Patient-related factors influencing management and procedural outcomes of de novo cardiac electronic device implantation

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A thesis submitted for the degree of Doctor of Philosophy

October 2021

Keele University

ACKNOWLEDGMENTS

I would like to express my sincere gratitude to several people whose support and guidance were integral to my achievements over the past 3 years.

First, I would like to thank my lead supervisor, Professor Mamas, whose inspiration and unwavering support has driven me to higher standards as an early career scholar. Professor Mamas, your mentorship and insightful feedback has only furthered my academic potential and helped me realise my long-held ambitions for a career in academic cardiology.

Second, I would also like to thank my supervisors, Dr Ashish Patwala and Dr Glen Martin who have provided me with invaluable support throughout my research work and were always available whenever their advice was sought.

Third, I would like to thank my colleagues in Keele Cardiovascular Research Group who have supported me from day one. Most notably, I had the pleasure of working with Muhammad Rashid, Ahmad Shoaib and Chun Shing Kwok who were all sources of inspiration and led a great example to follow as esteemed colleagues and, fortunately, became dear friends as time went on.

Last but not least, I would like to thank my parents, Dr Osama Mohamed and Dr Amira Elsabe, and my brother, Dr Walid Mohamed, who mean the whole world to me and have selflessly supported me throughout my entire life. Without your love, sacrifice, and lifelong guidance, no milestone in my life would have been accomplished in the ways that they have.

PUBLICATIONS

The following publications were produced from the work in this thesis:

1. Mohamed MO, Barac A, Contractor T, Silvet H, Arroyo RC, Parwani P, Kwok CS, Martin GP, Patwala A and Mamas MA. Prevalence and in-hospital outcomes of patients with malignancies undergoing de novo cardiac electronic device implantation in the USA. Europace. 2020;22:1083-1096.
2. Mohamed MO, Contractor T, Zachariah D, van Spall HGC, Parwani P, Minissian MB, Rashid M, Martin GP, Barker D, Patwala A and Mamas MA. Sex Disparities in the Choice of Cardiac Resynchronization Therapy Device: An Analysis of Trends, Predictors, and Outcomes. Can J Cardiol. 2021 Jan;37(1):86-93.
3. Mohamed MO, Greenspon A, Contractor T, Rashid M, Kwok CS, Potts J, Barker D, Patwala A and Mamas MA. Outcomes of cardiac implantable electronic device transvenous lead extractions performed in centers without onsite cardiac surgery. Int J Cardiol. 2020;300:154-160.
4. Mohamed MO, Greenspon A, Van Spall H, Volgman AS, Sharma PS, Alraies MC, Kwok CS, Martin GP, Zachariah D, Patwala A and Mamas MA. Sex differences in rates and causes of 30-day readmissions after cardiac electronic device implantations: insights from the Nationwide Readmissions Database. Int J Cardiol. 2020;302:67-74.
5. Mohamed MO, Volgman AS, Contractor T, Sharma PS, Kwok CS, Rashid M, Martin GP, Barker D, Patwala A and Mamas MA. Trends of Sex Differences in Outcomes of Cardiac Electronic Device Implantations in the United States. Can J Cardiol. 2020;36:69-78.
6. Mohamed MO, Sharma PS, Volgman AS, Bhardwaj R, Kwok CS, Rashid M, Barker D, Patwala A and Mamas MA. Prevalence, outcomes and costs according to patient frailty status for 2.9 million cardiac electronic device implantations in the United States. Can J Cardiol. 2021 Jan;37(1):86-93.
7. Mohamed O. Mohamed, Harriette GC Van Spall, Carlos Morillo, Steve B. Wilton, Evangelos Kontopantelis, Muhammad Rashid, Pensee Wu, Ashish Patwala, Mamas A. Mamas. The impact of Charlson Comorbidity Index on de novo CIED procedural outcomes in the United States. Mayo Clin Proc (in press- June 2021).

ABSTRACT

Cardiac implantable electronic devices (CIED) are an essential part of the management of patients with life-threatening arrhythmias. While many patient-related factors have been previously shown to play a role in the choice of CIED type offered to patients as well as outcomes of CIED implantation procedures, many patient characteristics remain understudied. Furthermore, little is known about the rates and causes of short-term readmissions after CIED implantation.

The present thesis provides answers to some of the gaps in evidence around the relationship between several patient-related factors and the management as well as outcomes of CIED implantation as a de novo procedure.

The first phase, presented in Chapter 4, examined patient characteristics that predict the choice of cardiac resynchronisation therapy (CRT) device offered to patients with severe left-sided heart failure. Factors such as patient sex, history of ventricular arrhythmias, active malignancy and renal failure were among the strongest predictors of the type of CRT offered to patients.

The second phase, which is discussed in Chapters 5 to 8 of this thesis, focused on the impact of several patient-related factors on in-hospital outcomes after CIED implantation, including mortality and procedure-related complications (thoracic, cardiac and bleeding). Females were associated with worse in-hospital outcomes, despite adjustment for multiple confounders, as were patients with active cancer and intermediate to high-risk frailty. While the overall burden of comorbidity correlated with increased odds of in-hospital mortality and acute stroke, it did not confer worse procedure-related outcomes.

The third and final phase, in Chapter 9 of the thesis, looked at the rates and causes of 30-day readmissions after CIED implantation and showed that these were common (1 in 7

patients), with a significant proportion being due to cardiac and device-related causes. In the relevant chapter, I report several important patient characteristics that are predictive of 30-day cardiac readmission.

In my discussion, I reflect on the clinical implications of my findings including the need for risk scoring systems that incorporate the patient-related factors studies in this thesis as well as risk reduction technical strategies to address the inherent risk of procedural complications in certain high-risk patient groups.

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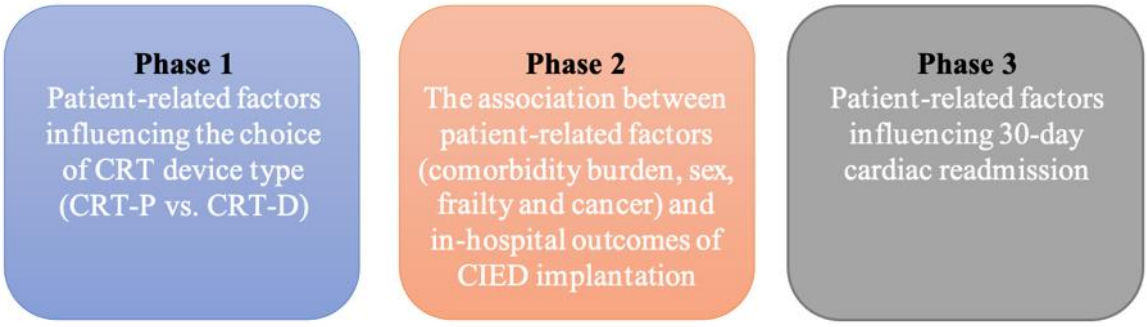
Chapter 1. Introduction

1. Overview

My thesis focused on investigating patient-related factors influencing the choice of management and in-hospital outcomes of de novo cardiac implantable electronic device (CIED) procedures in adults (≥18 years). Overall, there were three main phases for this thesis (illustrated in **Figure 1**). The first phase focused on patient-related factors predicting the choice of cardiac resynchronisation therapy (CRT) device type, including CRT with pacemaker (CRT-P) and CRT with defibrillator (CRT-D). The second phase looked at patient characteristics influencing in-hospital outcomes of CIED implantation. The third and final phase focused on patient-related factors predicting 30-day cardiac readmission.

Figure 1. Phases of the PhD thesis



CRT: cardiac resynchronisation therapy, **CRT-P:** CRT with pacemaker; **CRT-D:** CRT with defibrillator

2. Objectives

The main objectives of the present thesis were to study the following:

- The influence of patient related factors on the choice of CRT device type amongst those who are eligible for such device.
- The influence of patient-related factors, including sex and comorbidities such as cancer and frailty as well as overall comorbidity burden, on post-procedural outcomes of de novo CIED implantation.

- Causes of 30-day readmissions after CIED implantation and patient characteristics associated with 30-day readmission for cardiac and device-related causes.

3. Thesis Chapters Layout

a) Chapter 2

This chapter reviews gives an overview of technical aspects of the CIED procedure as well as common indications. This is followed by a review of the existing evidence on patient-related factors influencing procedural outcomes of CIED implantation as well as the gaps in current literature that form the basis of this thesis.

b) Chapter 3

In this chapter I provide a description of the two datasets from which the work in this PhD was performed: The United States National Inpatient Sample (NIS) and the Nationwide Readmissions Database (NRD). A comprehensive overview of data curation, including cohort extraction and restructure, identification of procedures and diagnoses, and handling of missing data. Furthermore, I discuss the statistical methodology used in my studies.

c) Chapter 4

The chapter focuses on the first objective of the thesis, the association between patient-related factors and choice of CRT device (CRT-P vs. CRT-D) was examined. Furthermore, I focused on sex differences in receipt of device type and the trends of these differences between 2004 and 2014.

d) Chapter 5

This chapter addresses the second objective of my thesis. I discuss my study of the influence of sex on in-hospital outcomes of de novo CIED implantation, stratified by type of CIED (permanent pacemaker (PPM), CRT-P, CRT-D and implantable cardioverter

defibrillator (ICD)), and explore the trends of these differences over an 11-year period (2004 to 2014).

e) Chapter 6

This chapter also relates to the second objective of my thesis and focuses on outcomes of de novo CIED implantation in patients with historical and current cancer. Procedural outcomes were compared according to type of prevalent cancer as well as type of CIED device (PPM, CRT and ICD).

f) Chapter 7

This chapter relates to the second objective of my thesis. I discuss the impact of frailty risk (low, intermediate and high) on procedural outcomes of de novo CIED implantation using the Hospital Frailty Risk Score. Comparisons were made between different device types (PPM, CRT-P, CRT-D and ICD) for a range of in-hospital outcomes.

g) Chapter 8

This is the final chapter of my second objective of the thesis, in which I discuss the effect of overall comorbidity burden, objectively measured using the Charlson Comorbidity Index, on procedures outcomes of de novo CIED implantation. Outcomes were examined in the overall CIED cohort and according to CIED subtype (PPM, CRT-P, CRT-D and ICD).

h) Chapter 9

This is the first of two chapters looking at causes of 30-day readmissions after CIED implantation from the NRD database. This chapter looked at overall, cardiac and device-related causes of 30-day readmissions, stratified by type of CIED device (PPM, CRT-P, CRT-D, ICD), as well as patient-related factors predictive of 30-day cardiac and device-

related readmissions. Furthermore, I study differences in 30-day readmission rates and causes between sexes.

i) Chapter 10

The final chapter draws on the main conclusions of studies undertaken during my thesis, providing insight into their clinical implications as well as future research directions that would further our understanding of the impact of patient-related factors on outcomes of de novo CIED implantation.

Chapter 2. Background

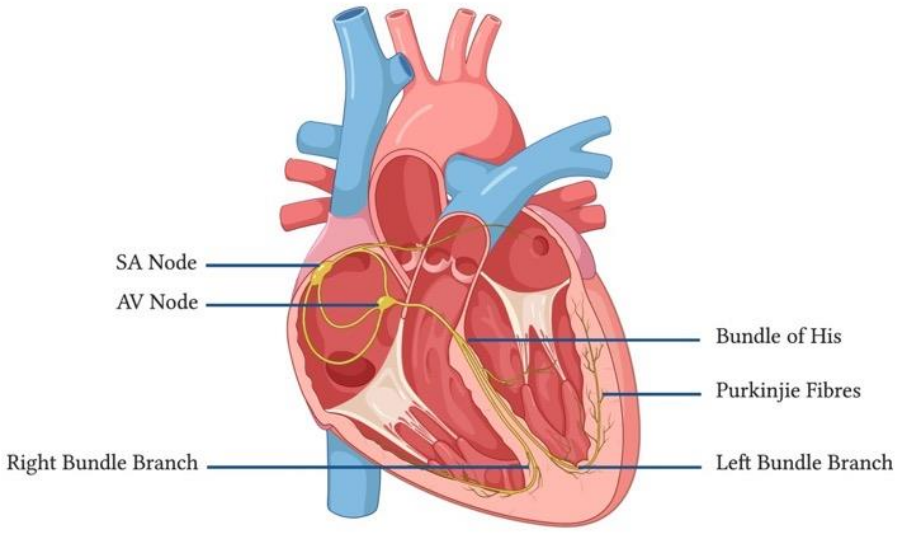
In this chapter, I provide an overview of the cardiac conduction system, cardiac rhythm disorders and heart failure, all of which are indications for cardiac implantable electronic device (CIED) implantation. Furthermore, I summarise the current evidence on CIED implantation outcomes and the gaps in current evidence that form the basis of my thesis.

