	aortocoronary sequential bypass graft(double)
3631	Open chest transmyocardial revascularisation	K418	Other specified other autograft replacement of coronary artery	12304	3612	aortocoronary bypass with saphenous vein graft(double)
3632	Other transmyocardial revascularisation	K419	Unspecified other autograft replacement of coronary artery	12305	3613	aortocoronary sequential bypass graft(triple)
3633	Endoscopic transmyocardial revascularisation	K421	Allograft replacement of one coronary artery	12306	3613	aortocoronary bypass with saphenous vein graft(triple)
3634	Percutaneous transmyocardial revascularisation	K422	Allograft replacement of two coronary arteries	12307	3614	aortocoronary sequential bypass graft(quadruple or more)
3639	Other heart revascularisation	K423	Allograft replacement of three coronary arteries	12308	3614	aortocoronary bypass with saphenous vein graft(quadruple and more)
		K424	Allograft replacement of four or more coronary arteries	12309	3615	internal thoracic artery to coronary artery anastomosis with sequential bypass
		K428	Other specified allograft replacement of coronary artery	12310	3615	internal thoracic artery to coronary artery anastomosis
		K429	Unspecified allograft replacement of coronary artery	12312	3615	internal mammary-coronary artery anastomosis
		K431	Prosthetic replacement of one coronary artery	12314	3616	internal mammary-coronary artery anastomosis
		K432	Prosthetic replacement of two coronary arteries	12315	362	[heart revascularisation by]implantation of internal thoracic artery into heart muscle
		K433	Prosthetic replacement of three coronary arteries	12316	362	[heart revascularisation by]implantation of aortic branches
		K434	Prosthetic replacement of four or more coronary arteries	12317	362	heart revascularisation by arterial implant
		K438	Other specified prosthetic replacement of coronary artery	12318	362	internal mammary artery implantation
		K439	Unspecified prosthetic replacement of coronary artery			

ICD-9-CM (United States and Taiwan)		OPCS4.6 (United Kingdom)		ICD-9-CM (Japan)		
Code	Description	Code	Description	Procedure ID	ICD-9-CM	Description
		K441	Replacement of coronary arteries using multiple methods			
		K442	Revision of replacement of coronary artery			
		K448	Other specified other replacement of coronary artery			
		K449	Unspecified other replacement of coronary artery			
		K451	Double anastomosis of mammary arteries to coronary arteries			
		K452	Double anastomosis of thoracic arteries to coronary arteries NEC			
		K453	Anastomosis of mammary artery to left anterior descending coronary artery			
		K454	Anastomosis of mammary artery to coronary artery NEC			
		K455	Anastomosis of thoracic artery to coronary artery NEC			
		K456	Revision of connection of thoracic artery to coronary artery			
		K458	Other specified connection of thoracic artery to coronary artery			
		K459	Unspecified connection of thoracic artery to coronary artery			
		K461	Double implantation of mammary arteries into heart			
		K462	Double implantation of thoracic arteries into heart NEC			
		K463	Implantation of mammary artery into heart NEC			
		K464	Implantation of thoracic artery into heart NEC			
		K465	Revision of implantation of thoracic artery into heart			
		K468	Other specified other bypass of coronary artery			

ICD-9-CM (United States and Taiwan)		OPCS4.6 (United Kingdom)		ICD-9-CM (Japan)		
Code	**Description**	**Code**	**Description**	**Procedure ID**	**ICD-9-CM**	**Description**
		K469	Unspecified other bypass of coronary artery			
Cardioversion						
9961	Atrial cardioversion	X501	Direct current cardioversion	15042	9962	external defibrillator
9962	Other electric countershock of heart	X502	External cardioversion NEC	33904	9962	electric countershock of heart
				36149	9962	electric countershock of heart
Ablation						
3734	Excision or destruction of other lesion or tissue of heart, endovascular approach	K575	Percutaneous transluminal ablation of atrial wall NEC	35073	3734	catheter ablation of heart tissue
		K576	Percutaneous transluminal ablation of ventricular wall	36318	3734	catheter ablation of heart tissue
		K621	Percutaneous transluminal ablation of pulmonary vein to left atrium conducting system	30931	3734	catheter ablation of heart tissue
		K622	Percutaneous transluminal ablation of atrial wall for atrial flutter			
		K623	Percutaneous transluminal ablation of conducting system of heart for atrial flutter NEC			
		K641	Percutaneous radiofrequency ablation of epicardium			
Mechanical hemodynamic support						
3965	Extracorporeal membrane oxygenation [ECMO]	K541	Open implantation of ventricular assist device	12360	3761	intraaortic balloon pumping (IABP)
3966	Percutaneous cardiopulmonary bypass	K548	Other specified open heart assist operations	12361	3761	intra-aortic balloon pump
3761	Implant of pulsation balloon	K549	Unspecified open heart assist operations	12362	3761	intraaortic balloon pumping (IABP)
3760	Implantation or insertion of biventricular external heart assist system	K561	Transluminal insertion of pulsation balloon into aorta	30935	3761	intra-aortic balloon pump
3752	Implantation of total internal biventricular heart replacement system	K562	Transluminal insertion of heart assist system NEC	30936	3761	balloon pump
3768	Insertion of percutaneous external heart assist device	X581	Extracorporeal membrane oxygenation	30937	3761	balloon pump
3766	Insertion of implantable heart assist system			12363	3762	implant of right heart assist device
3762	Insertion of temporary non-implantable extracorporeal circulatory assist device			12364	3762	implant of left heart assist device

ICD-9-CM (United States and Taiwan)		OPCS4.6 (United Kingdom)		ICD-9-CM (Japan)		
Code	**Description**	**Code**	**Description**	**Procedure ID**	**ICD-9-CM**	**Description**
3751	Heart transplantation			12365	3762	implant of heart assist system
3765	Implant of single ventricular (extracorporeal) external heart assist system			12366	3762	artificial heart implantation
				12367	3762	implant of right and left heart assist device

SUPPLEMENTARY TABLE 4: READ CODES FOR IDENTIFICATION OF DIFFERENT HEART FAILURE PHENOTYPES IN THIN EHR

9.1.22 Non-specific heart failure codes

MEDCODE	READ TERM
G580.00	Congestive heart failure
G580.00	Left ventricular failure
G58..11	Cardiac failure
G58..00	Heart failure
G580.11	Congestive cardiac failure
G58z.00	Heart failure NOS
G581000	Acute left ventricular failure
1O1..00	Heart failure confirmed
G580200	Compensated cardiac failure
662T.00	Congestive heart failure monitoring
662g.00	New York Heart Association classification - class II
G58z.12	Cardiac failure NOS
9N2p.00	seen by community heart failure nurse
662h.00	New York Heart Association classification - class III
G232.00	hypertensive heart&renal dis wth (congestive) heart failure
G581.11	asthma - cardiac
G580000	Acute congestive heart failure
8B29.00	Cardiac failure therapy
8HHb.00	referral to heart failure nurse
G580200	Decompensated cardiac failure
G582.00	Acute heart failure
662W.00	Heart failure annual review
G580100	Chronic congestive heart failure
8H2S.00	admit heart failure emergency
9Or..00	Heart failure monitoring administration
8CL3.00	Heart failure care plan discussed with patient
ZRad.00	new york heart assoc classification heart failure symptoms

662i.00	New York Heart Association classification - class IV
G211100	benign hypertensive heart disease with ccf
G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail
67D4.00	Heart failure information given to patient
SP11111	Heart failure as a complication of care
9N6T.00	Referred by heart failure nurse specialist
8HHz.00	referral to heart failure exercise programme
8Hk0.00	Referred to heart failure education group
9Or4.00	heart failure monitoring second letter
G210100	malignant hypertensive heart disease with ccf
9Or3.00	Heart failure monitoring first letter
662p.00	Heart failure 6 month review
9Or5.00	Heart failure monitoring third letter
9Or2.00	heart failure monitoring verbal invite
9Or1.00	heart failure monitoring telephone invite
679X.00	Heart failure education
8CMK.00	Has heart failure management plan
8CeC.00	preferred place of care for next exacerbation heart failure
8CMW800	Heart failure clinical pathway
661M500	heart failure self-management plan agreed
1736.00	Paroxysmal nocturnal dyspnoea
G5yyA00	Left ventricular diastolic dysfunction
9N0k.00	Seen in heart failure clinic
14A6.00	h/o: heart failure
8HBE.00	Heart failure follow-up
14AM.00	H/O: Heart failure in last year
8HTL.00	Referral to heart failure clinic
G21z100	Hypertensive heart disease NOS with CCF
8HTL000	referral to rapid access heart failure clinic
2JZ..00	On optimal heart failure therapy
388D.00	New York Heart Assoc classification heart failure symptoms

9.1.23 Definite HFrEF codes

MEDCODE	READ TERM
G581000	Acute left ventricular failure
33BA.00	Impaired left ventricular function
G5yy900	Left ventricular systolic dysfunction
G580.14	Biventricular failure
585f.00	Echocardiogram shows left ventricular systolic dysfunction
9On..00	Left ventricular dysfunction monitoring administration
G5yyD00	Left ventricular cardiac dysfunction
9On0.00	Left ventricular dysfunction monitoring first letter

9.1.24 Possible HFrEF codes

MEDCODE	READ TERM
G55..00	Cardiomyopathy
G343.00	Ischaemic cardiomyopathy
G554400	Primary dilated cardiomyopathy
G55y.11	Secondary dilated cardiomyopathy
G55z.00	Cardiomyopathy NOS
G554z00	Other primary cardiomyopathy NOS
G55y.00	Secondary cardiomyopathy NOS
G558.00	Cardiomyopathy in disease EC
G555.00	Alcoholic cardiomyopathy
G558z00	Cardiomyopathy in diseases EC, NOS
G55A.00	Tachycardiomyopathy
G55A.11	Tachycardia-induced cardiomyopathy
12CJ.00FH	Cardiomyopathy
G554200	Familial Cardiomyopathy

9.1.25 HFpEF codes

MEDCODE	READ TERM
G583.11	HFNEF - heart failure with normal ejection fraction
G583.00	Heart failure with normal ejection fraction

G583.12	Heart failure with preserved ejection fraction
G5yyC00	Diastolic dysfunction
G5yyA00	Left ventricular diastolic dysfunction

SUPPLEMENTARY TABLE 5: OTHER FILES

9.1.26 GP Questionnaire

Please answer all the <u>questions</u> according to the information held in the patients written records by ticking the appropriate box or writing in the space provided.

1. Do you think this patient has Heart failure with:-

- ☐ **Reduced Ejection Fraction (HFrEF) (Ejection Fraction <=40%)**
- ☐ **Preserved Ejection Fraction (HFpEF) (Ejection Fraction >= 50%)**
- ☐ **Mid-range Ejection Fraction (HFmrEF) (Ejection Fraction 41-49 %)**
- ☐ **Unknown Ejection Fraction**

2. What was the diagnosis based on? (Please circle all that apply)

Echocardiogram Biomarkers Signs and Symptoms other

(please describe)

3. Has a cardiologist seen the patient and confirmed a diagnosis of HF?

☐ Yes ☐ No ☐ Uncertain

4. Does the patient have any other cardiac condition?

☐ Yes ☐ No ☐ Uncertain

If yes, please state

5. Was the patient hospitalised for heart failure (HF) at any point?

☐ Yes ☐ No ☐ Uncertain

6. Has the patient received intravenous diuretics as an outpatient or at home?

☐ Yes ☐ No

7. Will you be able to send copies of any relevant material, such as extracts from patient notes, echocardiogram, relevant lab tests (eg. BNP, NT-pro BNP) cardiology outpatient letters or hospital discharge letters?

Researcher's Ref:

We would appreciate receiving depersonalized copies of all relevant material, such as extracts from patient's notes or hospital discharge letters.