1. Cardiac rhythm disorders

a) Overview of the cardiac conduction system

It is essential to gain a conceptual understanding of the heart conduction system in order to identify the aetiology of different conduction disorders and abnormal heart rhythms (arrhythmias), which are common indications of cardiac implantable electronic device (CIED) implantation. An illustration of the conduction system is provided in **Figure 1**. The cardiac conduction sequence starts in the sinoatrial (SA) node, commonly known as the anatomical pacemaker, which releases an electrical stimulus that travels rapidly (conduction velocity: 0.5 m/sec) through both atria, resulting in their contraction, before passing through the atrioventricular (AV) node where the impulse is conducted at a much slower rate (0.05 m/sec). The slower rate of conduction through the AV node acts as a protective mechanism in the case of abnormally rapid heart rhythms (tachyarrhythmias). After the impulse passes through the AV node, it travels rapidly (2 m/sec) through the Bundle of His in to the left and right bundle branches, before reaching the network of Purkinjie fibres, which have the fastest conduction velocity (4 m/sec), all of which lead to the contraction of the ventricles.

Figure 1. Illustration of the heart conduction system



SA: sinoatrial; **AV:** atrioventricular

b) Types and prevalence of cardiac rhythm disorders

Conduction disorders could arise from any of the previously described conduction pathways (SA node, AV node, Bundle of His, and left and right bundle branches). Collectively, these cause slow heart rhythms (bradyarrhythmia), although certain exceptions are highlighted below. In a study of more than 500,000 individuals the prevalence of bradyarrhythmia was reported to be 0.89 per 1000 person-years (95% CI 0.86–0.92).[1] Bradyarrhythmias are classified as follows:

i. Sinus node dysfunction (SND)

SND is increasingly common with advanced age due to gradual decrease in the number of pacemaker cells and, in turn, activity of the SA node. Several subtypes of SND exists including 1) inappropriate sinus bradycardia, 2) alternating sinus bradycardia and tachyarrhythmia (sick sinus syndrome (SSS)), 3) sinus pause or block, and 4) sinoatrial exit block. Although there is limited data on the prevalence of cardiac rhythm disorders, SSS is thought to occur in 1 in 600 cardiac patients ages above 65 years old. [2]

ii. Atrioventricular (AV) blocks

Progressive fibrosis of the cardiac conduction system occurs with ageing, leading to various types of acquired AV blocks. The three main types of AV block (**Figure 2**) include:

- **First degree AV block:** progressive delay in atrial conduction resulting in a prolonged PR interval (>200 msec). The prevalence of first degree AV block is estimated to be found in 3-4% of healthy individuals.[3]
- **Second degree AV block**

  -**Mobitz I:** progressive prolongation of the PR interval until one atrial impulse is eventually not conducted to the ventricle (no QRS complex). Prevalence is estimated to be 2.2%.[4]

  -**Mobitz II:** intermittently dropped QRS complexes, which means that an atrial complex was not conducted to the ventricle. There is limited data on the prevalence of Mobitz II AV block. This type of conduction disorder is likely to progress to asystole (complete heart pause/stop).

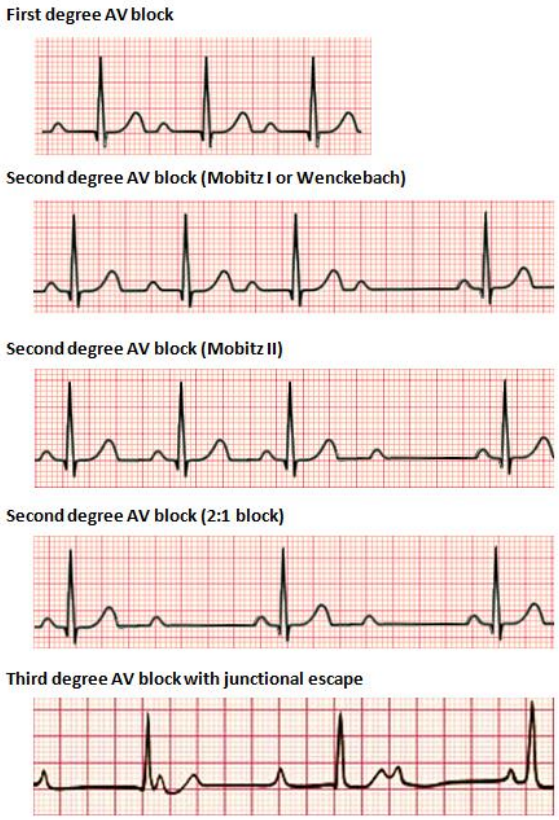
  -**Third degree AV block:** complete dissociation in electrical communication between atria and ventricles. The prevalence of third-degree AV block is estimated to be approximately 0.04%.[5] Third degree AV block is highly likely to progress to asystole.

Of the previously discussed conduction disorders, sick sinus syndrome and Mobitz II and third-degree AV blocks are the most frequent indication for permanent pacemaker (PPM) implantation. Overall, bradyarrhythmia forms 30-50% of all PPM indications, although this varies by country and type of arrhythmia. [6] However, there is limited data from large surveys and reports on the rate of PPM utilisation for each type of cardiac rhythm disorder.

Several other arrhythmias are indications for CIED implantation and, therefore, are relevant to this thesis. These include ventricular tachycardia (VT) and ventricular

fibrillation (VF), collectively referred to as ventricular arrhythmias in this chapter. There are numerous aetiologies of ventricular arrhythmia including (but not restricted to) damage and/or scarring to the ventricle from a recent/old heart attack (myocardial infarction), diseases of the heart muscle (cardiomyopathy) or valves, and infection. Ventricular arrhythmias are the most common cause of sudden cardiac death (SCD), which is responsible for more than 100,000 deaths in the UK and up to 420000 deaths in the United States (US) every year. [4, 7]

Figure 2. Types of AV block



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2. Heart failure

Heart failure (HF) is a clinical syndrome used to describe symptoms (e.g. breathlessness) and/or signs (e.g. peripheral oedema) that reflect the heart's inability to maintain its usual function, that being to provide a sufficient output to match the body's demands.[8] There are various types and stages of HF that are outside the scope of this thesis.

HF is one of the leading causes of morbidity worldwide, with an estimated prevalence of more than 37.7 million patients globally.[9, 10] In the UK, it is estimated that 920,000 patients are living with HF, with more than 200,000 new diagnoses every year according to the latest British Heart Foundation (BHF) report in 2021. [11] Similarly, in the US there were more than 5.7 million patients living with heart failure in 2011 and more than 870,000 new cases every year. [12] The lifetime risk of HF is estimated to be as high as 33% in patients aged 55 years and over, depending on their sex.[13]

There are numerous aetiologies of heart failure, including ischaemic heart disease, rheumatic and valvular heart disease, hypertension and several genetic and metabolic factors.[14] The mortality from HF has stabilised and, in many countries decreased, in recent years, commensurate with advancements in pharmacotherapy as well as the increased utilisation of cardiac resynchronisation therapy (CRT) in patients with advanced HF. [8, 15-17] The latter is a type of CIED also known as a biventricular pacemaker and sends electrical impulses (pacing) to both ventricles in a synchronised manner to help restore their synchrony, which is lost in many patients with HF. In England alone, age and sex-standardised mortality from HF declined by 60% over a 30-year period (1981-2010).[16] Notwithstanding, there is limited information on the exact mortality of HF since it is often considered as a "mode of death" and the cause of death is attributed to its underlying aetiology (e.g., ischaemic heart disease). [17, 18]

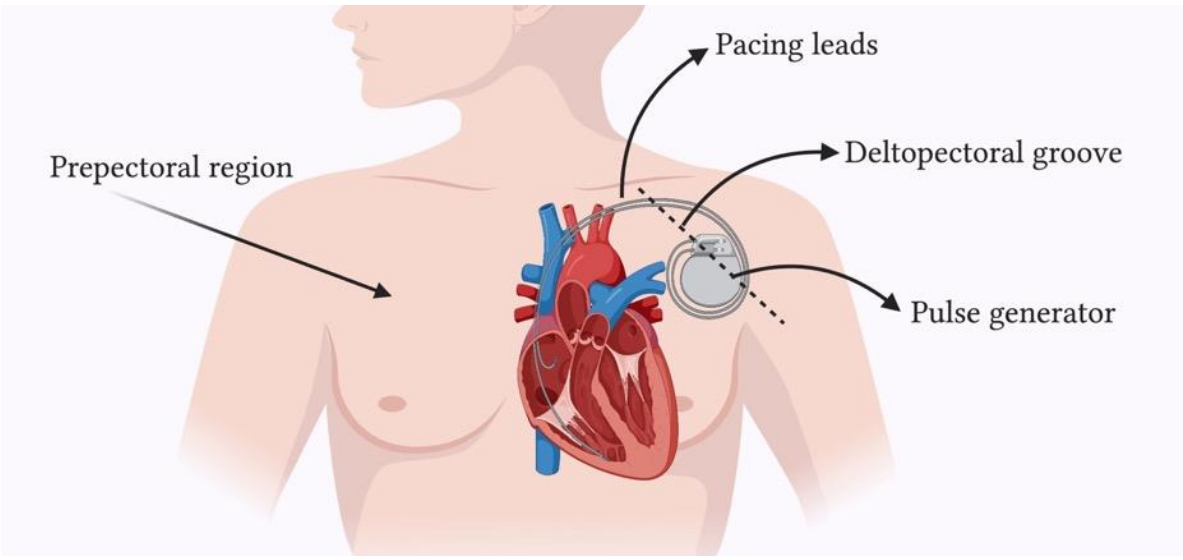
While pharmacotherapy is the mainstay of treatment for patients with HF, the condition will continue to progress in a subset of patients whose quality of life significantly deteriorates and become at an increased risk of mortality. [8] CRT has been shown to improve heart function and quality of life in this group. [8, 19, 20] However, certain criteria have to be met for a patient to be eligible for a CRT device, including 1) advanced heart failure (New York Heart Association (NYHA) classes III or IV) despite optimal medical therapy ≥3

months, 2) evidence of severely impaired left ventricular (LV) function (ejection fraction (EF) ≤35%), and 3) QRS duration ≥130 msec on ECG.

3. Overview of CIED implantation procedure

A cardiac implantable electronic device (CIED) is an umbrella term encompassing a range of devices used to treat cardiac rhythm disorders, including bradyarrhythmia and ventricular arrhythmias. CIED systems typically consists of a pulse generator (battery and programmer), inserted in the pre-pectoral region of the chest (**Figure 3**), that is attached to one or more leads inserted in the heart chambers targeted for therapy. The programmer has built-in pacing modes to deal with any sense cardiac rhythm disorders. For access, an incision is made along the deltopectoral groove (**Figure 3**), followed by dissection until the cephalic vein is visualised, which is often the first choice of access to introduce the pacemaker lead(s) into the heart owing to the lower risk of vascular complications and pneumothorax with this approach. Other choices of access include axillary and subclavian veins. Implantation and fixation of the pacemaker leads is performed under fluoroscopic guidance.

Figure 3. A dual chamber PPM with two leads in the RV and RA.



PPM: permanent pacemaker; **RA**: right atrium; **RV**: right ventricle

4. Types and indications of CIED devices

Depending on the indication and intended therapy, CIED options include permanent pacemakers (PPM), cardiac resynchronisation therapy devices, with (CRT-D) or without (CRT-P) defibrillators, and implantable cardioverter-defibrillators (ICD). The indications for CIED use according to the 2013 ESC guidelines are illustrated in **Figure 5.** [19]

a) PPM

A PPM is a type of CIED that sends electrical impulses to one or more heart chambers, from the pulse generator and through the pacing lead, allowing them to contract when the native conduction system of the heart fails to work properly. It is primarily indicated for the management of bradyarrhythmia. [8, 19, 21] The leads are inserted into the right ventricle (RV) and also occasionally into the right atrium (RA), depending on the type of rhythm requiring therapy (single chamber or dual chamber PPM). The programming of the pacemaker may either be synchronous (on demand if an abnormal rhythm is detected) or asynchronous (active at all times). There are numerous indications of PPM, however, summarised in **Figure 5** are the most common and relevant indications to this thesis.