9.1.27 Extracts of '.do' files

CLEANING PATIENT FILES IN CPRD

```
PATIENT FILES FIRST
*********************************************************************
* PATH FOR WORKING FOLDER:
local path "G:\TRANSMED\transmed_unzipped/"
*********************************************************************
clear
set more off, perm
import delimited using "`path'TRANSMED_Extract_Patient_001.txt", clear
tabstat patid,stats(count)
***Cleaning***
*identify duplicates - if any with same patid, investigate and remove
duplicates report patid
*Generating date of birth* drop month and year variables
gen day_birth=1
replace mob=7 if mob==0
gen dob=mdy(mob, day_birth, yob)
format dob % td
drop day_birth mob
label var dob DOB
*generating practice id (last three digits of patid):
gen pracid =mod(patid, 1000)/* this divides the patid by 1000 and displays the remainder as pracid.*/
order pracid, after(patid)
lab var pracid "Practice Identifier"
tabstat patid,stats(count)
save "G:\TRANSMED\transmed_stata\transmed_patient_files.dta", replace
```

CLEANING PRACTICE FILES IN CPRD

```
* PATH FOR WORKING FOLDER:
local path "G:\TRANSMED\transmed_unzipped/"
*********************************************************************
clear
set more off, perm
import delimited using "`path'TRANSMED_Extract_Practice_001.txt", clear
tabstat pracid,stats(count)
*406 practices
***Cleaning
*identify duplicates
duplicates report pracid
***Investigating
*browse variables
codebook  pracid-uts
foreach i in lcd uts {
rename `i' orig_`i'
gen `i'=date(orig_`i', "DMY")
format `i' %td
}
order orig_*, last
*Identify range of LCD and UTS
gen year_lcd=year(lcd)
```

```
tab year_l
gen year_uts=year(uts)
tab year_u
drop year*
tabstat pracid,stats(count)
save "G:\TRANSMED\transmed_stata\transmed_practice_files", replace
```

MERGING PRACTICE AND PATIENT FILES

```
* HOUSEKEEPING
clear
set more off, perm
 ******************************************************************
* STEP1: Merging patient and practice files
use "G:\TRANSMED\transmed_stata\transmed_patient_files.dta", clear
merge m:1 pracid using "G:\TRANSMED\transmed_stata\transmed_practice_files.dta"
assert _m==3
drop _m
* 240974 patients merged
**********************************************************************************
* STEP2: Gen 18th birthday date
gen date18=date("01/07/"+string(yob+18), "DMY")
format date18 %td
**********************************************************************************
* STEP3: Change study start and end dates
* change these to your study start and end dates - they are macros, so you need to run these lines and
the startid/endid lines all at once.
local startdate = date("01/01/2012", "DMY")
display %td (`startdate')
local enddate = date("31/12/2013", "DMY")
display %td (`enddate')
foreach i in tod crd {
 rename `i' orig_`i'
 gen `i'=date(orig_`i', "DMY")
 format `i' %td
 }
 order orig_*, last
* gen start and end dates for each patient
gen startid = max(crd, uts, date18, `startdate')
gen endid = min(tod, lcd, `enddate')
forat startid endid %td
* gen lead in year for each pt
gen leadin_start = startid - 366
gen leadin_end = startid - 1
format leadin_start leadin_end %td
gen period = leadin_end - leadin_start
hist period
drop period
order startid endid leadin_start leadin_end, after (pracid)
codebook patid
hist startid
hist endid
hist leadin_start
```

```
hist leadin_end
tabstat patid,stats(count)
compress
save "G:\TRANSMED\transmed_stata\transmed_patient_practice_files.dta", replac
```

CLEANING AND MERGING CLINICAL FILES

```
 ************************************************************************
* PATH FOR WORKING FOLDER:
local path "G:\TRANSMED\transmed_unzipped/"
************************************************************************
* HOUSEKEEPING
clear
set more off, perm
*defines some label values prior to use:
label define SED 0 "[0] Missing" 1 "[1] Symptom" 2 "[2] Examination" 3 "[3] Diagnosis" 4 "[4] Intervention" 5 "[5] Management" 6 "[6] Administration" 7 "[7] Presenting complaint"
label define EPI 0 "[0] Data not entered" 1 "[1] First ever" 2 "[2] New event" 3 "[3] Continuing" 4 "[4] Other"
************************************************************************************
*
insheet using "`path'TRANSMED_Extract_Clinical_01.txt", clear
count
codebook patid
duplicates report
duplicates drop patid eventdate medcode, force
count
codebook patid
label var patid "Patient identifier"
label var eventdate "Event date (according to GP)"
label var sysdate "Date event entered onto system"
label var constype "Event type as coded by GP"
label var consid "Consultation identifier"
label var medcode "Medical code"
label var staffid "Staff identifier"
label var episode "Episode type for clinical event"
label var enttype "Entity type"
label var adid "Additional information identifier"
compress
save "G:\TRANSMED\transmed_stata\transmed_clinicalextract_files.dta", replace
*** 10,981 unique patients

***************************** end of options *********************************
disp c(current_date)
disp c(current_time)
log close
```

IDENTIFYING INDEX HF ADMISSION

```
** STEP 1: Identifying all hospitalisations
clear all
import delimited G:\TRANSMED\HES\hes_primary_diag_hosp_18_068R.txt
gen admidate2=date(admidate, "DMY")
format admidate2 %td
drop admidate
rename admidate2 admidate
gen discharged2=date(discharged, "DMY")
format discharged2 %td
drop discharged
rename discharged2 discharged
di mdy(01,01,2012)
drop if admidate <18993
di mdy(01,01,2015)
drop if admidate >20089
save "G:\TRANSMED\transmed_stata\primary_hosp.dta", replace

** STEP 2: Identifying index HF hospitalisation for the study period
clear all
use "G:\TRANSMED\transmed_stata\primary_hosp.dta"
merge m:1 icd_primary using "H:\Bayer_comorbidities_codes\HF_ICD10_codes.dta"
gen HF =1 if _merge ==3
keep if HF==1
**15,791 patients after this step
sort patid admidate
codebook patid
by patid: gen patid_n=_n
keep if patid_n==1
rename admidate admidate2
drop _merge patid_n HF
rename discharged discharged2
rename icd_primary icd_primary2
rename Diagnosis Diagnosis2
save "G:\TRANSMED\transmed_stata\Index_HF_admission.dta", replace
**11,011 patients in this group

** STEP 3: Calculating length of hospital stay
clear all
use "G:\TRANSMED\transmed_stata\Index_HF_admission.dta"
gen los = discharged2 - admidate2
```

MERGING HF ADMISSION FILE WITH COMORBIDITIES

```
clear all
use "G:\TRANSMED\transmed_stata\Index_HF_admission.dta"
merge 1:m patid using "G:\TRANSMED\transmed_stata\transmed_clinicalextract_files.dta"
keep if _merge ==3
drop adid enttype episode staffid consid constype sysdate icdx spno
drop _merge Diagnosis2
gen evendate2=date(eventdate, "DMY")
format evendate2 %td
```

```
drop eventdate
rename evendate2 eventdate
drop if eventdate>admidate2
drop icd_primary2
drop discharged2
save "G:\TRANSMED\transmed_stata\Index_HF_comorbidities.dta", replace
```

IDENTIFYING COMORBIDITES IN HEART FAILURE PATIENTS

```
** S|TEP 1: Identifying patients with CAD
clear all
use "G:\TRANSMED\transmed_stata\Index_HF_comorbidities.dta"
merge m:1 medcode using "H:\Bayer_comorbidities_codes\All_CAD_codes.dta"
generate CAD=1 if _merge ==3
egen  CADmax = max(CAD), by (patid)
browse if CADmax == 1
codebook patid if CADmax == 1
keep if CADmax==1
duplicates drop patid, force
save "G:\TRANSMED\transmed_stata\HF_CAD.dta", replace
***4329 patients with CAD

*** STEP2: Identifying patients with AF
clear all
use "G:\TRANSMED\transmed_stata\Index_HF_comorbidities.dta"
merge m:1 medcode using "H:\Bayer_comorbidities_codes\AF_codes.dta"
generate AF=1 if _merge ==3
egen  AFmax = max(AF), by (patid)
codebook patid if AFmax == 1
keep if AFmax==1
duplicates drop patid, force
keep patid
save "G:\TRANSMED\transmed_stata\HF_AF.dta", replace
*** 3640 patients with AF

*** STEP3: Identifying patients with DM
clear all
use "G:\TRANSMED\transmed_stata\Index_HF_comorbidities.dta"
merge m:1 medcode using "H:\AHF comorbidity files\Transmed_DM_Read_codes.dta"
generate DM=1 if _merge ==3
egen  DMmax = max(DM), by (patid)
codebook patid if DMmax == 1
keep if DMmax==1
duplicates drop patid, force
keep patid
save "G:\TRANSMED\transmed_stata\HF_DM.dta", replace
**3076 patients with DM

*** STEP4: Identifying patients with HTN
clear all
use "G:\TRANSMED\transmed_stata\Index_HF_comorbidities.dta"
merge m:1 medcode using "H:\AHF comorbidity files\Transmed_HTN_Read_codes.dta"
generate HTN=1 if _merge ==3
egen  HTNmax = max(HTN), by (patid)
```

```
codebook patid if HTNmax == 1
keep if HTNmax==1
duplicates drop patid, force
keep patid
save "G:\TRANSMED\transmed_stata\HF_HTN.dta", replace
**6,827 patients with HTN

*** STEP5: Identifying patients with Chronic Lung Disease
clear all
use "G:\TRANSMED\transmed_stata\Index_HF_comorbidities.dta"
merge m:1 medcode using "H:\AHF comorbidity files\Transmed_Lung_Read_codes.dta"
generate HTN=1 if _merge ==3
egen  HTNmax = max(HTN), by (patid)
codebook patid if HTNmax == 1
keep if HTNmax==1
duplicates drop patid, force
keep patid
save "G:\TRANSMED\transmed_stata\HF_Lung_Disease.dta", replace
**2,691 patients with CLD

*** STEP6: Identifying patients with Chronic Kidney Disease
clear all
use "G:\TRANSMED\transmed_stata\Index_HF_comorbidities.dta"
merge m:1 medcode using "H:\Bayer_comorbidities_codes\CKD_codes"
generate HTN=1 if _merge ==3
egen  HTNmax = max(HTN), by (patid)
codebook patid if HTNmax == 1
keep if HTNmax==1
duplicates drop patid, force
keep patid
save "G:\TRANSMED\transmed_stata\HF_CKD.dta", replace
**3731 patients with CKD

*** STEP7: Identifying patients with Chronic Liver Disease
clear all
use "G:\TRANSMED\transmed_stata\Index_HF_comorbidities.dta"
merge m:1 medcode using "H:\AHF comorbidity files\Transmed_CLD_Read_codes.dta"
generate HTN=1 if _merge ==3
egen  HTNmax = max(HTN), by (patid)
codebook patid if HTNmax == 1
keep if HTNmax==1
duplicates drop patid, force
keep patid
save "G:\TRANSMED\transmed_stata\HF_CLD.dta", replace

*** STEP8: Identifying patients with Peripheral Arterial Disease
clear all
use "G:\TRANSMED\transmed_stata\Index_HF_comorbidities.dta"
merge m:1 medcode using "H:\AHF comorbidity files\Transmed_PAD_Read_codes.dta"
generate HTN=1 if _merge ==3
egen  HTNmax = max(HTN), by (patid)
codebook patid if HTNmax == 1
keep if HTNmax==1
duplicates drop patid, force
keep patid
```

```
save "G:\TRANSMED\transmed_stata\HF_PAD.dta", replace
**1,440 patients with PAD

*** STEP9: Identifying patients with Obesity
clear all
use "G:\TRANSMED\transmed_stata\Index_HF_comorbidities.dta"
merge m:1 medcode using "H:\AHF comorbidity files\Transmed_Obesity_Read_codes.dta"
generate HTN=1 if _merge ==3
egen  HTNmax = max(HTN), by (patid)
codebook patid if HTNmax == 1
keep if HTNmax==1
duplicates drop patid, force
keep patid
save "G:\TRANSMED\transmed_stata\HF_Obesity.dta", replace
**1,186 patients with obesity

*** STEP10: Identifying patients with Chronic Anemia
clear all
use "G:\TRANSMED\transmed_stata\Index_HF_comorbidities.dta"
merge m:1 medcode using "H:\AHF comorbidity files\Transmed_Anemia_Read_codes.dta"
generate HTN=1 if _merge ==3
egen  HTNmax = max(HTN), by (patid)
codebook patid if HTNmax == 1
keep if HTNmax==1
duplicates drop patid, force
keep patid
save "G:\TRANSMED\transmed_stata\HF_Anemia.dta", replace
**1,352 patients with chronic anemia

*** STEP11: Identifying patients with Pulmonary circulation disrders
clear all
use "G:\TRANSMED\transmed_stata\Index_HF_comorbidities.dta"
merge m:1 medcode using "H:\AHF comorbidity files\Transmed_Pulm_Circ_Read_codes.dta"
generate HTN=1 if _merge ==3
egen  HTNmax = max(HTN), by (patid)
codebook patid if HTNmax == 1
keep if HTNmax==1
duplicates drop patid, force
keep patid
save "G:\TRANSMED\transmed_stata\HF_Pulm_Circ.dta", replace
**131 patients with pulmonary circulation disroders

*** STEP12: Identifying patients with Alcohol Abuse
clear all
use "G:\TRANSMED\transmed_stata\Index_HF_comorbidities.dta"
merge m:1 medcode using "H:\AHF comorbidity files\Transmed_Alcohol_Read_codes.dta"
generate HTN=1 if _merge ==3
egen  HTNmax = max(HTN), by (patid)
codebook patid if HTNmax == 1
keep if HTNmax==1
duplicates drop patid, force
keep patid
save "G:\TRANSMED\transmed_stata\HF_Alcohol.dta", replace
**218 patients with AAA
```

IDENTIFYING PATIENTS WITH IN-HOSPITAL MORTALITY

```
clear all
import delimited G:\TRANSMED\HES\death_patient_18_068R.txt
codebook patid
keep patid dod
gen dod2=date(dod, "DMY")
format dod2 %td
drop dod
rename dod2 dod
merge 1:1 patid using "G:\TRANSMED\transmed_stata\Index_HF_admission.dta"
keep if _merge==3
gen death=1 if discharged2 == dod
tab death
keep if death ==1
keep patid
save "G:\TRANSMED\transmed_stata\HF_in_hospital_mortality.dta", replace
** 1,350 patients with in-hospitals mortality
** 12.2 % in-hospital mortality
```

IDENTIFYING AGE AND SEX OF ALL PATIENTS

```
clear all
use "G:\TRANSMED\transmed_stata\Index_HF_admission.dta"
merge 1:1 patid using "G:\TRANSMED\transmed_stata\transmed_patient_practice_files.dta"
replace yob =yob+1800
gen HFyear = year(admidate2)
gen age = HFyear - yob
summarize age, detail
count if age==.
count if age==0
drop if age ==0
summarize age, detail
tab age
order patid admidate2 yob region HFyear
order patid admidate2 yob dob region HFyear
summarize age, detail
drop if age <18
summarize age, detail
egen age_gp =cut(age), at (18,25,35,45,55,65,75, 85,95)
tab age_gp
tab gender
```

IDENTIFYING PATIENTS I MECHANICAL VENTILAT“ON

```
use "G:\TRANSMED\transmed_stata\Index_HF_admi”sion.dta"
merge 1:m pat“d using "G:\TRANSMED\transmed_stata\TRANSMED_proce”ures.dta"
keep if _merge ==3
drop if admidate < admidate2
drop _merge
merge m:1 op“s using "H:\AHF comorbidity files\Transmed_intubation_”odes.dta"
keep if _merge ==3
keep patid admidate2 discharged2 admidate discharged
```

```
gen eventdate4 = admidate -discharged2
drop if eventdate4 >1
drop if eventdate4 ==1
keep patid
duplicates drop patid, fo“ce
save "G:\TRANSMED\transmed_stata\”F_MV.dta", replace
```

LOGISTIC REGRESSION ANALYSES

```
STEP 1: Identifying co-morbidities
clear all

** Merging with“CAD
use "G:\TRANSMED\transmed_stata\Index_HF_admi”sion.dta"
merge 1:1 pat“d using "G:\TRANSMED\transmed_stata\H”_CAD.dta"
gen CAD =1 if _merge ==3
drop _merge
replace CAD = 0 if CAD==.
drop icdx
drop spno
** Merging with AF
merge 1:1 pat“d using "G:\TRANSMED\transmed_stata\”F_AF.dta"
gen AF =1 if _merge ==3
drop _merge
replace AF = 0 if AF==.
** Merging with CKD
merge 1:1 pat“d using "G:\TRANSMED\transmed_stata\H”_CKD.dta"
gen CKD =1 if _merge ==3
drop _merge
replace CKD = 0 if CKD==.
** Merging with DM
merge 1:1 pat“d using "G:\TRANSMED\transmed_stata\”F_DM.dta"
gen DM =1 if _merge ==3
drop _merge
replace DM = 0 if DM==.
** Merging with HTN
merge 1:1 pat“d using "G:\TRANSMED\transmed_stata\H”_HTN.dta"
gen HTN =1 if _merge ==3
drop _merge
replace HTN = 0 if HTN==.
** Merging with anemia
merge 1:1 pat“d using "G:\TRANSMED\transmed_stata\HF_A”emia.dta"
gen anemia =1 if _merge ==3
drop _merge
replace anemia = 0 if anemia==.
** Merging with CLD
merge 1:1 pat“d using "G:\TRANSMED\transmed_stata\H”_CLD.dta"
gen CLD =1 if _merge ==3
drop _merge
replace CLD = 0 if CLD==.
** Merging with obesity
merge 1:1 pat“d using "G:\TRANSMED\transmed_stata\HF_Ob”sity.dta"
gen obesity =1 if _merge ==3
```

```
drop _merge
replace obesity = 0 if obesity==.
** Merging with PAD
merge 1:1 pat“d using "G:\TRANSMED\transmed_stata\H”_PAD.dta"
gen PAD =1 if _merge ==3
drop _merge
replace PAD = 0 if PAD==.
** Merging with PCD
merge 1:1 pat“d using "G:\TRANSMED\transmed_stata\HF_Pulm”Circ.dta"
gen PCD =1 if _merge ==3
drop _merge
replace PCD = 0 if PCD==.
** Merging with alcohol abuse
merge 1:1 pat“d using "G:\TRANSMED\transmed_stata\HF_Al”ohol.dta"
gen alcohol =1 if _merge ==3
drop _merge
replace alcohol = 0 if alcohol==
** Merging with lung disease
merge 1:1 pat“d using "G:\TRANSMED\transmed_stata\HF_Lung_di”ease.dta"
gen lung_disease =1 if _merge ==3
drop _merge
replace lung_disease = 0 if lung_disease==.
*** STEP 2: Merging with death status (in-hospital mortality)
merge 1:1 pat“d using "G:\TRANSMED\transmed_stata\HF_in_hospital_mort”lity.dta"
gen died = 1 if _merge ==3
replace died = 0 if died==.
drop _merge
*** STEP 3: Merging with 30 day readmission status
merge 1:1 pat“d using "G:\TRANSMED\transmed_stata\HF_30_day_readmis”ions.dta"
gen readmission = 1 if _merge ==3
replace readmission = 0 if readmission==.
drop _merge
drop icdx patid_n spno cause
order patid icd_primary2 Diagnosis2 admidate2 discharged2 admidate discharged readmission TDR died dod CAD AF CKD DM HTN anemia CLD lung_disease obesity PAD PCD alcohol
*** STEP 4: Identifying sex
merge 1:1 pat“d using "G:\TRANSMED\transmed_stata\transmed_patient_practice_”iles.dta"
keep patid icd_primary2 Diagnosis2 admidate2 discharged2 admidate discharged readmission TDR died dod CAD AF CKD DM HTN anemia CLD obesity PAD PCD alcohol outofhospmort pracid yob gender icd_primary lung_disease
tab gender

*** STEP 5: Identifying patients on mechanical ventilation
merge 1:1 pat“d using "G:\TRANSMED\transmed_stata\”F_MV.dta"
drop if _merge ==2
gen MV = 1 if _merge==3
replace MV = 0 if MV==.
*** STEP 6: Categorizing them into multiple age categories
replace yob =yob+1800
gen HFyear = year(admidate2)
gen age – HFyear - yob
drop if age <18
**20 observations dropped
gen agegrp= age
recode agegrp (18/35 = 1) (35/49 = 2) (50/74 = 3) (75/max = 4)
```

```
*** STEP 7: Generating weekend days
gen dow =dow(admidate2)
gen aweekend = 1 if dow ==0 | dow ==6
replace aweekend = 0 if aweekend==.
*** STEP 6: Identifying patients discharged less than 24 hours
gen los = discharged2-admidate2
gen twentyfourreadmin=1 if los <2
tab twentyfourread“in
save "G:\TRANSMED\transmed_stata\HF_LR_ana”ysis.dta", replace
drop if twentyfourreadmin “=1
save "G:\TRANSMED\transmed_stata\HF_LR_analysis_witho”t_24.dta", replace

clear“all
use "G:\TRANSMED\transmed_stata\HF_LR_ana”ysis.dta"
gen fortyhrreadmin=1 if los <3
drop if fortyhrreadmin=“1
save "G:\TRANSMED\transmed_stata\HF_LR_analysis_witho”t_48.dta", replace
clear“all
use "G:\TRANSMED\transmed_stata\HF_LR_ana”ysis.dta"
drop _merge
merge 1:1 pat“d using "G:\TRANSMED\transmed_stata\HF_PCI”CABG.dta"
drop if _merge ==3
drop _me“ge
save "G:\TRANSMED\transmed_stata\HF_LR_analysis_without_proce”ures.dta", replace
30 DAY READMISSION
clear“all
use "G:\TRANSMED\transmed_stata\HF_LR_ana”ysis.dta"
*** Univariate analysis for in-hospital mortality
mhodds readmission agegrp if died ==0
** OR = 0.90 p <0.001
logistic readmission i.gender if died ==0
**OR = 0.93 p = 0.175
logistic readmission i.CAD if died ==0
** OR = 1.02 p = 0.56
logistic readmission i.AF if died ==0
** OR = 1.01 p = 0.84
logistic readmission i.CKD if died ==0
** OR = 1.00 p =NS
logistic readmission i.DM if died ==0
** OR = 1.27 p =0.000
logistic readmission i.HTN if died ==0
** OR = 0.97 p =0.55
logistic readmission i.anemia if died ==0
** OR = 1.15 p = 0.06
logistic readmission i.CLD if died ==0
** OR = 0.87 p = 0.57
logistic readmission i.PAD if died ==0
** OR = 1.10 p = 0.15
logistic readmission i.PCD if died ==0
** OR = 1.17 p = 0.47
logistic readmission i.obesity if died ==0
** OR = 1.00 p = 0.96
logistic readmission i.lung_disease if died ==0
** OR = 1.08 p = 0.16
```

age, sex, AF, CAD, CKD, HTN, Anemia, PAD, obesity are associated with in-hospital mor*****
** Multivariate LR analysis
logistic readmission i.obesity i.CAD i.AF i.CKD i.DM i.HTN i.anemia i.CLD i.obesity i.PAD i.PCD agegrp i.gender i.lung_disease if died ==0

IN HOSPITAL MORTALITY

clear all
use "G:\TRANSMED\transmed_stata\HF_LR_analysis.dta"
*** Univariate analysis for in-hospital mortality
mhodds died agegrp
** OR = 1.65 p <0.00
logistic died i.gender
** OR = 1.19 p = 0.002
logistic died i.CAD
** OR = 1.08 p = 0.19
logistic died i.AF
** OR = 1.13 p = 0.03
logistic died i.CKD
** OR = 1.42 p <0.001
logistic died i.DM
** OR = 0.95 p =0.4
logistic died i.HTN
** OR = 1.25 p <0.001
logistic died i.anemia
** OR = 1.23 p = 0.01
logistic died i.CLD
** OR = 0.7 p = 0.25
logistic died i.PAD
** OR = 1.27 p = 0.002
logistic died i.PCD
** OR = 0.92 p = 0.77
logistic died i.obesity
** OR = 0.74 p = 0.003
logistic died i.lung_disease
** OR = 0.97 p = 0.73
***age, sex, AF, CAD, CKD, HTN, Anemia, PAD, obesity are associated with in-hospital mortality
****
** Multivariate LR analysis
logistic died i.obesity i.CAD i.AF i.CKD i.DM i.HTN i.anemia i.CLD i.obesity i.PAD i.PCD agegrp i.gender i.lung_disease
PATIENTS UNDERGOING CABG PCI
clear all
use "G:\TRANSMED\transmed_stata\Index_HF_admission.dta"
merge 1:m patid using "G:\TRANSMED\transmed_stata\TRANSMED_procedures.dta"
keep if _merge ==3
drop if admidate < admidate2
drop _merge
merge m:1 opcs using "H:\Bayer_comorbidities_codes\PCI_CABG_OPCS4_codes.dta"
keep if _merge ==3
keep patid admidate2 discharged2 admidate discharged

```
gen eventdate4 = admidate -discharged2
drop if eventdate4 >1
drop if eventdate4 ==1
keep patid
duplicates drop patid, force
save "G:\TRANSMED\transmed_stata\HF_PCI_CABG.dta", replace
```

SENSITIVITY ANALYSES EXCLUDING THOSE DISCHARGED WITHIN 24 HOURS OF ADMISSION

```
clear all
import delimited G:\TRANSMED\HES\death_patient_18_068R.txt
codebook patid
keep patid dod
gen dod2=date(dod, "DMY")
format dod2 %td
drop dod
rename dod2 dod
merge 1:1 patid using "G:\TRANSMED\transmed_stata\Index_HF_admission.dta"
gen death=1 if discharged2 == dod
gen twentyfourhr = 1 if los<2
replace twentyfourhr =0 if twentyfourhr==.
tab death twentyfourhr
**1,178 deaths out of 9,139 patients after excluding those discharged within 24 hours of admission
gen fortyeighthr = 1 if los<3
replace fortyeighthr =0 if fortyeighthr ==.
tab death  fortyeighthr
tab fortyeighthr
**1,083 deaths out of 8,042 patients after excluding those discharged within 48 hours of admission
drop _merge
merge 1:1 patid using "G:\TRANSMED\transmed_stata\HF_PCI_CABG.dta"
drop if _merge==3
tab death
summarize los, detail
```