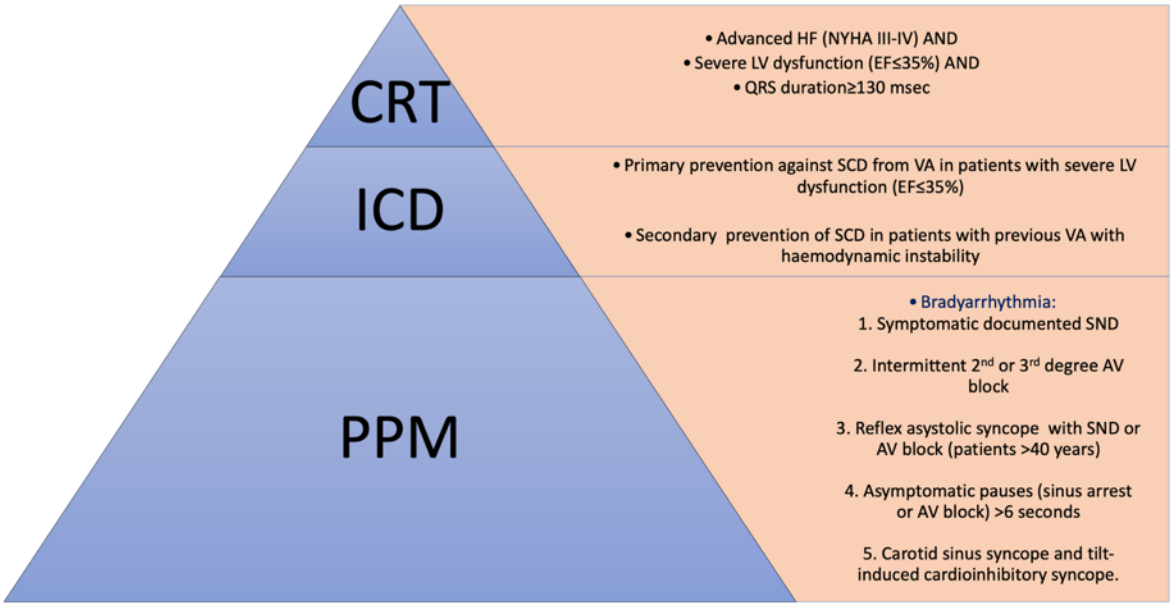
b) ICD

An ICD works in a similar mechanism to PPM, pacing the right ventricle in the event of a bradyarrhythmia, but has the additional feature of terminating dangerous ventricular arrhythmias that could lead to sudden cardiac death by delivering a shock through a coil in the implanted lead when it senses them, known as defibrillation, typically at an energy level between 20 and 35 joules. [22] ICD devices can either be implanted for primary prevention, in those at risk of fatal ventricular arrhythmias due to severely impaired LV function (EF ≤35%), or as a secondary prevention in those with a history of ventricular arrythmias with haemodynamic instability (severe drop in blood pressure and cardiac output, collapse or cardiac arrest). [8, 19]

c) CRT

CRT devices work in a similar mechanism to pacemakers, i.e., providing pacing in patients with bradyarrhythmia, but also coordinate the contraction of dyssynchronous left and right ventricles in patients with heart failure (HF) who often have a more impaired contraction in the left ventricle.[21] There are two types of CRT device, CRT with pacemaker (CRT-P) and CRT with defibrillator (CRT-D). The latter provides all the functions of a CRT device but also has the capabilities of a defibrillator, similar to an ICD, to terminate any sustained ventricular arrhythmias that may result in sudden cardiac death. The indications for CRT therapy are summarised in **Figure 5**.

Figure 5. Types and indications of CIED arranged by frequency of use in real-world practice



HF: heart failure; **LV:** left ventricular; **NYHA:** New York Heart Association; **VA**: ventricular arrhythmias

5. Epidemiology

Despite the paucity of epidemiological data on rates and characteristics of patients undergoing different types of devices, there is no doubt that the global number of procedures has increased in the last decade in proportion to the increasingly ageing and comorbid population in which electrical conduction disorders are more likely to occur.[6, 23-27] Furthermore, the growing evidence supporting the use of ICD and CRT devices contributes to this rise in CIED implantation procedures.[28-30]

a) PPM

The rate of utilisation of PPM has increased in recent years. The European Society Cardiology (ESC) survey in 2017 reported a 12% increase in PPM procedures in Europe, including the UK, between 2007 and 2016 (788 to 886 per million inhabitants). [31] Greenspon et al. reported a similar increase in the use of dual chamber pacemakers in the United States between 1993 and 2009 (29.1 to 50.4 per 100,000 population).[32]

b) ICD

Data from the ESC survey suggests that ICD implantations have risen by 42% in Europe between 2007 and 2016 (125 to 177 per million inhabitants). [31] Similar trends were observed in the US National Cardiovascular Data ICD Registry (NCDR-ICD), in which the number of single chamber ICD's increased from approximately 28,000 implantations in 2011 to 40,000 in 2014. [33]

c) CRT

The utilisation of CRT in managing patients with advanced heart failure who fulfil the eligibility requirements for the device has significantly increased in the last decade. In Europe, the use of CRT has doubled over a decade (2007-2016: 72 to 157 per million inhabitants). [31] A similar trend was observed in the UK over the same period (110 to 177 per million inhabitants). [31] Data from the National Health Insurance Service database in

Korea suggests a similar trend where CRT implantations have increased from 0.1 to 0.5 per 100,000 population between 2009 and 2016.

6. Importance of real-world evidence

Although randomised controlled trials (RCT's) are considered the most robust form of evidence, they often enrol highly selected cohorts with strict inclusion/exclusion criteria, meaning that their findings may not necessarily be extrapolated to the overall population of interest. [34-37] This has led to a growing interest in real-world outcomes research to fill a gap in evidence for those who may otherwise be excluded from RCT's, including patients with specific comorbidities and characteristics undergoing de novo CIED implantation. Bodies that appraise the latest technology and pharmaceuticals prior to their use in healthcare systems such as the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK), and the Food and Drug Administration (FDA) in the US, have the recognised the importance of real-world evidence in guiding their assessments. [38, 39] The present study utilised two large national datasets from the United States to study the relationship between patient-related factors and several real-world outcomes after CIED implantation with a focus on differences between types of CIED devices.

7. Factors influencing choice of CRT device (CRT-P vs. CRT-D)

Current guidelines do not provide clear recommendations on factors favouring implantation of CRT-D over CRT-P in patients eligible for CRT therapy.[40] A recent European study was the first to examine factors affecting the choice of device (CRT-P vs. CRT-D) in a multicentre survey, and showed that women, elderly patients (>75 years), and those with non-ischaemic heart failure and atrial fibrillation were less likely to receive CRT-D (vs. CRT-P).[41] However, their sample size was limited and it was believed that the survey captured no more than 11% of patients undergoing CRT therapy during that period, making them less generalizable to the wider CRT implantation population. The first

objective of my thesis aimed to address the current gap in evidence in that area by examining patient-related and institutional factors favouring therapy with either device.

8. Patient-related factors influencing procedural outcomes

a) Overview of procedural complications

While there have been significant advances in CIED implantation techniques, device and lead technology, as well as increased operator proficiency through dedicated training programmes, [42, 43] the reported rate of procedure-related complications has increased in proportion to the rise in global procedural volume.[44, 45]

Postprocedural complications range from 3 to 10%, [46-51] and range from **minor complications** such as pericardial effusion (fluid around the heart resulting from injury to heart vessels or chambers), haematoma at site of access (due to leaking vessels), pneumothorax (air in the chest), and venous thrombosis (clotting in the vein), to **major complications** including device-related infections, pericardial perforation (injury form the leads), venous tears or occlusion (during lead manipulation) and even death.[52] However, there is significant variability in the definitions of major and minor complications between studies. Although major complications are uncommon, they can be potentially fatal, and more complex device types (CRT and ICD) carry a higher risk of complications due to prolonged procedure time and lead manipulation, and bulkier leads. [53, 54]

In a Danish registry of more than 5000 patients, one in ten patients (9.5%) experienced a complication after CIED implantation, half of which were major complications (5.6%) including lead reinterventions, pneumothoraces, and local and systemic infection. [55] Infection is one of the most feared complications as it is associated with high risk of mortality and is the most common indication for a total CIED system extraction, an even more risky procedure than CIED implantation.[56] Greenspon et al. reported doubling of CIED-related infection rates (210% increase; 1.6% overall rate)

between 1993 and 2008, primarily due to increased utilisation of more complex devices (ICD) than pacemakers as well as rise in number of comorbidities.[44] Although rare, mortality is a recognised complication of CIED implantations. The majority of studies have reported an incidence of all-cause mortality between 0.2 and 0.8%, rising up to 4% in patients with concomitant infection.[44, 57, 58]

b) Patient-related predictors of complications

Data from several 'real-world' studies suggests that complications are common after CIED implantation and increase with advancing age and overall patient risk profile.[25, 44-50, 55]

A summary of the major studies reporting associations between patient-related factors and CIED procedural outcomes to date, along with their inclusion criteria, outcomes and limitations, are presented in Table 2.1. The findings from these studies are summarised in Table 2.2.

Age is the one of the most studied predictors of CIED procedural outcomes and has been shown to correlate with in-hospital mortality and overall complications as well as 1-year mortality in some but not all studies, with variations observed between device types. (Table 2.2) [23, 55, 59-61] Similarly, some studies have reported an increased risk of major and minor postprocedural complications among females undergoing different types of CIED, but sex was shown to have no correlation with 1-year mortality in those undergoing ICD implantation (HR males 0.97 (0.84–1.12)). [23, 55, 59, 60, 62-64] Patients of black ethnicity have also been shown to be at an increased risk of in-hospital complications including death (1.14 (1.05–1.24)) but not 1-year mortality (HR 1.08 (0.85–1.36)) compared with white ethnicity. [59, 60] Chronic kidney disease (CKD) and advanced HF are also a risk factor for in-hospital adverse outcomes, including death, (CKD: OR 1.50 (1.33–1.70); NYHA class III and IV OR: 1.15 (1.01–1.31) and 1.38 (1.17–1.63), respectively) after implantation of

all device types as well as 1-year mortality (HR CKD: 1.19 (1.04-1.36); HF: 2.15 (1.56–2.95)) after ICD implantation. [59, 60]

Some studies have reported a correlation between comorbidity burden as well frailty and procedural outcomes after CIED implantation, however these have been subject to limitations as discussed in the next section. A high comorbidity burden as measured by the Charlson Comorbidity index (CCI) score, was associated with increased odds of in-hospital mortality in heart failure patients undergoing ICD and CRT devices (OR CCI ≥3 vs. 0: ICD: 2.44 (1.47-4.05); CRT-P: 3.01 (1.17-7.77); CRT-D: 2.74 (1.62-4.65)).[61] Another study by Bhavnani et al. demonstrated a positive correlation between CCI score and 1-year mortality in those undergoing ICD implantations (de novo and upgrades) in a single tertiary centre (per unit CCI score: HR 1.40 (1.20–1.60)).[65]

c) Limitations of the current evidence

There is a lack of validated and well-established scoring systems for the risk assessment of patients undergoing CIED implantation, unlike with other procedures such as percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery. [66-70] This stresses the importance of studying the relationship between common patient characteristics and procedural outcomes in this procedural group, which would provide operators with a thorough evidence base for risk stratification and optimisation of patients prior to CIED implantation.

Although many studies have focused on associations between patient-related factors and outcomes of CIED implantations (Table 2.1), the majority of these have been subject to several limitations including 1) the focus on specific device types (e.g., ICD only) or patient groups (e.g. 65 years or those with heart failure only), 2) combined analysis of de novo as well as upgrade/replacement procedures (despite well-recognised differences in risks between each of these procedures), 3) the focus on single or composite outcomes (e.g.

death or any hospital complication) with variations in the definitions of complications in many studies. Furthermore, there is a significant variation in complication rates between different institutions, depending on their staffing level, procedural and operator volumes, and operator experience, stressing the importance of national level data.[71] For example, Kirkfeldt et al reported at least 1.5-fold rise in risk of complications in patients undergoing CIED implantation in centres with an annual procedural volume <750 procedures (0–249 procedures: aRR 1.6; 95% CI 1.1–2.2, 250–499: aRR 2.0; 95% CI 1.6–2.7, 500–749: aRR 1.5; 95% CI 1.2–1.8).[55] High hospital procedural volume (>190 cases per annum) was also shown to correlate with a lower odds of surgical complications (OR 0.64; 95% CI 0.50-0.82) and lead dislocation (ventricular leads: OR 0.39; 95% CI 0.30-0.50; atrial leads: OR 0.39; 95% CI 0.30-0.53) compared to hospitals with a low procedural volume (<50 cases per annum) in a German registry of 430,416 CIED implantations between 2007 and 2012. [43]

The previously described limitations could easily explain the inconsistencies in the current literature on patient-related factors influencing procedural outcomes. For example, Zhan et al. reported increased odds in the composite endpoint of 'any in-hospital complication' after CIED implantation (de novo and upgrades/replacements) in females undergoing CRT-D, ICD and PPM implantation and lower odds in females undergoing CRT-P implantation. [23] However, their cohort was outdated (1997-2004) with no CRT cases until 2003 and so does not reflect contemporary practice, and their single composite endpoint does not inform operators of the role of sex in individual procedural outcomes of CIED implantation. In contrast, an analysis by Shakya et al. demonstrated no difference in the composite endpoint of 'any hospital complication' undergoing PPM, CRT and ICD implantation. [64] Similarly, a study by Tsai et al. reported an increased risk of in-hospital complications including death in black (vs. white) patients undergoing ICD implantation

for primary prevention (OR 1.14 (1.05–1.24)) whereas a study by Al-Khatib et al. demonstrated no difference in 1-year mortality between black and white patients undergoing ICD implantation (HR 1.08 (0.85–1.36)), including de novo and upgrade procedures.[59, 60]

Most of the studies examining the role of frailty and comorbidity burden in CIED procedural outcomes to date have either measured frailty and/or comorbidity burden subjectively using age and number of comorbidities as a surrogate for these factors. [23, 61, 65, 72-75] However, not all frail individuals are elderly or are multimorbid.[76, 77] Similarly, not all comorbidities are similar in their prognostic impact, which is why established scoring systems such as the Elixhauser Comorbidity Score (ECS) and CCI are widely used as measures of overall comorbidity burden.[78] Each of the two scores assigns different weights to individual comorbidities, with a total score being generated to measure the level of comorbidity burden of an individual. However, few studies have employed the CCI score to examine the association between comorbidity burden and procedural outcomes, however, these were subject to the limitations mentioned above (e.g., specific device types, combined de novo and upgrade procedures, or single outcomes).