OTHER SENSITIVITY ANALYSES

```
clear all
use "G:\TRANSMED\transmed_stata\Index_HF_admission.dta"
merge 1:1 patid using "G:\TRANSMED\transmed_stata\transmed_patient_practice_files.dta"
replace yob =yob+1800
gen HFyear = year(admidate2)
gen age = HFyear - yob
summarize age, detail
count if age==.
count if age==0
drop if age ==0
summarize age, detail
tab age
order patid admidate2 yob region HFyear
order patid admidate2 yob dob region HFyear
summarize age, detail
```

```
drop if age <18
summarize age, detail
drop _merge
merge m:1 patid using "G:\TRANSMED\transmed_stata\HF_in_hospital_mortality.dta"
drop if _merge ==2
** Identifying patients discharged within 24 hours and their mortality rates
preserve
drop if los <2
tab death
gen died =1 if _merge ==3
replace died =0 if died==.
tab died
gen age_gp = age
recode age_gp (18/35 =1) (36/50=2) (51/75 =3) (75/max =4)
tab age_gp died
disp 4/51
disp 8/241
disp 177/2328
disp 987/6507
restore
** Identifying patients discharged within 48 hours and their mortality rates
preserve
drop if los<3
gen died =1 if _merge ==3
replace died =0 if died==.
gen age_gp = age
recode age_gp (18/35 =1) (36/50=2) (51/75 =3) (75/max =4)
tab age_gp died
disp 4/46
disp 7/225
disp 164/2115
disp 906/6026
restore
*** Identifying patients with major procedures
gen died = 1 if _merge==3
replace died = 0 if died ==.
drop _merge
merge m:1 patid using "G:\TRANSMED\transmed_stata\HF_PCI_CABG.dta"

clear all
use "G:\TRANSMED\transmed_stata\HF_PCI_CABG.dta"
append using "G:\TRANSMED\transmed_stata\Device.dta"
append using "G:\TRANSMED\transmed_stata\ablation.dta"
duplicates drop patid, force
save "G:\TRANSMED\transmed_stata\major_CV_procedures.dta", replace
```

IDENTIFYING PATIENTS WITH A DEVICE

```
clear all
use "G:\TRANSMED\transmed_stata\Index_HF_admission.dta"
merge 1:m patid using "G:\TRANSMED\transmed_stata\TRANSMED_procedures.dta"
keep if _merge ==3
drop if admidate < admidate2
drop _merge
merge m:1 opcs using "H:\Bayer_comorbidities_codes\ablation.dta"
```

```
keep if _merge ==3
keep patid admidate2 discharged2 admidate discharged
gen eventdate4 = admidate -discharged2
drop if eventdate4 >1
drop if eventdate4 ==1
keep patid
duplicates drop patid, force
save "G:\TRANSMED\transmed_stata\ablation.dta", replace
**9patients
clear all
use "G:\TRANSMED\transmed_stata\Index_HF_admission.dta"
merge 1:m patid using "G:\TRANSMED\transmed_stata\TRANSMED_procedures.dta"
keep if _merge ==3
drop if admidate < admidate2
drop _merge
merge m:m opcs using "H:\Bayer_comorbidities_codes\Device_codes.dta"
keep if _merge ==3
keep patid admidate2 discharged2 admidate discharged
gen eventdate4 = admidate -discharged2
drop if eventdate4 >1
drop if eventdate4 ==1
keep patid
duplicates drop patid, force
save "G:\TRANSMED\transmed_stata\device.dta", replace
```

COMBINING US AND UK DATA

```
clear all
use "G:\TRANSMED\transmed_stata\HF_LR_analysis.dta"
tostring patid, replace
drop _merge
merge 1:1 patid using "G:\NRD_HF\NRD_2012_HF_LR.dta"
gen country =0 if _merge ==2
replace country = 1 if _merge ==1
drop _merge
mhodds died country, by(agegrp)
logistic died i.country i.agegrp i.gender i.CAD i.AF i.CKD i.HTN i.DM i.obesity i.anemia i.lung_disease i.PAD i.CLD i.PCD
```

PROPENSITY ANALYSES

```
clear all
use "G:\TRANSMED\transmed_stata\HF_LR_analysis.dta"
tostring patid, replace
drop _merge
merge 1:1 patid using "G:\NRD_HF\NRD_2012_HF_LR.dta"
gen country =0 if _merge ==2
replace country = 1 if _merge ==1
drop _merge

logistic country i.agegrp i.gender i.CAD i.AF i.CKD i.HTN i.DM i.obesity i.anemia i.lung_disease i.PAD i.CLD i.PCD i.alcohol
```

```
lroc
predict p
gen q=1-p if country==0
gen weight=.
replace weight=1/p if country==1
replace weight=1/q if country==0
pbalchk country agegrp gender CAD AF CKD HTN DM obesity anemia lung_disease PAD CLD PCD
alcohol, wt(weight)

graph tw kdensity p if country == 0 || ///
kdensity p if country == 1

gen p2=p if p>0.1 & p<0.9
gen q2=q if q>0.1 & q<0.9
gen weight2=.
replace weight2=1/p2 if country==1
replace weight2=1/q2 if country==0
pbalchk country agegrp gender CAD AF CKD HTN DM obesity anemia lung_disease PAD CLD PCD
alcohol, wt(weight2)

gen p3=p if p>0.05 & p<0.95
gen q3=q if q>0.05 & q<0.95
gen weight3=.
replace weight3=1/p3 if country==1
replace weight3=1/q3 if country==0
pbalchk country agegrp gender CAD AF CKD HTN DM obesity anemia lung_disease PAD CLD PCD
alcohol, wt(weight3)

gen p4=p if p>0.15 & p<0.85
gen q4=q if q>0.15 & q<0.85
gen weight4=.
replace weight4=1/p4 if country==1
replace weight4=1/q4 if country==0
pbalchk country agegrp gender CAD AF CKD HTN DM obesity anemia lung_disease PAD CLD PCD,
wt(weight4)
* Graph for PS in each group
graph tw kdensity p3 if country == 1 || kdensity p3 if country == 0
* Outcome measure
logistic died i.country i.agegrp i.gender i.CAD i.AF i.CKD i.HTN i.DM i.obesity i.anemia
i.lung_disease i.PAD i.CLD i.PCD i.alcohol[pweight = weight3]

logistic died i.country  [pweight = weight3]
* trim the PS and 1-PS to just between 0.1-0.9 to get rid of extreme scores
* might want to try different trimming - eg 0.05-0.95....
drop p3 q3
gen p3=p if p>0.1 & p<0.9
gen q3=q if q>0.1 & q<0.9
gen weight3=.
replace weight3=1/p3 if country==1
replace weight3=1/q3 if country==0
pbalchk country agegrp gender DM HTN CAD AF CKD lung_disease PAD obesity anemia CLD
alcohol, wt(weight3)
```

THIN ANALYSES

CLEANING PATIENT FILES IN THIN

```
clear
clear all
set more off, perm
macro drop _all
global data "E:\"
global dict "G:\THIN_Dict\"
global clean "G:\THIN_Validation\"
local path_log "G:\Thin_Validation_logfiles\THIN_logfiles"
capture log close
log using "`path_log'Cleaning_patient_files.log", replace

infix using ${dict}patdic, using("${data}patient.txt") clear

keep if patflag=="A" | patflag=="C"
gen yob2=substr(yob,1,4)
gen mob=substr(yob,5,2)
drop yob
destring mob yob2, replace
replace deathdate="" if deathdate=="00000000"
gen deathdate2=date(deathdate, "YMD")
format deathdate2 %td
drop deathdate
rename deathdate2 deathdate
gen dead=1 if deathdate!=.

gen regdate2=date(regdate, "YMD")
format regdate2 %td
drop regdate
rename regdate2 regdate

gen day_birth=1
replace mob=7 if mob==0
gen dob=mdy(mob, day_birth, yob)
format dob % td
drop day_birth mob
label var dob DOB

tostring pracid, replace
gen patid3= patid + pracid

save ${clean}pat_all, replace
log close
```

CLEANING THERAPY FILES IN THIN

```
clear
clear all
set more off, perm
macro drop _all
global data "E:\"
global dict "G:\THIN_Dict\"
```

```
global clean "G:\THIN_Validation\"
local path_log "G:\Thin_Validation_logfiles\THIN_logfiles"
capture log close
log using "`path_log'Cleaning_Therapy_files.log", replace

infix using ${dict}therdic, using("${data}therapy.txt") clear
keep if therflag=="Y"
tostring pracid, replace
gen patid3= patid + pracid
merge m:1 patid3 using ${clean}pat_all
keep if _m==3
drop _m
save ${clean}therapy, replace
clear
log close
```

CLEANING MEDICAL FILES IN THIN

```
clear
clear all
set more off, perm
macro drop _all
global data "E:\"
global dict "G:\THIN_Dict\"
global clean "G:\THIN_Validation\"
local path_log "G:\Thin_Validation_logfiles\THIN_logfiles"
capture log close
log using "`path_log'Cleaning_Medical_files.log", replace
infix using ${dict}meddic, using("${data}medical.txt") clear
tostring pracid, replace
gen patid3= patid + pracid
merge m:1 patid3 using ${clean}pat_all
keep if _m==3
drop _m
save ${clean}med, replace
clear
log close
```

CLEANING PRACTICE FILES IN THIN

```
clear
clear all
set more off, perm
macro drop _all
global data "E:\"
global dict "G:\THIN_Dict\"
global clean "G:\Thin_Validation\"
local path_log "G:\Thin_Validation_logfiles\THIN_logfiles"
capture log close
log using "`path_log'Cleaning_Practice_files.log", replace
infix using ${dict}pracdic.dct, using(${data}THINprac1709.txt) clear
gen pracid=_n
foreach var of varlist compdate visiondate amr collectdate{
```

```
gen `var'2=date(`var', "DMY")
drop `var'
rename `var'2 `var'
format `var' %td
}
save ${clean}pracs, replace
count if dataflag!=""
drop if dataflag!=""
save ${clean}pracs, replace
log close
```

CLEANING AHD_FILES IN THIN

```
clear
clear all
set more off, perm
macro drop _all
global data "E:\"
global dict "G:\THIN_Dict\"
global clean "G:\THIN_Validation\"
local path_log "G:\Thin_Validation_logfiles\THIN_logfiles"
capture log close
log using "`path_log'Cleaning_ahd_files.log", replace
infix using ${dict}ahddic, using("${data}ahd.txt") clear
tostring pracid, replace
gen patid3= patid + pracid
merge m:1 patid3 using ${clean}pat_all
keep if _m==3
drop _m
save ${clean}ahd, replace
clear
log close
```

CLEANING CONSULT FILES

```
clear
clear all
set more off, perm
macro drop _all

global data "E:\"
global dict "G:\THIN_Dict\"
global clean "G:\THIN_Validation\"
local path_log "G:\Thin_Validation_logfiles\THIN_logfiles"

capture log close
log using "`path_log'Cleaning_consult_files.log", replace

infix using ${dict}consultdic, using("${data}consult.txt") clear
tostring pracid, replace
gen patid3= patid + pracid
merge m:1 patid3 using ${clean}pat_all
keep if _m==3
```

```
drop _m
save ${clean}consult, replace
clear
log close
```

CLEANING STAFF FILES

```
clear
clear all
set more off, perm
macro drop _all
local path_log "G:\Thin_Validation_logfiles\THIN_logfiles"
capture log close
log using "`path_log'Cleaning_Therapy_files.log", replace
global data "E:\"
global dict "G:\THIN_Dict\"
global clean "G:\THIN_Validation\"
infix using ${dict}staffdic.dct, using("${data}staff.txt") clear
log close
**** STEP 1: Excluding HF patients with congenital heart disease
**** STEP 2: Excluding LD patients with Rheumatic and Valvular heart disease
**** STEP 3: Excluding LD patients with Restrictive cardiomyopathy and pericardial disease

*************************************************************************
local path_log "G:\Thin_Validation_logfiles\THIN_logfiles"
clear
clear all
set more off, perm
capture log close
log using "`path_log'Excluding_CHD_VHD_RCMfiles.log", replace

**** STEP 1: Including only AIS consenting practices
use "E:\Thin_Validation\med.dta"
keep pracid patid eventdate medcode patid3 yob2 deathdate dead regdate dob
compress
destring eventdate, replace
merge m:1 pracid using "G:\Thin_Validation\AIS_consenting_practices.dta"
keep if _merge ==3
codebook patid3
drop _merge

**15,922 patients after including only AIS consenting practices
*************************************************************************

**** STEP 2: Excluding HF patients with congenital heart disease
merge m:1 medcode using "G:\Thin_Validation\CHD_codes.dta"
gen CHD = 1 if _merge == 3
egen  CHDmax = max(CHD), by (patid3)
codebook patid3 if _merge == 3
codebook patid3 if CHDmax == 1
drop if CHDmax == 1
codebook patid3
drop _merge CHD CHDmax diagnosis
** 217 HF patients had congenital heart disease. 15,705 patients after excluding CHD
*************************************************************************
```

```
**** STEP 3: Excluding HF patients with Rheumatic and Valvular heart disease
merge m:1 medcode using "G:\Thin_Validation\RHD_VHD_codes.dta"
gen RHD = 1 if _merge == 3
egen  RHDmax = max(RHD), by (patid3)
codebook patid3 if _merge == 3
codebook patid3 if RHDmax == 1
drop if RHDmax == 1
codebook patid3
sort patid3
drop _merge RHD RHDmax diagnosis
** 755 HF patients had Rheumatic and Valvular Heart disease. 14,930 patients
* after this step
*******************************************************************************
**** STEP 4: Excluding HF patients with Restrictive cardiomyopathy and pericardial disease

merge m:1 medcode using "G:\Thin_Validation\RCM_ICM_codes.dta"
gen RCM = 1 if _merge == 3
egen  RCMmax = max(RCM), by (patid3)
codebook patid3 if _merge == 3
codebook patid3 if RCMmax == 1
drop if RCMmax == 1
codebook patid3
drop _merge RCM RCMmax diagnosis

** 198 HF patients had restrictive cardiomyopathy and pericardial disease. 14,732 patients
* after this step
save "G:\Thin_Validation\medfiles_after_exclusion.dta", replace
log clos
clear all
set more off
set more off, perm
local path_log "G:\Thin_Validation_logfiles\THIN_logfiles"
capture log close
log using "`path_log'Identifying_HFrEF.log", replace
*** STEP1: Identifying patients with HFrEF codes
use "G:\Thin_Validation\medfiles_after_exclusion.dta"
merge m:1 medcode using "G:\Thin_Validation\HFrEF_codes.dta"
keep if _merge ==3
codebook patid3
tab medcode
drop _merge
duplicates drop patid3, force
save "G:\Thin_Validation\HFrEF_patients.dta",replace
*** 5,149 patients with HFrEF codes
*** STEP2: Identifying patients with definite HFrEF codes
clear all
set more off
use "G:\Thin_Validation\medfiles_after_exclusion.dta"
merge m:1 medcode using "G:\Thin_Validation\Definite_HFrEF_codes.dta"
keep if _merge ==3
codebook patid3
tab medcode
duplicates drop patid3, force
save "G:\Thin_Validation\Definite_HFrEF_patients.dta",replace
*** 3,917 patients with possible HfrEF codes
```

```
*** STEP3: Identifying patients with possible HFrEF codes
clear all
set more off
use "G:\Thin_Validation\medfiles_after_exclusion.dta"
merge m:1 medcode using "G:\Thin_Validation\Possible_HFrEF_codes.dta",
keep if _merge ==3
codebook patid3
tab medcode
duplicates drop patid3, force
save "G:\Thin_Validation\Possible_HFrEF_patients.dta", replace
*** STEP4: Excluding patients with both Definite HFrEF and Possible HFrEF codes
clear all
set more off
use "G:\Thin_Validation\Possible_HFrEF_patients.dta", replace
merge m:1 patid3 using
save "G:\Thin_Validation\Possible_HFrEF_patients.dta", replace
*** 1,491 patients with possible HFrEF codes
```

IDENTIFYING HFPEF PATIENTS

```
log close
clear all
set more off
set more off, perm
local path_log "G:\Thin_Validation_logfiles\THIN_logfiles"
capture log close
log using "`path_log'Identifying_HFpEF.log", replace
*** STEP 1: Identifying patients with HFrEF and exclude them
use "G:\Thin_Validation\medfiles_after_exclusion.dta"
merge m:1 medcode using "G:\Thin_Validation\HFrEF_codes.dta"
gen HFrEF = 1 if _merge == 3
egen  HFrEFmax = max(HFrEF), by (patid3)
browse if HFrEFmax == 1
codebook patid3 if _merge == 3
codebook patid3 if HFrEFmax == 1
drop if HFrEFmax == 1
codebook patid3
*** 5,149 patients with HFrEF codes excluded

*** STEP 2: Identifying patients with HFpEF and exclude them
drop _merge
merge m:1 medcode using "G:\Thin_Validation\HFpEF_codes.dta"
keep if _merge ==3
codebook patid3
tab medcode
*** 288 patients with specific HFpEF codes
save "G:\Thin_Validation\HFpEF_patients.dta", replace
log close
```

IDENTIFYING NON-SPECIFIC HF CODES

```
clear all
set more off
set more off, perm
local path_log "G:\Thin_Validation_logfiles\THIN_logfiles"
```

```
capture log close
log using "`path_log'Identifying_Non_specific_HF_patients.log", replace
*** STEP1: Identifying patients with HFrEF codes
use "G:\Thin_Validation\medfiles_after_exclusion.dta"
merge m:1 medcode using "G:\Thin_Validation\Non_specific_HF_codes.dta"
keep if _merge ==3
codebook patid3
tab medcode
drop _merge
duplicates drop patid3, force
save "G:\Thin_Validation\Non_specific_HF_patients_Initial.dta", replace
*** 11,827 patients with HFrEF codes
*** STEP2: Excluding patients with definite HFrEF codes
merge m:1 patid3 using "G:\Thin_Validation\Definite_HFrEF_patients.dta"
keep if _merge ==1
codebook patid3
tab medcode
duplicates drop patid3, force
*** 2867 patients with definite HFrEF codes
*** STEP3: Excluding patients with possible HFrEF codes
drop _merge
merge m:1 patid3 using "G:\Thin_Validation\Possible_HFrEF_patients.dta"
keep if _merge ==1
codebook patid3
tab medcode
duplicates drop patid3, force
drop _merge du
*** 687 patients with possible HFpEF codes
*** STEP4: Excluding patients with HFpEF codes
merge m:1 patid3 using "G:\Thin_Validation\HFpEF_patients.dta"
keep if _merge ==1
codebook patid3
tab medcode
duplicates drop patid3, force
drop _merge
*** 209 patinets with HFpEF codes
save "G:\Thin_Validation\Non_specific_HF_patients.dta", replace
*** 8064  patients with non Specific HF codes
log close
```

IDENTIFYING PATIENTS WITH DEFINITE HFrEF AND POSSIBLE HFrEF

```
** STEP1: Drop HFrEF patients with non specific HF codes
clear all
set more off
use "G:\Thin_Validation\HFrEF_patients.dta",replace
merge m:1 patid3 using "G:\Thin_Validation\Non_Specific_HF_patients_initial.dta"
keep if _merge ==1
drop _merge
keep patid3
duplicates drop patid3, force
save "G:\Thin_Validation\Final_HFrEF_patients.dta",replace
** 1,595 patients with only HFrEF codes (3554 patients excluded)
*** STEP2: Identify only definite HFrEF patients
clear all
```

```
set more off
use "G:\Thin_Validation\Final_HFrEF_patients.dta"
merge 1:m patid3 using "G:\Thin_Validation\medfiles_after_exclusion.dta"
keep if _merge ==3
drop _merge
merge m:1 medcode using "G:\Thin_Validation\Definite_HFrEF_codes.dta"
keep if _merge ==3
codebook patid3
tab medcode
duplicates drop patid3, force
save "G:\Thin_Validation\Definite_HFrEF_patients_Initial.dta",replace
*** 1050 patients with definite HFrEF
*** STEP3: Identify only possible HFrEF patients
clear all
set more off
use "G:\Thin_Validation\Final_HFrEF_patients.dta",replace
merge 1:m patid3 using "G:\Thin_Validation\medfiles_after_exclusion.dta"
keep if _merge ==3
drop _merge
merge m:1 medcode using "G:\Thin_Validation\Possible_HFrEF_codes.dta"
keep if _merge ==3
codebook patid3
tab medcode
duplicates drop patid3, force
save "G:\Thin_Validation\Possible_HFrEF_patients_Initial.dta",replace
*** 652 patients with possible HFrEF
*** STEP4: Exclude possible HFrEF pateints from Definite HFrEF
clear all
set more off
use "G:\Thin_Validation\Definite_HFrEF_patients_Initial.dta"
merge m:1 patid3 using "G:\Thin_Validation\Possible_HFrEF_patients_Initial.dta"
keep if _merge ==1
codebook patid3
duplicates drop patid3, force
save "G:\Thin_Validation\Definite_HFrEF_patients.dta",replace
*** 943 patients with definite HFrEF codes aonly
*** STEP5: Exclude definite HFrEf patients from Possible HFrEF
clear all
set more off
use "G:\Thin_Validation\Possible_HFrEF_patients_Initial.dta"
merge m:1 patid3 using "G:\Thin_Validation\Definite_HFrEF_patients_Initial.dta"
keep if _merge ==1
codebook patid3
duplicates drop patid3, force
save "G:\Thin_Validation\Possible_HFrEF_patients.dta",replace
*** 545 patients with possible HFrEf codes only
```

EXCLUDING HFPEF PATIENTS WITH HFREF CODES

```
clear all
set more off
set more off, perm
local path_log "G:\Thin_Validation_logfiles\THIN_logfiles"
capture log close
log using "`path_log'Identifying_HFpEF.log", replace
```

```
*** STEP 1: Identifying patients with HFrEF and exclude them
use "G:\Thin_Validation\medfiles_after_exclusion.dta"
merge m:1 medcode using "G:\Thin_Validation\HFrEF_codes.dta"
gen HFrEF = 1 if _merge == 3
egen  HFrEFmax = max(HFrEF), by (patid3)
browse if HFrEFmax == 1
codebook patid3 if _merge == 3
codebook patid3 if HFrEFmax == 1
drop if HFrEFmax == 1
codebook patid3
*** 5,149 patients with HFrEF codes excluded
*** STEP 2: Identifying patients with HFpEF and exclude them
drop _merge
merge m:1 medcode using "G:\Thin_Validation\HFpEF_codes.dta"
keep if _merge ==3
codebook patid3
tab medcode
*** 288 patients with specific HFpEF codes
save "G:\Thin_Validation\HFpEF_patients.dta", replace
log close
```

IDENTIFYING PRESCRIPTIONS FROM 2015-2017

```
use "G:\Thin_Validation\therapy.dta"
gen prscdate2=date(prscdate, "YMD")
format prscdate2 %td
drop prscdate
rename prscdate2 prscdate
di mdy(01,01,2015)
drop if prscdate < 20089
di mdy(12,31,2017)
drop if eventdate> 21184
drop pracid patid doscode private staffid opno seqnoiss maxnoiss packsize dosgval locate drugsource
inprac consultid modified sex xferdate regrea accept institute dispensing marital
save "G:\Thin_Validation\Limited_therapy_2015_2017.dta"
```

9.1.28 ISAC application form

PROTOCOLS FOR RESEARCH USING THE CLINICAL PRACTICE RESEARCH DATALINK - CPRD

For ISAC use only		
Protocol No. Submission date (DD/MM/YYYY)	....	***IMPORTANT*** *Please refer to the **guidance** for '**Completing the ISAC application form'** found on the CPRD website (www.cprd.com/isac). If you have any queries, please contact the ISAC Secretariat at isac@cprd.com.*

SECTION A: GENERAL INFORMATION ABOUT THE PROPOSED RESEARCH STUDY
1. Study Title§ (*Please state the study title below)* Comparison of Outcomes for Patients Hospitalised for Heart Failure (HHF) in the UK, Japan, USA and Taiwan §*Please note: This information will be published on the CPRD's website as part of its transparency policy.*
2. Has any part of this research proposal or a related proposal been previously submitted to ISAC? Yes*X No ☐ **If yes, please provide the previous protocol number/s below. Please also state in your current submission how this/these are related or relevant to this study.* The protocol number for the previous submission was 17_113R. In that submission we were looking at in-hospital mortality of all Heart Failure patients in the UK and Japan. Here we are interested in comparing outcomes with other countries including Taiwan and USA. We have changed the subgroup analyses and outcomes as well as the study population from the previous ISAC and hence have done a new submission rather than an amendment.
3. Has this protocol been peer reviewed by another Committee? (e.g. grant award or ethics committee) Yes* ☐ No X

**If Yes, please state the name of the reviewing Committee(s) below and provide an outline of the review process and outcome as an Appendix to this protocol :*

4. Type of Study (please tick all the relevant boxes which apply)

Adverse Drug Reaction/Drug Safety	☐	Drug Effectiveness	☐
Drug Utilisation	☐	Pharmacoeconomics	☐
Disease Epidemiology	☒	Post-authorisation Safety	☐
Health care resource utilisation	☒	Methodological Research	☐
Health/Public Health Services Research	☐	Other*	☐

**If Other, please specify the type of study in the lay summary*

5. Health Outcomes to be Measured§

§*Please note: This information will be published on CPRD's website as part of its transparency policy.*

Please summarise below the primary/secondary health outcomes to be measured in this research protocol:

- All-cause mortality
- Health care resource utilization
- Length of hospital stay
- 30 day readmissions

[Please add more bullet points as necessary]

6. Publication: This study is intended for (please tick all the relevant boxes which apply)**:**

Publication in peer-reviewed journals ☒ Presentation at scientific conference ☒

Presentation at company/institutional meetings ☐ Regulatory purposes ☐

Other* ☐

**If Other, please provide further information:*

SECTION B: INFORMATION ON INVESTIGATORS AND COLLABORATORS

7. Chief Investigator[§]

Please state the full name, job title, organisation name & e-mail address for correspondence - see guidance notes for eligibility. Please note that there can only be one Chief Investigator per protocol.