For studies examining the impact of CCI score on procedural outcomes, these have mainly focused on specific outcomes such as in-hospital or 1-year mortality, or a composite outcome of death and cardiac transplant. Therefore, there is limited information on the relationship between comorbidity burden, as measured by CCI, and post-procedural outcomes such as thoracic, cardiac complications and device-related complications in the context of de novo CIED implantation. One study by Swindle et. al. reported increased odds of in-hospital mortality with a high CCI score (≥3 vs. 0) in HF patients undergoing ICD and CRT devices.[61] However, this study included specific patient groups (HF) receiving specific device types (ICD and CRT, including de novo and upgrades).

Furthermore, a significant limitation in their analysis is that CCI≥3 was compared with a CCI score of 0, which is very unusual since patients with heart failure should have a minimum score of 1 for this very condition.

d) Gaps in the current evidence

- ***Device-specific outcomes***

  Despite the current evidence on factors that influence the clinical outcomes of CIED implantations to date, a myriad of patient-related factors remains understudied, especially according to the type of device. More complex devices (CRT and ICD) require longer procedure time and more prolonged lead manipulation, which may increase the risk of infection and vascular complications. [79, 80] Furthermore, patients undergoing more complex devices are often older and more comorbid and therefore more likely to experience a procedure-related complication. However, the majority of studies have not stratified outcomes by device type and only report outcomes of overall cohorts that may include a combination of PPM, CRT and ICD devices.

- ***Sex-differences in procedural outcomes***

  Several studies have looked at the associations between several patient characteristics such as sex and age, and adverse outcomes after CIED implantation. Notwithstanding, the studies looking at sex differences in procedural outcomes have been limited by the factors previously described (e.g., inclusion of specific devices or patient groups, combined analysis of de novo and upgrade/replacement procedures). Furthermore, it is unclear what trend such sex differences followed over the years in light of technical and technological advancements in CIED implantation procedures.

- ***Frailty***

Outcome data in specific population groups remains lacking. For example, no study has looked at the effect of frailty on CIED implantations. While age is often an indicator of frailty, there are many patients with biological frailty who fall outside commonly defined elderly age groups (>65 years) as described above in detail. [76, 77]

- ***Cancer patients***

  Similarly, there is a lack of evidence on patients with cancer (both historical and current diagnoses) undergoing CIED implantation, and how their outcomes compare with patients without cancer.

- ***Overall comorbidity burden***

  Another important factor is the overall burden of comorbidities and whether this has a role in procedural outcomes in patients undergoing *de novo* CIED implantation. Very few studies have considered the overall burden of comorbidity and measured it objectively using validated measures such as the CCI score to look at procedural outcomes of *de novo* CIED implantation.

All these gaps in evidence drive the need for outcomes data for these increasingly encountered risk groups, which would be of interest to patients, operators and stakeholders.

9. Current literature on patient-related factors predicting 30-day readmissions

a) Incidence and causes of 30-day readmission

Although the majority of procedure-related complications occur in the peri-procedural or immediate phase, some complications, especially device-related ones, can occur after discharge. [55, 81] Hospital readmissions are often seen as an indicator of the quality of care received in hospital and a burden for patients as well as healthcare systems, which led to certain countries such as the UK (since 2011) and US (since 2012) imposing fines or withholding payments for unplanned readmissions within 30 days. [82, 83]

Furthermore, data on the trends and causes of 30-day readmissions can help identify patients at risk of readmissions who would benefit from interventions to reduce their readmission rates as well as closer follow-up and monitoring post-discharge.

Studies looking at readmissions within 30 days show that this is quite common after CIED implantation, with the reported rates ranging between 12 and 15%. [84-88] Pasupula et al reported a modest decline in 30-day readmissions (14% to 13%) in patients undergoing CIED implantation between 2010 and 2014 in the US, with similar decline in device-related causes over the same period (4.5% to 3.9%).[89] In a tertiary centre analysis of 229 consecutive patients undergoing pacemaker implantation in the UK 30-day readmission rates were between 3.7% and 9.8% depending on discharge timing (same day vs. next day).[88]

Overall, cardiac causes represent a significant proportion of 30-day readmissions after CIED implantation. In a national study by Pasupula et al, heart failure represented nearly 10% of 30-day readmissions throughout the study period (2010-2014). [86] In another study by Patel et al. heart failure accounted for 11-26% of 30-day readmissions, highest in patients who underwent CRT-D implantation, with arrhythmias being the second most common cause of 30-day readmissions (4.7-10.8%). [87] Another study by Gillam et al. from the Australian Government Department of Veterans' Affairs database reported 30-day readmission rates of 5.2% for device-related complications.[85]

b) Patient-related predictors of 30-day readmission

There are limited data on patient-related factors that predict 30-day readmission, particularly for cardiovascular causes and device-related complications. Only two studies have looked at 30-day readmissions after CIED implantation to date and these were from the Nationwide Readmissions Database (NRD), which I will also be using to conduct my studies that focus on this outcome. [84, 87] A summary of predictors of 30-day readmission in

presented in Table 2.2. However, both studies examined patient-related predictors of overall 30-day readmission, without focusing on cardiovascular-specific causes. Furthermore, there were conflicting data on predictors of readmission between studies, which is likely due to their analytical strategy as discussed in detail in the relevant chapter (Chapter 9). For example, the lack of difference in 30-day readmissions in patients with congestive heart failure (CHF) in the study by Patel et. al (OR 1.05 (0.97-1.13)) despite it being associated with increased odds of readmission in the study by Ahmad et al. (OR 1.39 (1.30, 1.48)). [84, 87] On a similar note, older age (>50 years) was associated with reduced odds of all-cause 30-day readmission in the study by Ahmad et al. whereas no difference was found for the same outcome in those aged >50 years by Patel et al. [84, 87] Female sex has been shown to be correlate with all-cause 30-day readmission in two studies (OR 1.07 (1.04-1.11) and 1.09 (1.04-1.14) in two studies) as was chronic kidney disease in a study by Ahmad et al. (OR 1.97 (1.90-2.04)). [84, 87]

c) Gaps in evidence

- Although there is emerging evidence on the decline of 30-day readmissions in patients undergoing CIED implantation in general, there is no data on device-specific readmission rates and causes.[89]
- There is currently a lack of data on predictors of cardiac and device-specific 30-day readmissions after de novo CIED implantation, with the majority of studies reporting predictors of overall readmission and not specifically cardiac and device-related causes.

10. Chapter Tables

a) Table 2.1. Summary of studies reporting patient-related predictors of adverse outcomes and 30-day readmissions after CIED implantation (by year of publication)

Study/Year	Population	Type	Period	n=	Device Types	Outcome	Limitations
Al-Khatib 2008[59]	Stratified 5% sample of Medicare patients aged>65 years undergoing ICD implantation	Retrospective cohort study	2002-2005	8581	ICD (de novo or upgrades)	Mortality and any ICD complication at 1-year	Specific age group and type of device, old cohort, included do novo and upgrade procedures, analysed all ICD complications collectively
Zhan 2008[23]	CIED implantations in the US from the NIS database	Retrospective cohort study	1997-2004	2,230,677	PPM, ICD, CRT (de novo or upgrades)	Any in-hospital complication	Old cohort with virtually no CRT devices until 2003 coinciding with FDA approval at the time. Composite outcome. Non-specific and subjective measure of frailty based on age and comorbidities.
Peterson 2009[63]	De novo ICD implantations from the US National Cardiovascular Data Registry's (NCDR) ICD Registry	Retrospective cohort study	2006-2007	161,470	Single and dual chamber ICD's and CRT (de novo)	In-hospital major adverse events[c]	Relatively old cohort, specific device types, expansive composite outcome only.
Lee 2010[90]	Provincial (Ontario) registry of patients undergoing de novo ICD and CRT-D implantation	Retrospective cohort study	2007-2009	3,340	Single and dual chamber ICD's and CRT (de novo)	Major[a] and minor[b] device-related complications within 45 days	Specific device types, combined analysis of all ICD's, only focused on major and minor complications, regional cohort.
Swindle 2010[61]	Adults (≥18 years) with a diagnosis of heart failure who underwent ICD and CRT implantation from the PREMIER database.	Retrospective cohort study	2004-2005	26,887	ICD, CRT-P and CRT-D (de novo or upgrades)	In-hospital mortality	Single outcome, specific patient group (heart failure).
Tsai 2011[60]	Patients undergoing ICD for primary	Retrospective cohort study	2006-2008	150,264	ICD	Any adverse event or in-hospital mortality	Specific device type and patient group (primary prevention), single composite outcome

	prevention from the US NCDR ICD Registry						
MacFadden 2012[62]	Provincial (Ontario) registry of patients undergoing de novo ICD implantation	Retrospective cohort study	2007-2010	6,021	ICD (de novo)	Early (<45 days) and Late (≤1 year) Major[a] and Minor[b] Complications	Specific device type, only focused on major and minor complications, regional cohort.
Bhavnani 2013[65]	ICD implantation for the primary or secondary prevention of sudden cardiac death in a single tertiary centre	Retrospective cohort study	1997-2007	1,062	ICD and CRT-D	Early mortality (1-year)	Specific device, not clear if these were only de novo procedures or also included upgrades. Single centre analysis from a tertiary facility which may not be reflective or practice in other smaller centres.
Kirkfeldt 2014[55]	All Danish patients who underwent CIED procedures from May 2010 to April 2011	Retrospective cohort study	2010-2011	5,918	PPM, ICD, CRT (de novo or upgrades)	Major[d] and minor[e] device complications	Included de novo and upgrade procedures
Boriani 2016[72]	Consecutive HF patients undergoing de novo ICD or CRT-D device implant	Retrospective cohort study	2006-2010	1600	ICD, CRT-D (de novo)	Death/cardiac transplant (median follow up 1487 days (ICD) and 1516 days (CRT-D))	Small regional cohort, composite endpoint in regard to post-procedure mortality.
Green 2017[73]	De novo ICD implants for primary prevention amongst 65-year-olds from the NCDR ICD registry	Retrospective cohort study	2006-2009	83,792	ICD (de novo or upgrades)	1-year mortality	Specific device type and patient group (≥65 years), outdated cohort, single outcome.
Ruwald 2017[75]	All de novo ICD implants for primary and secondary prevention from the Danish nationwide clinical register	Retrospective cohort study	2007-2012	4334	ICD (de novo)	All-cause mortality (median follow up 2.52 years)	Non-specific and subjective measure of frailty based on number comorbidities.
Shakya 2017[64]	All CIED implantations from the Japanese	Retrospective cohort study	2010-2014	77,324	PPM, ICD, CRT (de	Any in-hospital complication	Cohort primarily pacemakers (84%), include de novo and upgrades/replacements, predictors are for a composite endpoint

	Diagnosis Procedure Combination database				novo or upgrades)		
Patel 2018[87]	All CIED implantation procedures from the US NRD database	Retrospective cohort study	2014	70,223	PPM, ICD, CRT (de novo or upgrades)	All-cause 30-day readmission	Included de novo and upgrade procedures. Predictors are for all-cause 30-day readmissions without a sub-analysis for cardiac-specific causes. Unusually low number of CIED procedures in comparison to studies from the same dataset for different years.
Ahmad 2018[84]	All CIED implantation procedures from the US NRD database	Retrospective cohort study	2013	290,420	PPM, ICD, CRT (de novo or upgrades)	All-cause 30-day readmission	Included de novo and upgrade procedures. Predictors are for all-cause 30-day readmissions without a sub-analysis for cardiac-specific causes.
Moore 2019 [91]	All adult CIED procedures in Australia and New Zealand	Retrospective cohort study	2010-2015	81,304	PPM, ICD, CRT (de novo or upgrades)	Major in-hospital complications	Included de novo and upgrade procedures. No stratification of in-hospital complication risk in females by CIED type.
Poupin 2020[74] (after PhD commencement)	Single-centre analysis of elderly (≥75 years) patients undergoing ICD implantation	Retrospective cohort study	2009-2017	363 (propensity matched)	ICD (de novo or upgrades)	5-year mortality (effect of comorbidity burden)	Specific device type and patient group (≥75 years), de novo as well as upgrades, single outcome, small sample size.