Dr Jennifer K. Quint, Clinical Senior Lecturer Respiratory Epidemiology, Imperial College London, j.quint@imperial.ac.uk

[§]*Please note: The name and organisation of the Chief Investigator and will be published on CPRD's website as part of its transparency policy*

CV has been previously submitted to ISAC ☒ **CV number:** 042_15CEPSL

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

8. Affiliation of Chief Investigator (full address)

Respiratory Epidemiology, Occupational Medicine and Public Health

G48, Emmanuel Kaye Building

Manresa Road

National Heart and Lung Institute

Imperial College

London, SW3 6LR

Tel: +44 (0) 207 594 8821

9. Corresponding Applicant[§]

Please state the full name, affiliation(s) and e-mail address below:

Dr. Varun Sundaram MD,

National Heart and Lung Institute, Imperial College

London

v.sundaram@imperial.ac.uk

Same as chief investigator ☐

CV has been previously submitted to ISAC ☐ **CV number: 206_17**

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☒

10. List of all investigators/collaborators§

Please list the full name, affiliation(s) and e-mail address* of all collaborators, other than the Chief Investigator below:

Dr. Toshiyuki Nagai MD, PhD, Sponsored Researcher, National Heart and Lung Institute, Imperial College London

Email address: t.nagai@imperial.ac.uk

§*Please note: The name of all investigators and their organisations/institutions will be published on CPRD's website as part of its transparency policy*

CV has been previously submitted to ISAC ☒ **CV number:304_17**

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

Other investigator:

CV has been previously submitted to ISAC ☐ **CV number:**

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

Other investigator:

CV has been previously submitted to ISAC ☐ **CV number:**

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

Other investigator:

CV has been previously submitted to ISAC ☐ **CV number:**

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

[Please add more investigators as necessary]

Please note that your ISAC application form and protocol **must be copied to all e-mail addresses listed above at the time of submission of your application to the ISAC mailbox. Failure to do so will result in delays in the processing of your application.*

11. Conflict of interest statement*

Please provide a draft of the conflict (or competing) of interest (COI) statement that you intend to include in any publication which might result from this work

Dr Quint's research group has received funding from MRC, Wellcome Trust, BLF, GSK, Insmed, AZ, Bayer and BI for other projects, none of which relate to this work. Dr Quint has received funds from AZ, GSK, Teva, Chiesi and BI for Advisory board participation or travel.

**Please refer to the International Committee of Medical Journal Editors (ICMJE) for guidance on what constitutes a COI.*

12. Experience/expertise available

Please complete the following questions to indicate the experience/ expertise available within the team of investigators/collaborators actively involved in the proposed research, including the analysis of data and interpretation of results.

	Previous GPRD/CPRD Studies	**Publications using GPRD/CPRD data**
None	☐	☐
1-3	☐	☐
> 3	☒	☒

Experience/Expertise available	Experience/Expertise available	Experience/Expertise available
Is statistical expertise available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Quint	**Is statistical expertise available within the research team?** *If yes, please indicate the name(s) of the relevant investigator(s)*	**Is statistical expertise available within the research team?** *If yes, please indicate the name(s) of the relevant investigator(s)*
Is experience of handling large data sets (>1 million records) available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Quint, Sundaram, Nagai	**Is experience of handling large data sets (>1 million records) available within the research team?** *If yes, please indicate the name(s) of the relevant investigator(s)*	**Is experience of handling large data sets (>1 million records) available within the research team?** *If yes, please indicate the name(s) of the relevant investigator(s)*
Is experience of practising in UK primary care available to or within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Quint	**Is experience of practising in UK primary care available to or within the research team?** *If yes, please indicate the name(s) of the relevant investigator(s)*	**Is experience of practising in UK primary care available to or within the research team?** *If yes, please indicate the name(s) of the relevant investigator(s)*

13. References relating to your study

Please list up to 3 references (most relevant) relating to your proposed study:

- Pfeffer MA, Claggett B, Assmann SF et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Circulation 2015;131:34-42.
- Kristensen SL, Martinez F, Jhund PS et al. Geographic variations in the PARADIGM-HF heart failure trial. Eur Heart J 2016;37:3167-3174.
- Kristensen SL, Kober L, Jhund PS et al. International geographic variation in event rates in trials of heart failure with preserved and reduced ejection fraction. Circulation 2015;131:43-53.

SECTION C: ACCESS TO THE DATA

14. Financial Sponsor of study[§]

[§]*Please note: The name of the source of funding will be published on CPRD's website as part of its transparency policy*

Pharmaceutical Industry ☐ *Please specify name and country:*

Academia ☒ *Please specify name and country:* Imperial College London

Government / NHS ☐ *Please specify name and country:*

Charity ☐ *Please specify name and country:*

Other ☐ *Please specify name and country:*

None ☐

15. Type of Institution conducting the research

Pharmaceutical Industry ☐ *Please specify name and country:*

Academia ☒ *Please specify name and country:* Imperial College London

Government Department ☐ *Please specify name and country:*

Research Service Provider ☐ *Please specify name and country:*

NHS ☐ *Please specify name and country:*

Other ☐ *Please specify name and country:*

16. Data access arrangements

The financial sponsor/ collaborator* has a licence for CPRD GOLD and will extract the data ☐

The institution carrying out the analysis has a licence for CPRD GOLD and will extract the data** ☒

A data set will be provided by the CPRD[¥€] ☐

CPRD has been commissioned to extract the data and perform the analyses[€] ☐

Other: ☐

If Other, please specify:

**Collaborators supplying data for this study must be named on the protocol as co-applicants.*

***If data sources other than CPRD GOLD are required, these will be supplied by CPRD*

[¥]*Please note that datasets provided by CPRD are limited in size; applicants should contact CPRD (kc@cprd.com) if a dataset of >300,000 patients is required.*

[€]*Investigators must discuss their request with a member of the CPRD Research team before submitting an ISAC application. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email (kc@cprd.com) to discuss your requirements. Please also state the name of CPRD Research team with whom you have discussed this request (provide the date of discussion and any relevant reference information):*

We have not discussed with a CPRD researcher as we will only be accessing datasets that we have prior experience of using for this study.

Name of CPRD Researcher:. Reference number (where available) Date of contact

17. Primary care data

Please specify which primary care data set(s) are required)

Vision only (Default for CPRD studies ☒ Both Vision and EMIS®* ☐

EMIS® only* ☐

Note: Vision and EMIS are different practice management systems. CPRD has traditionally collected data from Vision practice. Data collected from EMIS is currently under evaluation prior to wider release.

Investigators requiring the use of EMIS data **must discuss the study with a member of the CPRD Research team before submitting an ISAC application*

Please state the name of the CPRD Researcher with whom you have discussed your request for EMIS data:

Name of CPRD Researcher Reference number (where available) Date of contact

18. Site Location of Data

a) Processing location(s):

Location area - UK

Organisation address:

Respiratory Epidemiology, Occupational Medicine and Public Health

G05, Emmanuel Kaye Building

Manresa Road

National Heart and Lung Institute

Imperial College

London, SW3 6LR

Note: Please enter the location details of where the data for this study will be used (processed).

b) Storage Location(s)

Location area - UK

Organisation address:

Respiratory Epidemiology, Occupational Medicine and Public Health

G05, Emmanuel Kaye Building

Manresa Road

National Heart and Lung Institute

Imperial College

London, SW3 6L

Note: Please enter the location details of where the data for this study will be stored.

c) Territory of analysis - UK

Note: Please enter the details of where the data for this study will be analysed.

SECTION D: INFORMATION ON DATA LINKAGES

19. Does this protocol seek access to linked data

Yes*☒ No☐ If No, please move to section E.

Research groups which have not previously accessed CPRD linked data resources **must discuss access to these resources with a member of the CPRD Research team, before submitting an ISAC application. Investigators requiring access to HES Accident and Emergency data, HES Diagnostic Imaging Dataset and PROMS data **must** also discuss this with a member of the CPRD Research team before submitting an ISAC application. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email kc@cprd.com to discuss your requirements **before** submitting your application.*

Please state the name of the CPRD Researcher with whom you have discussed your linkage request.

Name of CPRD Researcher Reference number (where available) Date of contact

Please note that as part of the ISAC review of linkages, your protocol may be shared - in confidence - with a representative of the requested linked data set(s) and summary details may be shared - in confidence - with the Confidentiality Advisory Group of the Health Research Authority.

20. Please select the source(s) of linked data being requested§
§Please note: This information will be published on the CPRD's website as part of its transparency policy.

☒ ONS Death Registration Data	☐ MINAP (Myocardial Ischaemia National Audit Project)
☒ HES Admitted Patient Care	☐ Cancer Registration Data*
☐ HES Outpatient	☐ PROMS (Patient Reported Outcomes Measure)**
☐ HES Accident and Emergency	☐ CPRD Mother Baby Link

☐ HES Diagnostic Imaging Dataset

☐ Practice Level Index of Multiple Deprivation (Standard)

☐ Practice Level Index of Multiple Deprivation (Bespoke)

☐ Patient Level Index of Multiple Deprivation***

☐ Patient Level Townsend Score ***

☐ Other**** *Please specify:*

**Applicants seeking access to cancer registration data must complete a Cancer Dataset Agreement form (available from CPRD). This should be submitted to the ISAC as an appendix to your protocol. Please also note that applicants seeking access to cancer registry data must provide consent for publication of their study title and study institution on the UK Cancer Registry website.*

***Assessment of the quality of care delivered to NHS patients in England undergoing four procedures: hip replacement, knee replacement, groin hernia and varicose veins. Please note that patient level PROMS data are only accessible by academics*

**** 'Patient level IMD and Townsend scores will not be supplied for the same study*

*****If "Other" is specified, please provide the name of the individual in the CPRD Research team with whom this linkage has been discussed.*

Name of CPRD Researcher Reference number (where available) Date of contact

21. Total number of linked datasets requested <u>including</u> CPRD GOLD

Number of linked datasets requested *(practice/ 'patient' level Index of Multiple Deprivation, Townsend Score or the CPRD Mother Baby Link should **<u>not</u>** be included in this count)* 3

Please note: Where ≥5 linked datasets are requested, approval may be required from the Confidentiality Advisory Group (CAG) to access these data

22. Is linkage to a <u>local¥</u> dataset with <1 million patients being requested?

Yes*☐ No☒

If yes, please provide further details:

¥ *Data from defined geographical areas i.e. non-national datasets.*

23. If you have requested one or more linked data sets, please indicate whether the Chief Investigator or any of the collaborators listed in question 5 above, have access to these data in a patient identifiable form (e.g. full date of birth, NHS number, patient post code), or associated with an identifiable patient index.

Yes* ☐ No ☒

** If yes, please provide further details:*

24. Does this study involve linking to patient *identifiable* data (e.g. hold date of birth, NHS number, patient post code) from other sources?