[a] lead dislodgment with repositioning, lead repositioning, lead replacement lead extraction, device problem—setscrew, device problem—pocket revision, myocardial perforation, pericardial tamponade, pneumothorax/haemothorax, pocket infection, skin erosion, pocket hematoma requiring intervention, clinical complications, pulmonary oedema, electrical storm, cardiogenic shock, post implant myocardial infarction, hypotension requiring resuscitation, sepsis, stroke, noncerebral embolus, death

[b] coronary venous dissection, subclavian vein thrombosis, renal insufficiency, incisional infection, peripheral nerve injury, non-superficial venous thrombus, lead dislodgement not repositioned, diaphragmatic stimulation, site pain, lead fracture not requiring intervention, pocket hematoma

[c] composite of cardiac arrest, cardiac perforation, cardiac valve injury, coronary venous dissection, haemothorax, pneumothorax, deep phlebitis, transient ischemic attack, stroke, myocardial infarction, pericardial tamponade, and arteriovenous fistula

[d] composite of lead-related re-interventions, local infections requiring re-intervention, CIED-related systemic infections or endocarditis, pneumothorax requiring drainage, cardiac perforation, pocket revisions because of pain, generator-lead interface problems requiring re-intervention, haematomas requiring re-intervention, deep venous thrombosis, Twiddler's syndrome, wound revisions, stroke, myocardial infarctions, and procedure-related deaths

[e] composite of haematomas resulting in a prolonged hospital stay, hospital re-admissions, or additional out-patient visits, wound infections treated with antibiotics, pneumothorax conservatively treated, and lead dislodgements without re-intervention

b) Table 2.2. Summary of patient factors associated with adverse outcomes in previous studies

Factor	Study	Outcome	Estimate	Predictive value	p-value
Age	Al-Khatib[59]	1-year mortality	HR	Per 5 years: 1.26 (1.20–1.33)	<0.001
	Kirkfeldt[55]	Major and Minor complications	aRR	Age 60-79 yrs. - reference **0-30 yrs:** Major: 1.30 (0.70–2.20), Minor: 0.50 (0.20–1.50) **40-59 yrs:** Major: 1.10 (0.80–1.50), Minor: 1.00 (0.70–1.50) **≥80 yrs:** Major: 0.60 (0.50–0.80), Minor: 1.00 (0.70–1.30)	0.36, 0.23 0.38, 0.94 0.001, 0.81
	Tsai[60]	Any adverse event or in-hospital mortality	OR	Age<65 yrs reference **65-69 yrs:** 1.02 (0.92-1.12) **70-74 yrs:** 1.08 (0.98-1.19) **75-79 yrs:** 1.14 (1.03-1.25) **80-84 yrs:** 1.22 (1.10-1.36) **≥85 yrs:** 1.15 (1.01-1.32)	 0.76 0.11 <0.05 <0.001 <0.05
	Swindle[61]	In-hospital mortality	OR	Age (≥80 vs. 19-79 yrs) ICD: 2.12 (1.19-3.79) CRT-P: 2.98 (1.15-7.73) CRT-D: NS	 0.01 0.02 NS
	Zhan[23]	Any in-hospital complication	OR	Age 25-64 yrs reference **65-74 yrs:** 1.08 (CRT-D), 0.79 (CRT-P), 0.79 (ICD), 0.88 (PPM) **75-84 yrs:** 0.97 (CRT-D), 0.86 (CRT-P), 1.04 (ICD), 1.03 (PPM) **85+ yrs:** 1.09 (CRT-D), 0.45 (CRT-P), 1.34 (ICD), 0.86 (PPM)	 NS, NS, <0.01, NS NS, NS, NS, NS NS, <0.01, <0.05, <0.05
	Ahmad[84]	All-cause 30-day readmission	OR	Age (<50 yrs reference) **51-60 yrs:** 0.94 (0.89-1.01) **61-70 yrs:** 0.85 (0.80-0.90) **71-80 yrs:** 0.83 (0.78-0.88) **>80 yrs:** 0.87 (0.82-0.92)	 0.084 <0.001 <0.001 <0.001
	Patel [87]	All-cause 30-day readmission	OR	Age (18-50 yrs) – reference **51-75 yrs:** 0.94 (0.85-1.08) **≥76 yrs:** 0.95 (0.85-1.07)	 0.31 0.44
Sex	Al-Khatib[59]	1-year mortality	HR	Males: 0.97 (0.84–1.12)	0.67
	Lee 2010[90]	Major and Minor complications	HR	Women: Major: 1.49 (1.02-2.16) Minor: 1.28 (0.91-1.80)	0.037
	Moore[91]	Any major in-hospital complications	OR	Female: Overall: 1.20 [1.11, 1.30]	<0.001 0.06

				PPM: 1.06 [1.00, 1.13] ICD: 1.25 [1.09, 1.44] CRT: 1.22 [1.04, 1.43]	0.002 0.01
	Peterson[63]	Major adverse events	OR	Women 1.71 (1.57-1.86)	-
	Kirkfeldt[55]	Major and Minor complications	aRR	Women: Major: 1.40 (1.20–1.80) Minor: 1.20 (0.90–1.50)	 <0.001 0.22
	MacFadden[62]	Major and Minor complications	OR	Women: Major: 1.78 (1.24–2.58) Minor: 1.55 (1.09–2.20) Any: 1.50 (1.12–2.00)	 0.002 0.014 0.006
	Tsai[60]	Any adverse event or in-hospital mortality	OR	Women: 1.31 (1.24-1.39)	<0.001
	Zhan[23]	Any in-hospital complication	OR	Female: 1.28 (CRT-D), 0.64 (CRT-P), 1.58 (ICD), 1.62 (PPM)	<0.01 for all
	Shakya[64]	Any in-hospital complication	OR	Female: 1.09 (0.99-1.21)	0.086
	Ahmad[84]	All-cause 30-day readmission	OR	Female: 1.07 (1.04-1.11)	<0.001
	Patel [87]	All-cause 30-day readmission	OR	Female: 1.09 (1.04-1.14)	0.001
Race	Al-Khatib[59]	1-year mortality	HR	Black: 1.08 (0.85–1.36) – reference is white	0.55
	Tsai[60]	Any adverse event or in-hospital mortality	OR	Black: 1.14 (1.05–1.24) – reference is white	<0.01
CHF	Al-Khatib[59]	1-year mortality	HR	2.15 (1.56–2.95)	<0.001
	Tsai[60]	Any adverse event or in-hospital mortality	OR	NYHA I reference NYHA II: 0.92 (0.81–1.05) NYHA III: 1.15 (1.01–1.31) NYHA IV: 1.38 (1.17–1.63)	 0.23 <0.05 <0.001
	Ahmad[84]	All-cause 30-day readmission	OR	1.39 (1.30, 1.48)	<0.001
	Patel [87]	All-cause 30-day readmission	OR	1.05 (0.97-1.13)	0.23
CKD	Al-Khatib[59]	1-year mortality	HR	1.19 (1.04-1.36)	<0.001

	Tsai[60]	Any adverse event or in-hospital mortality	OR	1.50 (1.33–1.70)	<0.001
	Ahmad[84]	All-cause 30-day readmission	OR	1.97 (1.90-2.04)	<0.001
	Shakya[64]	Any in-hospital complication	OR	1.53 (1.24-1.88)	<0.001
PVD	Al-Khatib[59]	1-year mortality	HR	1.18 (1.02-1.37)	0.03
Frailty/ Comorbidity burden	Swindle[61]	In-hospital mortality	OR	Charlson comorbidity index ≥3 vs. 0 **ICD:** 2.44 (1.47-4.05) **CRT-P:** 3.01 (1.17-7.77) **CRT-D:** 2.74 (1.62-4.65)	 0.02 <0.001 <0.001
	Zhan[23]	Any in-hospital complication	OR	Comorbid disease (0 is reference) **1:** 1.18 (**CRT-D**), 0.90 (**CRT-P**), 0.87 (**ICD**), 0.84 (**PPM**) **2:** 0.99 (**CRT-D**), 1.75 (**CRT-P**), 0.99 (**ICD**), 0.84 (**PPM**) **≥3:** 1.31 (**CRT-D**), 1.08 (**CRT-P**), 1.03 (**ICD**), 0.96 (**PPM**)	 <0.01, NS, <0.05, <0.01 NS, <0.01, NS, <0.01 <0.01, NS, NS, NS
	Green[73]	1-year mortality	OR	Frailty: ~4.00 Frailty + Dementia: 8.68 (7.33–10.27)	- -
	Poupin[74]	5-year mortality	HR	Univariate HR (reference CCI score 0) **CCI score 1-3:** 1.40 (0.67–2.94) **CCI score ≥4:** 3.41 (1.64–7.11)	 0.37 0.001
	Ruwald[75]	All-cause mortality	HR	Reference: No comorbidity burden Primary prevention indication: **Comorbidity burden=1:** 2.10 (1.40-3.10) **Comorbidity burden=2:** 3.70 (2.40-5.70) **Comorbidity burden=3:** 6.60 (4.20-10.30) Secondary prevention indication: **Comorbidity burden=1:** 2.20 (1.60-3.00) **Comorbidity burden=2:** 3.80 (2.70-5.30) **Comorbidity burden=3:** 5.80 (4.00-8.40)	<0.001 for all
	Boriani[72]	Death or cardiac transplant	HR	CCI (per unit score) ICD patients: 1.23 (1.16, 1.30) CRT-D patients: 1.18 (1.11, 1.26)	<0.0001 for both
	Bhavnani[65]	1-year mortality	HR	CCI (per unit score): 1.40 (1.20–1.60) CCI class (CCI 0 is reference): **CCI 1:** 0.97 (0.45, 2.08) **CCI 2:** 2.38 (1.15, 4.97) **CCI 3:** 4.30 (2.10, 8.93) **CCI 4:** 4.81 (1.74, 8.34)	 -

				CCI ≥5: 5.14 (2.00, 15.10)	

NS: non-significant

Chapter 3. Methods

In this chapter, I provide an overview of methods used for conducting the work in my thesis, including information on the datasets from which the study cohorts were derived, the analytical strategies followed, and the pre-defined outcomes for all the chapters that follow.

1. Study datasets

I undertook the work in this thesis from two datasets: The National Inpatient Sample (years 2004 to 2014) and the Nationwide Readmissions Database (years 2010 to 2015, and 2015 to 2017 in one project). These years were specifically chosen owing to the availability of data at the time of the work since there is a two-year lag between hospitalisations in a calendar year and the availability of data for researchers. For example, in 2018, the latest available data was for 2016 hospitalizations. Another important aspect I considered was the difference in International Classification of Diseases (ICD) coding versions used in the earlier (2004 through September 2015; ICD-9) and later years (October 2015 onwards; ICD-10), meaning that they cannot be combined due to differences in diagnostic and procedural definitions between coding versions. Further information on the structure and content of both datasets is provided below.

a) The National Inpatient Sample

i. Overview

The National Inpatient Sample (NIS) is the largest publicly available all-payer database of hospitalized patients in the United States and is sponsored by the Agency for Healthcare Research and Quality as a part of the Healthcare Cost and Utilization Project (HCUP). [92] It includes anonymized data on primary and secondary discharge diagnoses and procedures from more than 7 million hospitalizations annually. The NIS dataset was

designed to approximate 20% stratified sample of United States hospitals and provides sampling weights to calculate national estimates that represent more than 95% of the US population The estimates of hospital characteristics, numbers of discharges, length of stay, and in-hospital mortality from the HCUP Nationwide Inpatient Sample (NIS) were highly comparable to three related data sources in a previous analysis: the American Hospital Association (AHA) Annual Survey Database, the National Hospital Discharge Survey (NHDS) from the National Center for Health Statistics, and the MedPAR inpatient data from the Centers for Medicare and Medicaid Services (CMS) [93]

ii. Data structure

Each record in NIS represents a unique hospitalization episode and there can be multiple episodes for each patient during the same calendar year. However, there is no way of tracking multiple admissions for the same patient over the year since the record number is unique to the hospitalization episode and not the patient. NIS contains sociodemographic information including patient age, sex, race, household income, hospital region, type of admission (elective vs emergency), day of admission (weekend vs weekday), type of admitting hospital (location, bed size, teaching status), in-hospital status at discharge (death vs no death) as well as 27 Elixhauser comorbidities (acquired immune deficiency syndrome, alcohol abuse, deficiency anaemia, chronic blood loss anaemia, rheumatoid arthritis/collagen vascular diseases, congestive heart failure, chronic pulmonary disease, coagulopathy, diabetes (uncomplicated), diabetes with chronic complications, drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurological disorders, obesity, paralysis, peripheral vascular disorders, pulmonary circulation disorders, renal failure, solid tumour without metastasis, peptic ulcer disease excluding bleeding, valvular heart disease, and weight loss) Furthermore, there are up to 30 diagnosis fields and 15 procedure fields codes using the

International Classification of Disease, Ninth Revision (ICD-9) and Clinical Classification Software (CCS) systems These fields are used to identify additional diagnoses and procedures in the admission episode.

b) The Nationwide Readmissions Database

i. Overview

The Nationwide Readmissions Database (NRD) is a nationally representative sample of all-age, all-payer discharges from United States (US) non-federal hospitals sponsored by the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality (AHRQ) and is a database of inpatient stays and readmissions that can be used to generate national estimates of readmissions. [94] The NRD dataset constitutes a stratified sample from 22 states with anonymized data from more than 17 million hospitalizations annually from 22 states and provides sampling weights to calculate national estimates that represent more than 50% of the US population (approximately 36 million hospitalizations per annum).

ii. Data Structure

Each individual record represents a unique hospitalization episode and there can be multiple episodes for each patient during the same calendar year. Unlike NIS, individual patient readmissions can be tracked across the calendar year in NRD and data on the 'days to readmission' between episodes is available within the dataset. However, patients may not be tracked across multiple years. This was not an issue for the purpose of my thesis since I only included patients with a de novo CIED implantation and looked at 30-day readmissions. Therefore, only patients admitted in December of each year were not possible to study in terms of 30-day readmissions. The NRD contains sociodemographic information including patient age, sex, race, median household income quartile, hospital region, type of admission (elective vs. emergency), day of admission (weekend vs. weekday), type of

admitting hospital (location, bed size, teaching status), in-hospital status at discharge (death vs no death) as well as 27 Elixhauser comorbidities (acquired immune deficiency syndrome, alcohol abuse, deficiency anaemia, chronic blood loss anaemia, rheumatoid arthritis/collagen vascular diseases, congestive heart failure, chronic pulmonary disease, coagulopathy, diabetes (uncomplicated), diabetes with chronic complications, drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurological disorders, obesity, paralysis, peripheral vascular disorders, pulmonary circulation disorders, renal failure, solid tumour without metastasis, peptic ulcer disease excluding bleeding, valvular heart disease, and weight loss). Furthermore, there are up to 30 diagnosis fields and 15 procedure fields codes using the International Classification of Disease, Ninth Revision (ICD-9) in the years 2010 to 2015 (30th September) and up to 40 diagnosis fields and 25 procedure fields using ICD-10 (Tenth Revision) from October 2015 onwards. These fields are used to identify additional diagnoses and procedures during the admission episode.

2. Data curation

a) Cohort extraction

Both NIS and NRD datasets are provided in separate calendar years, each formed of four individual files including core data (admission-related and sociodemographic information), diagnoses and procedure data, severity data and hospital data. Identification and extraction of cardiac implantable electronic device (CIED) cohorts for analysis were based on ICD-9 procedure codes (and ICD-10 in one study from NRD) from the diagnosis and procedure data: permanent pacemaker (ICD-9: PPM: [3770 or 3771 or 3772 or 3773] and [3780 or 3781 or 3782 or 3783]; ICD-10: Single chamber: 0JH634Z 0JH635Z 0JH604Z 0JH605Z and Dual chamber: 0JH636Z 0JH606Z) cardiac resynchronisation therapy with defibrillator (CRT-D, ICD-9: 0051, ICD-10: 0JH639Z 0JH609Z), cardiac resynchronisation

therapy with defibrillator (CRT-P, ICD-9: 0050, ICD-10: 0JH637Z 0JH607Z) and implantable cardioverter defibrillator (ICD, ICD-9: 3794 or [3795+3796], ICD-10: 0JH638Z or 0JH608Z). Following extraction of the procedure cohort for each year, all 4 files (core, diagnoses and procedure, severity and hospital) were merged. Data for other comorbidities, procedures and complications were also extracted using the ICD-9 and Clinical Classification Software (CCS) codes listed in Table 3.1 and ICD-10 codes in Table 3.2 for one study from NIS. ICD-9 codes for cancer diagnoses, which were used in one of the projects specifically, are presented in the relevant chapter (Table 6.1 in Chapter 6). A literature review was performed to agree on validated ICD codes that correctly identify in-hospital outcomes and patient characteristics from both administrative datasets (NIS and NRD). Causes of readmission in the NRD datasets were identified using CCS codes for the years 2010 to 2015 (September), a full list of which is presented in the relevant chapter (Table 9.1 in Chapter 9). All cohort extractions and generation of variables were performed using STATA 14 statistical software (College Station, Texas, USA) while analyses were performed using STATA 14 and the Statistical Package for the Social Sciences (SPSS) version 26 (Armonk, NY, USA) software.

b) Identifying de novo CIED implantations

De novo CIED implantations were identified by excluding patients with no prior PPM or ICD in situ (ICD-9 diagnosis codes V4500/V4501 and V4502, respectively, and ICD-10 codes Z950 and Z95810, respectively) as well CIED removal or replacement procedures (ICD-9 procedure codes: 3775, 3776, 3777 and 3797, ICD-10: OJPTOPZ, 02PA3MZ).

c) Specific considerations for NRD (including 30-day readmissions)

The primary outcome of interest in studies from NRD was 30-day readmission. After identification of the de novo CIED procedure for a patient, this was then considered the index episode. All previous episodes were excluded. I employed commands to generate a 'admissionnumber' variable that represents sequential numbering of all subsequent episodes after the index admission (N+1, N+2, N+3, etc) based on a byte sequence that takes in to account the patient's unique identifier (nrd_visitlink variable) and time to readmission variables. Unique identifiers with an 'admissionnumber' value>1 whose time to readmission from the index event was ≤30 days (identified in a variable labelled readmitted30days) were then exported to a new dataset as these represented the group of interest. All duplicates of these ID's were removed in the new datasets and the unique ID's were then merged back to the original dataset using a one-to-many merge command to flag all patient's unique identifiers who were readmitted within 30 days (flag variable: thirtydayreadmissionflag). An example of this process is provided below.

d) Missing data

Variables with missing data included in-hospital death, length of stay, median household income, primary expected payer (insurance status), elective or weekend admission status, and hospital bed-size, location and teaching status. Data inspection showed these were all missing at random at rates of less than 5%, therefore unlikely to influence any statistical

inferences if excluded. As such, cases with missing values for these variables were excluded and this was guided by previous statistical literature. [95, 96] The frequency of missing data for each of the studies is presented in the relevant chapters.

3. Outcomes

The NIS dataset only captures in-hospital outcomes. The following in-hospital outcomes will be looked at in each study, all identified using the International Classification of Diseases coding system (Table 3.1, Table 3.2):

a) **Mortality:** predefined in the dataset.
b) **Post-procedural haemorrhage:** Defined as any procedure-related bleeding, excluding haematomas, as these reflect small, localised bleeding and could lead to overestimation of bleeding events.
c) **Thoracic complications:** Composite of acute haemothorax and/or pneumothorax, thoracic vascular injury and chest drain insertion (for haemothorax or pneumothorax; to ensure full capture of both events)
d) **Cardiac complications:** Composite of cardiac tamponade, pericardial effusion and pericardiocentesis (usually for cardiac tamponade and significant pericardial effusion; to ensure full capture of both events)
e) **Device-related infection.**
f) **Device-related complications** in readmission studies from NRD with ICD-10 coding system: composite of device-related infection, lead revision, wound disruption, revision of pocket, and device-related complications.
g) **MACCE (Major adverse cardiovascular events):** Composite of all-cause mortality, acute ischaemic stroke, thoracic and cardiac complications, and device-related infection (or device-related complications in ICD-10 studies).

4. Descriptive Methods

Continuous variables in NIS and NRD were primarily age and length of stay, both of which were not normally distributed. Therefore, both were summarized using medians and interquartile range (IQR) and were compared using the Kruskal-Wallis test. In certain studies, means were compared for categorical variables using the ANOVA test. Categorical variables were summarized as percentages and analysed using the chi squared (X^2) test.

5. Multivariable modelling

Multivariable logistic regression modelling was performed to examine the association between the outcomes of interest (e.g., death, 30-day readmission) and the predictor variables in question (e.g., sex, type of CIED implanted). Further information on outcomes and predictor variables included in models for my studies are discussed in individual chapters. The goodness-of-fit of models was assessed using the Hosmer-Lemeshow statistic. [97]

6. Tables

Table 3.1 ICD-9 search codes for procedures and diagnoses

Variable	Source	Diagnostic (D)/ Procedural (P)	Codes
Diagnoses			
Dyslipidaemia	CCS	D	53
Smoking Status	ICD-9	D	V1582, 3051
AF	ICD-9	D	42731
History of IHD	ICD-9	D	41400-07, 4142-9
Previous MI	ICD-9	D	412
Previous PCI	ICD-9	D	V4582
Previous CABG	ICD-9	D	V4581
Previous CVA (TIA and Stroke)	ICD-9	D	V1254
PPM in situ	ICD-9	D	V4500 V4501
ICD in situ	ICD-9	D	V4502
Dementia (Presenile, Senile, Vascular and Alzheimer's)	ICD-9	D	29010-13, 29020-21, 29040-43, 29410-11, 3310
Thrombocytopenia	ICD-9	D	2875,28749
Heart Failure	ICD-9, CCS	D	428x plus CCS: 108, 72111, 72112
Ventricular Tachycardia/Fibrillation	ICD-9	D	4271 (VT – paroxysmal and/or sustained), 42741 (VF)
In-hospital procedures and outcomes			
PPM	ICD-9	P	[3770 or 3771 or 3772 or 3773] + [3780 or 3781 or 3782 or 3783]
CRT-P	ICD-9	P	0050
CRT-D	ICD-9	P	0051
ICD	ICD-9	P	3794 or (3795+3796)
Lead revision	ICD-9	P	3775
Revision or relocation of pocket	ICD-9	P	3779
Acute ischemic stroke	ICD-9	D	43301, 43311, 43321, 43331, 43381, 43391, 43401, 43411, 43491, 4350-1, 4358-9, 436
Major bleeding	ICD-9	D	430, 431, 432*, 4590, 578*, 7847, 7863, 99811 (procedure-related bleeding)
Shock during admission	ICD-9	D	78551
Hemopericardium	ICD-9	D	4230
Pericardiocentesis	ICD-9	P	370
Cardiac tamponade	ICD-9	D	4233
Pneumothorax	ICD-9	D	51289, 5121, 8600-1
Hemithorax	ICD-9	D	8602-3
Chest Drain Insertion	CCS	P	39
Cardiac Arrest	ICD-9	D	4275
Device related infection	ICD-9	D	99661
Fever	ICD-9	D	78060-64
Bacteraemia/Viremia	ICD-9	D	7907/7908
Septicaemia	ICD-9	D	038x
Thoracic/Upper Limb Vascular injury	ICD-9	D	901x, 9031, 9038-9, 9001

CCS: Clinical classification Software; ICD-9: International Classification of Diseases, Ninth Revision

Table 3.2 ICD-10 Search codes for procedures and diagnoses

Variable	Diagnostic (D)/ Procedural (P)	Codes
Diagnoses		
STEMI	D	I210* I211* I212* I213
NSTEACS	D	I214 I219 I200 (UA)
Type 2 MI	D	I21A1
CKD 3-5	D	NI83 NI84 NI85 NI86
Bradyarrhythmia	D	I440 I441 I442 R001
Tachyarrhythmias	D	R000 I47* I4901 I4902
Dyslipidaemia	D	E78*
Smoker	D	Z720
Cardiac arrest	D	I462 (due to cardiac condition); I468 and I469 (due to non-cardiac condition)
Heart Failure	D	I50* Cardiomyopathy: I42*
Ischemic cardiomyopathy	D	I25.5
Ventricular Tachycardia/Fibrillation	D	VF: I4901 I4902; VT: I470 I472
AF	D	I4891 I4820-21 I4811 I4819 I480
History of IHD	D	I2510 I25110 I25111 I25118 I25119 I257* I258* I259*
Previous MI	D	I252 I256
Previous PCI	D	Z9861
Previous CABG	D	Z951
Previous CVA (TIA and Stroke)	D	Z8673
PPM in situ	D	Z950
ICD in situ	D	Z95810
Dementia (Presenile Senile Vascular and Alzheimer's)	D	F01* F02* F03*
Thrombocytopenia	D	D694* D695* D696*
Homelessness	D	Z590
Transsexualism	D	F640
Chronic renal failure	D	N18*
Hypertension	D	I10*
Anaemias	D	D62* D63* D64*
Chronic Lung Disease (including bronchitis, COPD, asthma and bronchiectasis)	D	J41* J42* J43* J44* J45* J47*
Diabetes	D	E08* E09* E10* E11* E13*
Coagulopathies	D	D65 D66 D67 D68* D69*
Liver disease	D	K70* K721* K729* K73* K74* K75* K76* K77*
Metastatic disease	D	C77* C78* C79* R180* C7B*
Cancers	D	C00-C96
PVD	D	I70* I73*
Valvular heart disease	D	I34* I35* I36* I37*