Yes ☐ No ☒

SECTION E: VALIDATION/VERIFICATION

25. Does this protocol describe a purely observational study using CPRD data?

Yes* ☒ No** ☐

** Yes: If you will be using data obtained from the CPRD Group, this study does not require separate ethics approval from an NHS Research Ethics Committee.*

*** No: You may need to seek separate ethics approval from an NHS Research Ethics Committee for this study. The ISAC will provide advice on whether this may be needed.*

26. Does this protocol involve requesting any additional information from GPs?

Yes* ☐ No ☒

** If yes, please indicate what will be required:*

Completion of questionnaires by the GP[ψ] Yes ☐ No ☐

Is the questionnaire a validated instrument? Yes ☐ No ☐

If yes, has permission been obtained to use the instrument? Yes ☐ No ☐

Please provide further information:

Other (please describe)

[ψ] *Any questionnaire for completion by GPs or other health care professional must be approved by ISAC before circulation for completion.*

27. Does this study require contact with patients in order for them to complete a questionnaire?

Yes* ☐ No ☒

**Please note that any questionnaire for completion by patients must be approved by ISAC before circulation for completion.*

28. Does this study require contact with patients in order to collect a sample?

Yes* ☐ No ☒

** Please state what will be collected:*

SECTION F: DECLARATION

29. Signature from the Chief Investigator

- I have read the guidance on '***Completion of the ISAC application form***' and '***Contents of CPRD ISAC Research Protocols***' and have understood these;
- I have read the submitted version of this research protocol, including all supporting documents, and confirm that these are accurate.
- I am suitably qualified and experienced to perform and/or supervise the research study proposed.
- I agree to conduct or supervise the study described in accordance with the relevant, current protocol
- I agree to abide by all ethical, legal and scientific guidelines that relate to access and use of CPRD data for research
- I understand that the details provided in sections marked with (§) in the application form and protocol will be published on the CPRD website in line with CPRD's transparency policy.

- I agree to inform the CPRD of the final outcome of the research study: publication, prolonged delay, completion or termination of the study.

Name: Dr Jennifer Quint Date: 21/02/18 e-Signature (type name): JKQuint

PROTOCOL INFORMATION REQUIRED

The following sections below **must** be included in the CPRD ISAC research protocol. Please refer to the guidance on '***Contents of CPRD ISAC Research Protocols***' (www.cprd.com/isac) for more information on how to complete the sections below. Pages should be numbered. All abbreviations must be defined on first use.

Applicants must complete all sections listed below **Sections which do not apply should be completed as '*Not Applicable*'**
A. Study Title[§] [§]*Please note: This information will be published on CPRD's website as part of its transparency policy* Comparison of Outcomes of Patients Hospitalised for Heart Failure (HHF) in the UK, Japan, USA and Taiwan
B. Lay Summary (Max. 200 words)[§] [§]*Please note: This information will be published on CPRD's website as part of its transparency policy* Heart failure (HF) is a common cause of hospitalisation, often prolongs hospital stay and is associated with increased death rates. Substantial differences in patients' characteristics, patient management and outcomes during hospitalisation of HF patients are known to exist between the Western and the Asian countries. However, the studies are limited by middle-sized datasets of HF patients and based on indirect comparisons. Simultaneous access to individual patient-level data in large-scale nationwide databases would enable the outcomes and the treatment strategy of patients with similar attributes in different countries to be compared rather than merely comparing averages based on previous published papers. We propose to evaluate patients with acute (decompensated) heart failure in the UK, USA, Japan and Taiwan.
C. Technical Summary (Max. 200 words)[§] [§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

As a national sample of current practice, we will use linked Clinical Practice Research Datalink (CPRD) data with Hospital Episode Statistics (HES) and Office for National Statistics (ONS) to undertake a cohort study to provide an accurate estimate of the number of people with hospitalised heart failure in the United Kingdom (UK). Japanese data will be sourced from the 2012–2015 Nationwide Claim-Based Database, the Japanese Registry Of All cardiac and vascular Diseases - Diagnosis Procedure Combination (JROAD-DPC), US data from the National Inpatient Sampling Database and Taiwan data from National Health Insurance Research Database -NHIRD. Each cohort (UK, USA, Japan and Taiwan) will be analysed separately. All-cause mortality, length of hospital and health care resource utilisation will be analysed in each dataset. On completion of the analysis, pooled estimates will be compared across the datasets.

D. Objectives, Specific Aims and Rationale

Specific Aim 1: To compare LOHS and 30-day readmission rates of real world HHF patients in the UK, USA, Japan and Taiwan (January 1st, 2012 to December 31st, 2013).

Specific Aim 2: To compare health care resource utilisation during in-hospital stay of HHF patients in the UK, USA, Japan and Taiwan (January 1st, 2012 to December 31st, 2013).

Specific Aim 3: To identify individual patient characteristics that predict a high probability of in-hospital mortality among HHF patients in the UK, USA, Japan and Taiwan.

Specific Aim 4: To compare differences in patient characteristics, health resource utilisation, length of hospital stay, covariate adjusted in-hospital mortality and 30 day readmission rates among HHF patients in the UK and USA

E. Study Background

Heart Failure (HF) is an important cause of hospitalisation, especially in older adults, and is associated with a high mortality.

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

Although, international guidelines for the management of HF are very similar (1,2), important regional differences exist in patients' characteristics, medication prescribing patterns, length of hospital stay (LOHS), and clinical outcomes, especially between Western and Asian countries (3-14). For instance, post-hoc analysis from contemporary clinical trials suggest that LOHS for HF is substantially longer in Japan than in many other countries. The Acute Decompensated heart Failure Syndromes (ATTEND) registry revealed that the median LOHS in Japan was around 21 days, in contrast to 4.3 days in the United States (9,10). There may also be regional differences in mortality for HF (9-14). It is unclear whether differences in clinical outcomes are related to variations in the severity of HF, patient co-morbidities or practice pattern across different health care systems. Most of the data on regional differences comes from clinical trials or from registries of modest size. Access to de-identified, individual patient-level data (IPLD) in multiple large-scale national audits and administrative databases (CPRD, HES and ONS in the UK, National Inpatient Sampling Database in the USA, National Health Insurance Research Database in Taiwan and JROAD-DPC (15) in Japan) will enable us to evaluate differences in individual patient characteristics, prescribing patterns and clinical outcomes of HF patients with similar attributes in the UK, USA, Taiwan and Japan

F. Study Type

This is a descriptive and hypothesis testing study. We hypothesise that the LOHS, 30 day readmission rates **are** significantly different between countries. Aim 4: We hypothesise that the co-variate adjusted 30 day readmission rates and in-hospital mortality rates are higher in the UK when compared to the US.

G. Study Design

We propose a comparison of patients with a hospital admission for HF identified from an administrative claims cardiovascular database from Japan, National Readmissions Database from the USA, National Health Insurance Research Database from Taiwan and from CPRD, HES and ONS in the UK.

Each dataset will be analysed domestically and will remain in the respective countries. Approval for the use of anonymised data from the United States has been sought to carry out specific Aims 5. As far as possible between the datasets, we will use agreed definitions for the exposures, outcomes and covariates

Japan: JROAD-DPC: Approval and funding for the analysis of Japanese administrative data and hospitalised HF registry data has been obtained from the Japanese Circulation Society, all participant hospitals for the registry, and the Japan Research Foundation for Clinical Pharmacology, respectively. Institutional Review

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

Board approval for analyses of the Japanese data will be obtained from National Cerebral and Cardiovascular Centre, Osaka and is separate to what we are seeking approval for from the ISAC. Japanese administrative data will be sourced from the 2012-2015 JROAD-DPC (Japanese Registry Of All cardiac and vascular Diseases - Diagnosis Procedure Combination) Nationwide Claim-Based Database) The database contains de-identified claims for 2 to 3 million individuals who were admitted to 610 certificated hospitals of the Japanese Circulation Society. The database includes patient demographics (derived by ICD-10 codes), in-patient services, prescriptions, procedures performed and in-hospital. These data have already been used for investigating current status of cardiovascular care in Japan.

USA- National Readmissions Database (NRD) The NRD is a nationally representative survey of hospitalisations, conducted by the Healthcare Cost and Utilisation Project in collaboration with the participating states. It includes a 49% sample of all admissions to the United States hospitals. Each entry contains information on demographic details, including age, gender, race, insurance status, primary and secondary procedures, hospitalisation outcome, total cost, and length of stay. The NIS database (uses ICD-9 codes) contains clinical and resource use information, with safeguards to protect the privacy of patients, physicians, and hospitals. The database results have been shown to correlate well with other hospitalisation discharge databases in the United States.

Taiwan-National Health Insurance Database (NHIRD): The National Health Insurance program was established on March 1, 1995 and covers 99.9% of Taiwan's population. The National Health Insurance Research Database (NHIRD) service contains registration files and original claim data for reimbursement. The database (CD-9-CM code) contains information of all hospitalisations, outpatient visits, accident and emergency visits and prescription information.

H. Feasibility counts

The total number of hospitalised patients with ICD-10 codes for HF between 2012-2013 is 62,000 patients/year (for a total population of 56 million in England and Wales) based on the results of the National Heart Failure Audit (instead of the HES linked with CPRD). The expected annual admissions for HF in the CPRD database (~14 million) is around ~15,000 patients/year. Out of these patients we expect around 60-65% of them to be eligible for the HES linkage (~9,750 patients/year) which gives an estimated sample size of ~19,500 patients for our study inclusion period of three years (2012-2013).

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

I. Sample size considerations

Our preliminary analysis based on the previous ISAC gives us an estimated sample size of ~ 10,500 UK hospitalised HF patients for that study period (2012 -2013). Estimated sample size of the JROAD-DPC for this study period is ~ 150,000. The estimated sample sizes for HHF patients during the study period in the USA and Taiwan are 250,000 and 40,000 respectively. Our initial analysis revealed an in-hospital mortality of 3.5% in the US and 10% in the UK (specific aim4). Assuming an alpha of 0.05, our current sample size gives us a power > 95% for specific Aim 4

J. Data Linkage Required (if applicable):[§]

[§]*Please note that the data linkage/s requested in research protocols will be published by the CPRD as part of its transparency policy*

HES and ONS data are required for identification of admissions in hospitalised patients with HF and those who die

K. Study population

Data for patients who had unscheduled hospitalisation for HF will be extracted from the HES linked with CPRD, NIS, NHIRD and the JROAD-DPC (using International Classification of diseases tenth revision- ICD10 codes) between 2012-2013. We will identify HF patients by using ICD-10 codes for the JROAD-DPC, Read codes for the CPRD and ICD 9CM codes from the NIS and NHIRD. From these cohorts, patients under 18 years of age will be excluded.

L. Selection of comparison group(s) or controls

Not applicable, we are comparing different countries with one another

M. Exposures, Health Outcomes[§] and Covariates

- **Exposure:** We propose to identify cohorts of patients with first unscheduled hospitalisation due to HF from January 1, 2012 to December 31, 2013 in the UK, USA, Taiwan and Japan.

- **Outcomes:**

  - Specific Aim 1: LOHS and 30-day readmission (from the date of discharge)

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

- Specific Aim 2: Health Resource Utilisation (HRU) during in-hospital stay defined by A) Coronary angiogram B) Right heart catheterization C) Mechanical ventilation D) Mechanical hemodynamic support e.g.) percutaneous ventricular assisted device E) Percutaneous Coronary Intervention F) CABG G) Device implantation I) Ablations for atrial fibrillation/flutter, ventricular arrhythmias J) Cardioversion. Procedures will be identified from the HES data using OPCS4 codes

- Specific Aim 3: Individual patient characteristics that predict a high probability of in-hospital mortality among HHF patients in the UK, USA, Japan and Taiwan i.e. prognostic value of each co-morbidity on in-hospital mortality in each country (e.g. Atrial Fibrillation on in-hospital mortality in each country)

- Specific Aim 4: Co-variate adjusted in-hospital mortality, 30 day readmission (due to HF and all cause readmissions) of HHF patients admitted in the UK and USA

If there is no record of death documented in HES but one documented in ONS, we will adopt death documented in ONS if death occurs up to the date of discharge and that in HES if death occurs after the date of discharge.

- **Covariates:**

Demographics: Age, sex and ethnicity

Co-morbidities: Coronary artery disease, Atrial Fibrillation, Hypertension, Diabetes, alcohol abuse, obesity, peripheral vascular disease, chronic lung disease, chronic liver disease, chronic kidney disease, pulmonary circulation disorders, malignancy. Co-morbidities documented 12 months prior to HF hospitalisation will be used for the analysis for those comorbidities that are transient, for those that are long term and permanent, e.g. atrial fibrillation, we will use any prior.

N. Data/ Statistical Analysis

All data will be analysed using Stata Version 14 (StataCorp, Texas).