In-hospital procedures and outcomes		
Acute ischemic stroke	D	I63*
Major bleeding	D	I60* I61* I62* R58 K920 K921 K922
Procedure-related bleeding	D	Complicating CA or PCI: I97410 and I97610; Complicating CABG: I97411 and I97611 I976* I974*
Acute Kidney Injury	D	N17*
Cardiogenic shock	D	R570
Use of assist device or IABP	P	5A02110 5A0211D 5A02216 02HA3RJ 02HA3RZ
Hemopericardium	D	I312
Pericardial effusion	D	I313
Pericardiocentesis	P	0W9D40Z
Cardiac tamponade	D	I314
PPM	P	Single chamber: 0JH634Z 0JH635Z 0JH604Z 0JH605Z Dual chamber: 0JH636Z 0JH606Z
CRT-P	P	0JH637Z 0JH607Z
CRT-D	P	0JH639Z 0JH609Z
ICD	P	0JH638Z 0JH608Z
Leadless (intracardiac) pacemaker	P	LA: 02H73NZ RA: 02H63NZ RV: 02HK3NZ LV: 02HL3NZ
Removal of pulse generator or lead (exclusion criteria to identify de novo implants)	P	OJPTOPZ 02PA3MZ
CIED Device-related infection	D	T814* T827
Wound disruption	D	T813*
Mechanical complications of CIED implant	D	T821
Pneumothorax	D	J93*
Pleural effusion and haemothorax	D	Haemothorax: J942 Pleural effusion: J90 and J91
Pleural drainage	P	0W9900Z 0W9930Z 0W9940Z 0W9B00Z 0W9B30Z 0W9B40Z
Postprocedural shock	D	Other: T8110* and T8119* Cardiogenic: T8111* Septic: T8112*
Vascular complication of procedure	D	T817*
Lead revision	P	02WA3MZ
Revision or relocation of pocket	P	0JWT3PZ

ICD-10-CM: International Classification of Diseases Tenth Edition Clinical Modification

Chapter 4. Patient-related predictors of CRT device type

The work presented in this chapter is based on the study published in the Canadian Journal of Cardiology (Appendix 1).[98]

1. Introduction

International societies recommend cardiac resynchronization therapy (CRT) as a class I recommendation for the management of patients with symptomatic heart failure (New York Heart Association (NYHA) class III or IV) with reduced ejection fraction (<35%) despite 3 months of optimal medical therapy, as well as the presence of bundle branch block (≥130 milliseconds).[20, 21, 99-101] However, there are limited data in current guidelines to inform operators on the choice of device type (CRT with pacemaker or defibrillator; CRT-D and CRT-P, respectively) based on patient risk factors or comorbidities.[40] While guidance is given to consider factors such as life expectancy, severe renal failure and patient frailty status, the decision on device type is often left to the operators' judgement.[21, 40] This drives the need for data on patient-related factors that are predictive of receipt of CRT-D vs. CRT-P in the real-world setting.

Furthermore, limited data exist on sex differences in the rate of utilization of both CRT device types, and whether sex has an influence on the choice of device therapy. The European Society of Cardiology (ESC) CRT Survey II reported that females were more likely to receive a CRT-P than a CRT-D device.[41] This survey was the first to examine predictors of receipt of CRT-P in a European cohort of approximately 11,000 patients undergoing CRT implantation between October 2015 and January 2017. However, the survey was only representative of 11% of all CRT procedures in Europe, rendering their

findings less generalizable to the wider European population and other healthcare systems.

2. Objectives

My main objectives of this chapter were to study the following:

a) Patient-related predictors of type of CRT device offered to those who qualify for this therapy.

b) Whether sex differences in the choice of CRT device type exist and, if so, what trend has this disparity followed over the last decade.

3. Methods

A full description of the methodology relating to all chapters of my thesis is provided in Chapter 3.

a) Data Source

This section of my thesis was based on a retrospective analysis of all de novo CRT implantation procedures between 2004 and 2014 from the United States (US) National Inpatient Sample (NIS) database, which is sponsored by the Agency for Healthcare Research and Quality as a part of the Healthcare Cost and Utilization Project (HCUP). [92] Further details on the structure and validation of NIS are provided in Chapter 3 of this thesis. Importantly, NIS contains annual hospitalisations from approximately 49% of community hospitals in the US but does not offer linkage of patients over multiple years. Furthermore, the record identifier in NIS is unique to the hospitalization episode and not the patient. Therefore, multiple admissions for the same patient cannot be identified. However, this is not a limitation in the context of de novo CRT procedures and would have only posed an issue if I had included upgrades and/or revisions.

b) Study Design and Population

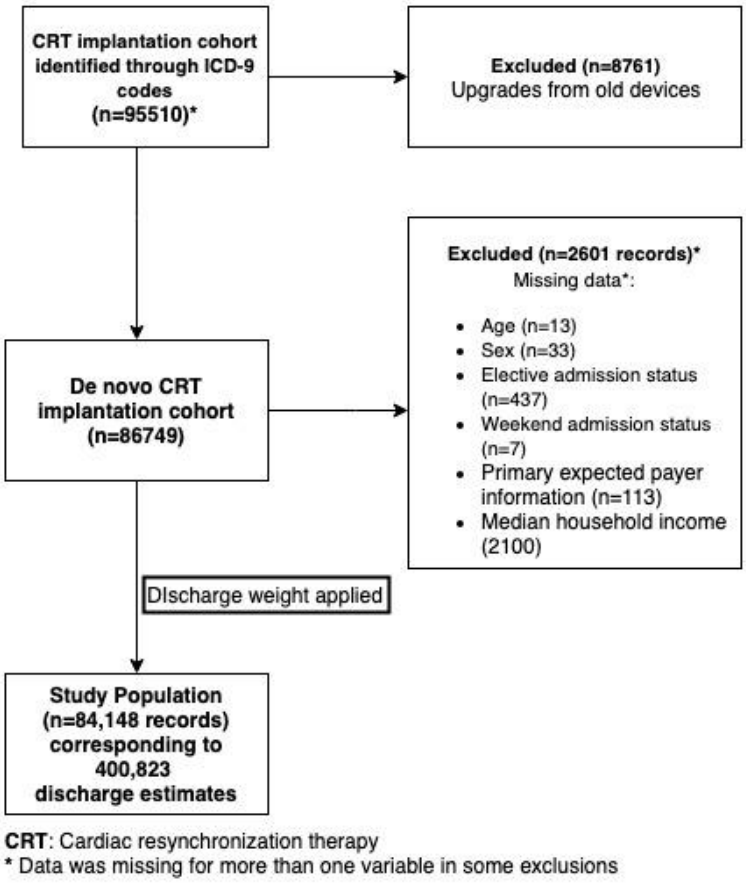
All adults (aged ≥18 years) undergoing *de novo* CRT implantation between 2004 and 2014 were included in my analysis, identified using the International Classification of Diseases, ninth revision (ICD-9) procedure codes (CRT-P 00.51; CRT-D 00.52), stratified in to two groups according to device type: CRT-P and CRT-D. I excluded CRT upgrades and records with missing data (study flow diagram for exact variables and frequencies: **Figure 4.1**). Cases excluded due to missing variables represented 3% (n=2601 unweighted records) of the cohort. Patient characteristics, comorbidities, and clinical outcomes were extracted using the ICD-9 procedure and diagnosis codes provided in **Table 3.1** in Chapter 3. A CRT response score (range 0-4) was also generated to assess the predicted response of patients to CRT, which may have influenced operators' choice of device type.[102] The 4 variables in the CRT score are: presence of 1) left bundle branch block (LBBB) and 2) non-ischemic cardiomyopathy and absence of 3) atrial fibrillation (AF) or 4) chronic kidney disease (CKD).

c) Outcomes

The primary outcome was receipt of CRT-D compared with CRT-P. Secondary outcomes were in-hospital adverse events, including major acute cardiovascular events (MACE), all-cause mortality and procedural-related complications (bleeding, thoracic and cardiac). In-hospital MACE was defined as a composite of all-cause mortality, cardiac complications, thoracic complications and device-related infection. Procedure-related bleeding included any post-procedural haemorrhage or anaemia after haemorrhage, cardiac complications were a composite of cardiac tamponade, hemopericardium, pericardial effusion and pericardiocentesis, whereas thoracic

complications were defined as a composite of acute pneumothorax or haemothorax, with or without drainage, or thoracic vascular injury.

Figure 4.1 Study flow diagram



d) Statistical Analysis

Descriptive statistics were performed as previously explained in Chapter 3. Sampling weights provided by the AHRQ were applied to all analyses. All statistical analyses were performed using SPSS version 24 (IBM Corp, Armonk, NY).

Several multivariable logistic regression models were constructed to examine predictors of receipt of CRT-D (reference CRT-P) as well as the association between female sex and in-hospital outcomes stratified by device type. All multivariable models adjusted for differences in socioeconomic, clinical, and hospital-level covariates that may directly influence in-hospital outcomes (age, race, weekend admission, primary

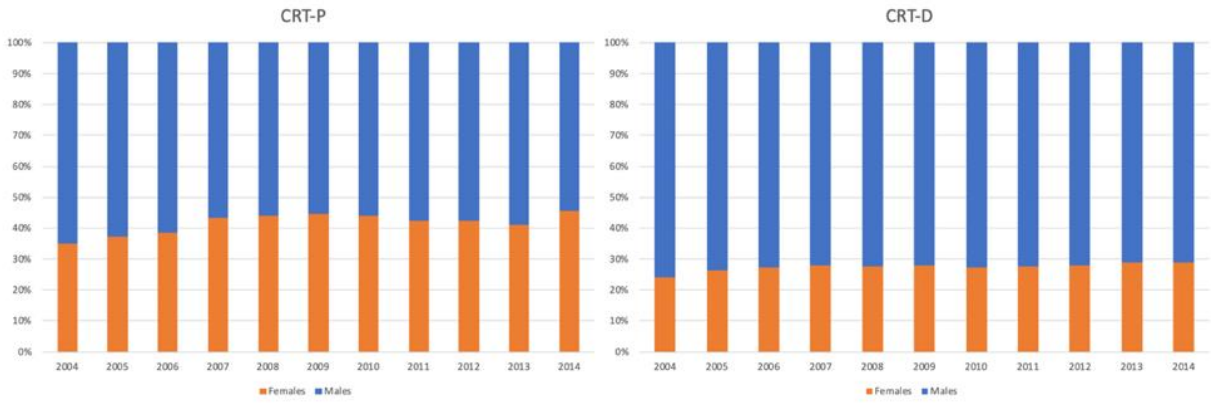
expected payer, median household income, dyslipidaemia, smoking status, previous acute myocardial infarction (AMI), previous coronary artery bypass graft (CABG), previous percutaneous coronary intervention (PCI), previous cerebrovascular accidents (CVA) including stroke and transient ischemic attacks (TIA), thrombocytopenia, history of cardiac arrest, ventricular tachycardia (VT) and fibrillation (VF), left bundle branch block (LBBB), non-ischemic cardiomyopathy, and Elixhauser comorbidities (acquired immune deficiency syndrome, alcohol abuse, deficiency anaemias, chronic blood loss anaemia, rheumatoid arthritis/collagen vascular diseases, congestive heart failure, chronic pulmonary disease, coagulopathy, depression, diabetes (uncomplicated), diabetes with chronic complications, drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurological disorders, obesity, peripheral vascular disease, pulmonary circulation disorders, renal failure, solid tumour without metastasis, valvular heart disease and weight loss), bed size of hospital, location/teaching status of hospital, hospital volume, year of admission. I included an interaction term between sex and time (year) to investigate potential temporal trends of association between sex and outcomes. All associations were expressed as odds ratios (ORs) with corresponding 95% confidence intervals (CIs).