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

Specific Aim 1: We will be analysing the proportion of HHF patients with in-hospital mortality and 30-day readmission rates in each country (%). The median LOHS deviation will be calculated in each country

Specific Aim 2: We will be comparing (number and %) the individual procedures performed in each country

Specific Aim 3: We will perform a nested case control study within the cohort. We will compare cases (patients who died during the hospital stay) with controls (alive) within each country. Baseline co-morbidities [Hypertension (HTN), Diabetes mellitus (DM), Coronary artery disease (CAD), Atrial fibrillation (AFIB), Chronic kidney disease (CKD), Chronic liver disease (CLD), Obesity, Peripheral arterial disease (PAD), Pulmonary circulation disorders, Age and Sex] which predict in-hospital mortality will be identified using conditional logistic regression analysis within each country. Co-morbidity specific odds ratio will be estimated and pooled across cohorts with the use of random-effects meta-analysis. The random effects meta-analysis will effectively control the within and between study variabilities. Heterogeneity will be estimated with the use of I2 statistic

Specific Aim 4: Differences in baseline characteristics and in-hospital procedures among HHF patients in the UK and US will be analysed. Differences in mean values of continuous variables will be assessed using the Kruskal-Wallis test statistic. The statistical significance of differences in the frequency of categorical variable values between groups was assessed using the chi-square test statistic. We will perform multivariate logistic regression analysis and propensity matching technique to compare odds of mortality and 30 day readmission in the UK and US HHF patients. Covariate adjusted outcome analysis is possible between the UK and US cohort as the US data has been approved for use outside the US

O. Plan for addressing confounding

We are aware we cannot account for all confounders and have discussed this further in the limitation section. The differences in exposure and covariates will be adjusted for using multivariate regression analysis.

P. Plans for addressing missing data

Decisions regarding how to deal with missing values will be based on the proportion of missing data, and assumptions regarding whether data is missing at random (MAR) or not. Where appropriate we will undertake a complete case analysis. If data is MAR we will consider using multiple imputation. Where data are not missing at random, where we expect the data to be 80%

complete (based on previous studies), we will use a complete case analysis but will discuss biases that may occur as a result of adopting that approach. Where multiple imputation is not appropriate and there are large quantities of data missing, we will consider using those covariates only as part of a secondary analysis and will discuss any biases and limitations that occur as a result of that.

Q. Patient or user group involvement (if applicable)
There will be no patient or user group involvement

G. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

The study findings will be submitted for publication in peer-reviewed scientific journals, and will be presented both at appropriate conferences and at other meetings; the latter will include scientific meetings externally, for example for the Japanese Circulation Society and the European Society of Cardiology meetings and within Imperial College London.

H. Limitations of the study design, data sources, and analytic methods

1) **Misclassification of exposure and outcomes: Although specific seven ICD-10 codes of HF that used in the National Heart Failure Audit have been chosen for the criteria of unscheduled hospitalisation in both the HES linked with CPRD to maximize the specificity of identifying people with HF, we are limited by the acumen of the reviewing clinician recording the diagnosis. This limitation is true for other countries**
2) **Identification of HF phenotype: Incomplete data makes partition of patients into HFrEF versus HF with preserved ejection fraction (HFPEF) difficult. However, using specific ICD-10 codes (e.g., dilated cardiomyopathy and ischaemic cardiomyopathy), it may be possible to phenotype a proportion of patients.**
3) **Confounders: Multivariable logistic regression analysis will reduce confounding (for specific Aim 5) but not eliminate it.**

R. References

1. **Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016; 37: 2129-200.**
2. **Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos G, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task**

Force on Clinical Practice Guidelines and the Heart Failure Society of America. WRITING COMMITTEE MEMBERS Circulation. 2016; 134: e282-93.

3. **Atherton JJ, Hayward CS, Wan Ahmad WA, Kwok B, Jorge J, Hernandez AF, Liang L, Kociol RD, Krum H; ADHERE International–Asia Pacific Scientific Advisory Committee. Patient characteristics from a regional multicenter database of acute decompensated heart failure in Asia Pacific (ADHERE International-Asia Pacific). J Card Fail. 2012; 18: 82-8.**
4. **Mentz RJ, Cotter G, Cleland JG et al. International differences in clinical characteristics, management, and outcomes in acute heart failure patients: better short-term outcomes in patients enrolled in Eastern Europe and Russia in the PROTECT trial. Eur J Heart Fail 2014;16:614-24.**
5. **Greene SJ, Fonarow GC, Solomon SD et al. Global variation in clinical profile, management, and post-discharge outcomes among patients hospitalized for worsening chronic heart failure: findings from the ASTRONAUT trial. Eur J Heart Fail 2015;17:591-600.**
6. **Pfeffer MA, Claggett B, Assmann SF et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Circulation 2015;131:34-42.**
7. **Kristensen SL, Martinez F, Jhund PS et al. Geographic variations in the PARADIGM-HF heart failure trial. Eur Heart J 2016;37:3167-3174.**
8. **Kristensen SL, Kober L, Jhund PS et al. International geographic variation in event rates in trials of heart failure with preserved and reduced ejection fraction. Circulation 2015;131:43-53.**
9. **Sato N, Kajimoto K, Keida T, Mizuno M, Minami Y, Yumino D, Asai K, Murai K, Muanakata R, Aokage T, Sakata Y, Mizuno K, Takano T; ATTEND Investigators. Clinical features and outcome in hospitalized heart failure in Japan (from the ATTEND Registry). Circ J. 2013;77(4):944-51.**
10. **Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M, Horton DP; ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005; 149: 209-16.**
11. **Harjola VP, Follath F, Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Hochadel M, Komajda M, Lopez-Sendon JL, Ponikowski P, Tavazzi L. Characteristics, outcomes, and predictors of mortality at 3 months and 1 year in patients hospitalized for acute heart failure. Eur J Heart Fail. 2010; 12: 239-48.**
12. **Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, Stough WG, Yancy CW, Young JB, Fonarow GC; OPTIMIZE-HF Investigators and Coordinators. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. JAMA. 2006; 296: 2217-26.**
13. **Maggioni AP, Dahlstrom U, Filippatos G et al. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail 2013;15:808-17.**
14. **Park JJ, Choi DJ, Yoon CH, Oh IY, Jeon ES, Kim JJ, Cho MC, Chae SC, Ryu KH, Yoo BS, Kang SM, Oh BH; KorHF Registry. Prognostic value of C-reactive protein as an inflammatory and N-terminal probrain natriuretic peptide as a neurohumoral marker in acute heart failure (from the Korean Heart Failure registry). Am J Cardiol. 2014; 113: 511-7.**
15. **Yasuda S, Nakao K, Nishimura K, Miyamoto Y, Sumita Y, Shishido T, Anzai T, Tsutsui H, Ito H, Komuro I, Saito Y, Ogawa H; on the behalf of JROAD Investigators. The Current Status of**

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
Cardiovascular Medicine in Japan - Analysis of a Large Number of Health Records From a Nationwide Claim-Based Database, JROAD-DPC. Circ J. 2016;80:2327-2335.
List of Appendices (Submit all appendices as separate documents to this application) **ICD 10 codes for HF hospitalisation**

Amendment

In this amendment, we have included another aim (specific Aim 5), where we propose to identify patients with HF and COPD and investigate the influence of COPD on mortality in the HF population in the UK and US. Please see below for the specifics.

ISAC APPLICATION FORM

Section A.2

The protocol number for the previous submission was 18_068R. We have added "specific aim 5", which will compare outcomes in the UK and USA populations, stratified by COPD status.

Section B.2

Added Other investigator: Claudia Gulea, PhD student, National Heart and Lung Institute, Imperial College London. Email address: c.gulea18@imperial.ac.uk, CV attached

PROTOCOL INFORMATION REQUIRED

Section B "Lay Summary"

Added: "Chronic Pulmonary Obstructive Disease (COPD) is one of the common conditions seen in patients with HF. propose to investigate outcomes of hospitalised HF patients with and without COPD, across the UK and the US." Sentenced added to highlight the importance of COPD in HF patients.

Section C. Technical Summary

Added study time frame for identifying new subgroup of patients : "between 2012 and 2013. Among these, we will identify and quantify the number of patients with comorbid COPD (HF-COPD group)." Clarified that "UK and USA data will be compared in a merged dataset and pooled estimates will be compared across the Asian datasets".

Section D. Objectives, Specific Aims and Rationale

Added "Specific aim 5" which will allow comparison of the hospitalised HF population in terms of characteristics and outcomes stratified by COPD comorbidity, across UK versus US data. **Specific Aim 5:** To compare differences in patient characteristics, health resource utilisation, length of hospital stay, covariate adjusted in-hospital mortality and 30 day readmission rates and cost of hospitalisation among HHF patients in the UK and USA, stratified by COPD status.

Section E. Study Background

Added clarification on link between COPD and HF and importance of including a subgroup of patients with both diseases: One of the most common comorbidities of HF is COPD, as both conditions share risk factors and pathogenic mechanisms. Between 10% and 40% of patients with HF also present with COPD (16). Both conditions are strongly associated with socioeconomic deprivation and pose challenges in diagnosis and treatment (16, 17). Evidence suggests COPD significantly decreases survival one year after hospitalisation for HF (17) whilst the number of hospital admissions in patients with HF and COPD is larger than in those with COPD alone (18).

Specified that we will be comparing US and UK data In addition we will be able to investigate whether COPD has a mediating effect on the outcomes of interest in two of the countries, namely UK and USA.

Section F. Study Design

Specified that the Asian dataset will be analysed domestically whilst approval for US data was granted to carry out specific aims 4 and 5.

Section H. Feasibility Counts

Added feasibility counts as well as sample size considerations pertaining to specific aim 5: Based on previous work, the annual admissions for HF in the CPRD database (~14 million) is around ~15,000 patients for 2 years. Out of these patients, 11,000 will be eligible for the HES linkage. for our study inclusion period of three years (2012-2013). Furthermore, out of these patients, we expect around 30% to have a comorbid diagnosis of COPD (~3,300).

Section I. Sample size considerations

Added sample size which will be derived from NRD: In the NRD database, around 30% of hospitalised HF patients are expected to have a COPD diagnosis (~75,000). Assuming an alpha of 0.05, our current sample size gives us a power > 95% for specific aim 5.

Section K. Study Population

Added data frame for identifying eligible patients in NRD: For specific aim 5, we will identify only patients admitted in 2012 in NRD.

Section L. Selection of comparison group(s) or controls

Added information pertaining to specific aim 5: Specific aim 5: We will compare outcomes in patients with a hospitalisation for HF and no COPD with patients with a hospitalization for HF and a COPD comorbid diagnosis, across UK and US.

Section M. Exposures, Health Outomes and Covariates

Added exposure for specific aim 4 separately than for the rest of the aims:

- **Specific aims 1 to 4:** We propose to identify cohorts of patients with first unscheduled hospitalisation due to HF from January 1, 2012 to December 31, 2013 in the UK, USA, Taiwan and Japan.
- **Specific aim 5:** We propose to identify cohorts of patients with first unscheduled hospitalisation due to HF from January 1, 2012 to 2013 (UK) and during 2012 only in NRD (US).

Added outcomes relating to specific aim 5: To compare differences in patient characteristics, length of stay, total cost of hospitalisation, as well as co-variate adjusted in-hospital mortality, 30 day readmission (due to HF and all cause readmissions) of HHF patients with and without COPD admitted in the UK and USA.

Section N. Data/Statistical Analysis

Added statistical software which will be used for data analysis: R.

Added statistical analysis plan for specific aim 5: Differences in baseline characteristics among patients admitted for with and without COPD in the UK and US will be analysed. Differences in mean values of continuous variables will be assessed using the Kruskal-Wallis test statistic. The statistical significance of differences in the frequency of categorical variable values between groups was assessed using the chi-square test statistic. We will perform multivariate logistic regression analysis and propensity matching technique to compare odds of mortality and 30 day readmission in the UK and US hospitalised HF patients with comorbid COPD diagnosis. Covariate adjusted outcome analysis is possible between the UK and US cohort as the US data has been approved for use outside the US.

Section R. References

Added the following references:

16. McMurray, J. J., & Stewart, S. (2000). Epidemiology, aetiology, and prognosis of heart failure. *Heart*, *83*(5), 596-602.
17. Rusinaru, D., Saaidi, I., Godard, S., Mahjoub, H., Battle, C., & Tribouilloy, C. (2008). Impact of chronic obstructive pulmonary disease on long-term outcome of patients hospitalized for heart failure. *American Journal of Cardiology*, *101*(3), 353-358.
18. Boudestein, L., Rutten, F. H., Cramer, M. J., Lammers, J. W. J., & Hoes, A. W. (2009). The impact of concurrent heart failure on prognosis in patients with chronic obstructive pulmonary disease. *European journal of heart failure*, *11*(12), 1182-1188.