4. Results

Of 400,823 de novo CRT implantation procedures between 2004 and 2014, 60,032 were CRT-P procedures (15%) and 340,791 were CRT-D procedures (85%). Overall, there was a higher utilisation CRT-D amongst males (88%) compared with females (77%). Within the CRT groups, females were more prevalent in the CRT-P group than the CRT-D group (41.5% vs. 27.8%). The percentage of females undergoing CRT-P and CRT-D implantations has increased over the study period, albeit more in the CRT-P group. For

example, the percentage of females undergoing CRT-P was 34.9% in 2004 compared with 45.6% in 2014 (absolute difference: 10.7%). (**Figure 4.2**)

Figure 4.2. Proportions of A) CRT-P and B) CRT-D procedures over the study period*



*p<0.001 for trend; **CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively

Patients who underwent CRT-D implantation were primarily younger (71 (62,78) vs. 77 (69,83) years) with a higher prevalence of in-hospital cardiac arrest (2.2 vs. 1.5%), VT (27.4 vs. 8.4%), VF (3.9 vs. 0.8%) and previous AMI (21.7% vs. 11.5%), PCI (12.1% vs. 9.4%) and CABG (22.4 vs. 15.2%). (**Table 4.1**) However, the CRT-D group had a lower prevalence of renal failure (19.1 vs. 20.6%) and anaemias (9.6 vs. 12.5%). Several sex differences in patient characteristics were observed in both CRT groups. Females in both groups had significantly lower prevalence of VT, VF, renal failure and previous AMI, PCI and CABG but a higher prevalence of non-ischemic cardiomyopathy. (**Table 4.1**)

Predictors of receipt of CRT-D

On multivariable analysis, several factors (patient-related and demographic) were predictive of receipt of CRT-D than CRT-P. (**Table 4.2, Figure 4.3**)

Female sex was associated with reduced odds of receipt of CRT-D compared with males (OR 0.66 95%CI 0.64-0.67), and this persisted over the study period (p_{trend}=0.06). (**Table 4.2, Figure 4.4**). Advanced age also negatively correlated with the odds of receipt

Table 4.1. Patient characteristics of study groups

	CRT-P (15.0)			CRT-D (85.0)			Total		
Variable/Group (%)	**Male (58.5)**	**Female (41.5)**	**p-value**	**Male (72.2)**	**Female (27.8)**	**p-value**	**CRT-P**	**CRT-D**	**p-value**
Number of weighted discharges	35107	24925		246015	94776		60032	340791	
Sociodemographic									
Age (years), median (IQR)	77(68,83)	78(69,84)	<0.001	71(62,78)	71(62,78)	0.08	77 (69,83)	71 (62,78)	<0.001
Ethnicity, %			<0.001			<0.001			<0.001
White	84.0	81.3		79.9	72.0		83.0	78.0	
Black	6.5	9.1		9.4	15.9		7.5	11.2	
Hispanic	5.3	5.4		6.2	7.5		5.3	6.4	
Asian/Pacific Islander	1.2	1.4		1.3	1.3		1.3	1.3	
Native American	0.7	0.8		0.5	0.6		0.7	0.5	
Other	2.4	2.1		2.6	2.7		2.2	2.6	
Elective Admission, %	44.5	42.9	<0.001	50.3	50.2	0.673	43.9	50.3	<0.001
Weekend admission, %	11.1	10.7	<0.001	9.0	8.9	0.429	10.9	9.0	<0.001
Primary expected payer, %			<0.001			<0.001			<0.001
Medicare	78.3	82.3		71.7	71.3		80.1	71.7	
Medicaid	3.0	3.2		4.5	6.5		3.0	5.0	
Private Insurance	15.9	12.4		20.3	19.2		14.5	20.0	
Self-pay	1.1	1.0		1.6	1.6		1.0	1.5	
No charge	0.0	0.1		0.2	0.2		0.1	0.2	
Other	1.7	0.9		1.7	1.2		1.3	1.6	
Median Household Income (Percentile), %			<0.001			<0.001			<0.001
0-25th	23.3	27.2		25.5	29.5		24.9	26.5	
26-50th	26.2	27.2		26.3	26.9		26.6	26.5	

	CRT-P (15.0)			CRT-D (85.0)			Total		
Variable/Group (%)	**Male (58.5)**	**Female (41.5)**	**p-value**	**Male (72.2)**	**Female (27.8)**	**p-value**	**CRT-P**	**CRT-D**	**p-value**
51-75th	26.7	24.8		25.3	23.5		25.9	24.8	
76-100th	23.9	20.9		22.9	20.1		22.7	22.2	
Hospital bed size, %			<0.001			<0.001			<0.001
Small	9.4	10.8		8.5	8.1		10.0	8.4	
Medium	19.6	19.1		18.4	19.7		19.4	18.7	
Large	71.0	70.1		73.1	72.2		70.6	72.9	
Hospital Region, %			<0.001			<0.001			<0.001
Northeast	15.8	14.3		20.7	19.6		15.0	20.4	
Midwest	28.6	29.2		25.1	25.9		29.1	25.5	
South	39.0	40.3		37.4	38.9		39.5	37.7	
West	16.6	16.2		16.9	15.6		16.3	16.3	
Location/ Teaching status, %			<0.001			<0.001			<0.001
Rural	5.4	6.5		3.3	3.2		5.8	3.2	
Urban non-teaching	32.7	33.1		35.4	34.1		32.8	35.0	
Urban- teaching	61.9	60.4		61.4	62.7		61.4	61.8	
Comorbidities, %									
All-cause infection*	2.5	1.9	<0.001	1.8	1.6	<0.001	2.2	1.7	<0.001
Cardiac Arrest	1.6	1.4	0.086	2.1	2.5	<0.001	1.5	2.2	<0.001
Shock	1.7	1.5	0.032	1.9	1.6	<0.001	1.6	1.8	<0.001
LBBB	73.3	70.4	<0.001	76.0	74.1	<0.001	74.6	72.8	<0.001
Atrial Fibrillation	52.0	58.3	<0.001	36.7	29.2	<0.001	54.7	34.8	<0.001
Ventricular Tachycardia	10.2	6.0	<0.001	29.3	22.1	<0.001	8.4	27.4	<0.001
Ventricular Fibrillation	0.9	0.8	0.712	3.9	4.1	0.017	0.8	3.9	<0.001
Anaemias	12.8	15.6	<0.001	9.2	11.7	<0.001	9.6	12.5	<0.001
Coagulation disorders	6.2	4.1	<0.001	4.1	3.0	<0.001	4.4	3.3	<0.001
Diabetes	29.0	27.1	0.015	33.4	34.1	0.063	32.9	32.7	0.576

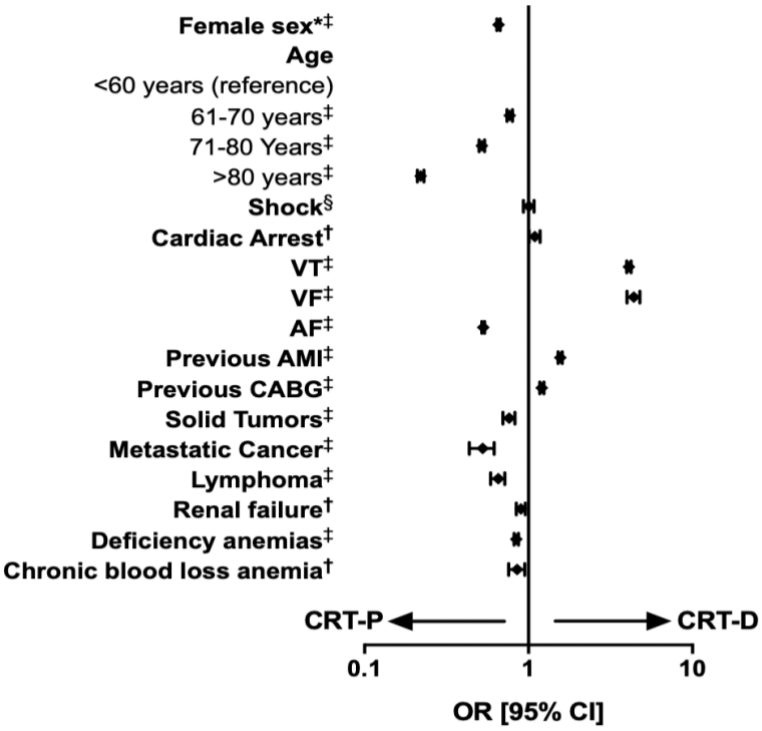
	CRT-P (15.0)			CRT-D (85.0)			Total		
Variable/Group (%)	**Male (58.5)**	**Female (41.5)**	**p-value**	**Male (72.2)**	**Female (27.8)**	**p-value**	**CRT-P**	**CRT-D**	**p-value**
Hypertension	57.1	61.4	<0.001	56.3	56.4	0.696	58.9	56.4	<0.001
Renal failure (chronic)	22.0	18.5	<0.001	20.2	15.9	<0.001	20.6	19.1	<0.001
Peripheral vascular disease	9.5	6.7	<0.001	9.7	6.7	<0.001	8.3	8.9	<0.001
Valvular heart disease	1.1	1.4	<0.001	0.6	0.8	<0.001	1.2	0.6	<0.001
Previous AMI	13.2	9.0	<0.001	23.9	15.5	<0.001	11.5	21.7	<0.001
History of IHD	58.9	41.4	<0.001	72.1	52.2	<0.001	51.6	66.7	<0.001
Previous PCI	10.2	8.1	<0.001	13.0	9.5	<0.001	9.4	12.1	<0.001
Previous CABG	19.7	8.9	<0.001	26.1	12.6	<0.001	15.2	22.4	<0.001
Previous CVA	4.4	5.3	<0.001	3.6	3.5	0.161	4.8	3.6	<0.001
Dyslipidaemia	39.6	38.4	0.001	42.7	38.5	<0.001	39.2	41.6	<0.001
Smoking	5.2	3.7	<0.001	7.7	6.1	<0.001	4.6	7.3	<0.001
Chronic pulmonary disease/ pulmonary circulation disorders	22.1	21.7	0.569	21.2	22.6	<0.001	21.3	22.4	0.001
Hypothyroidism	8.7	21.0	<0.001	7.1	15.2	<0.001	13.9	9.3	<0.001
RA/collagen vascular diseases	1.6	3.5	<0.001	1.1	2.9	<0.001	2.4	1.6	<0.001
Liver disease	1.1	0.8	<0.001	1.1	0.8	<0.001	1.0	1.0	0.679
Fluid and electrolyte disturbances	16.2	19.1	<0.001	12.8	14.7	<0.001	17.5	13.3	<0.001
Malignancies*	3.0	2.0	<0.001	1.5	1.3	0.066	1.7	1.3	0.017
Dementia	1.0	1.1	0.233	0.3	0.3	0.320	1.1	0.3	<0.001

*including haematological malignancies (e.g., lymphoma and leukaemia); **CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively; **IQR:** interquartile range; **AMI:** acute myocardial infarction; **IHD:** ischemic heart disease; **CABG:** coronary artery bypass graft; **PCI:** percutaneous coronary intervention; **CAD:** coronary artery disease; **LBBB:** left bundle branch block

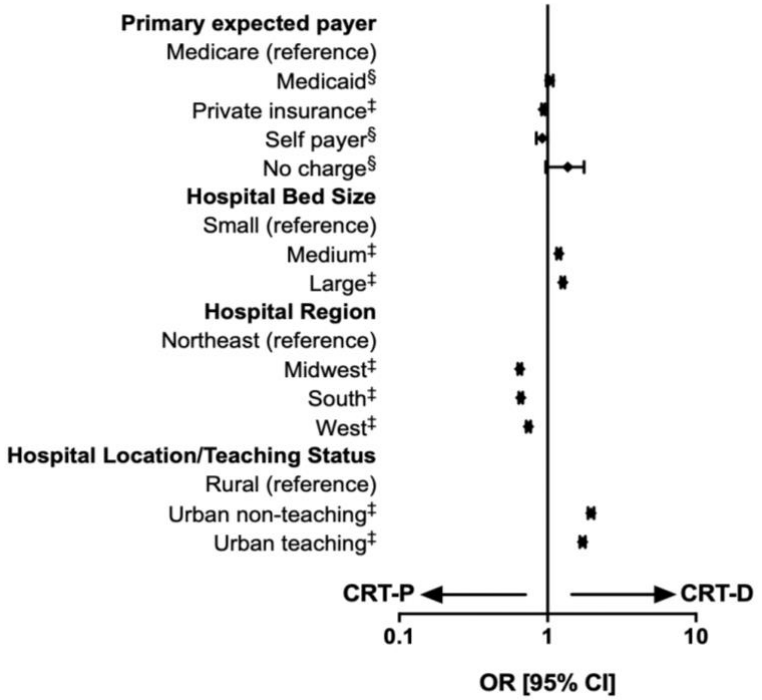
of CRT-D (age (years) **61-70**: OR 0.77 95% CI 0.74, 0.80; **71-80**: OR 0.52 95% CI 0.50-0.54; **>80**: OR 0.22 95% CI 0.21 - 0.23], p<0.001 for all). (**Figure 4.3**)

Figure 4.3. Patient-related (A) and non-patient-related (B) predictors of receipt of CRT-D (vs. CRT-P) *

A)



B)



Legend: *reference is male sex; **§** non-significant; † p<0.05; ‡ p<0.001; **CI:** confidence interval; OR: odds ratio; **CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively.

Comorbidities such as previous cardiovascular disease (AMI and CABG), previous cardiac arrest and ventricular arrhythmias (VT and VF) also favoured the receipt of CRT-D while history of AF, anaemia (deficiency and chronic), renal failure and malignancies were associated with reduced odds of receipt of CRT-D. (**Table 4.2, Figure 4.3).** Furthermore, patients admitted to urban hospitals (teaching and non-teaching) and hospitals with a bigger bed capacity (medium and large) were more likely to receive CRT-D.

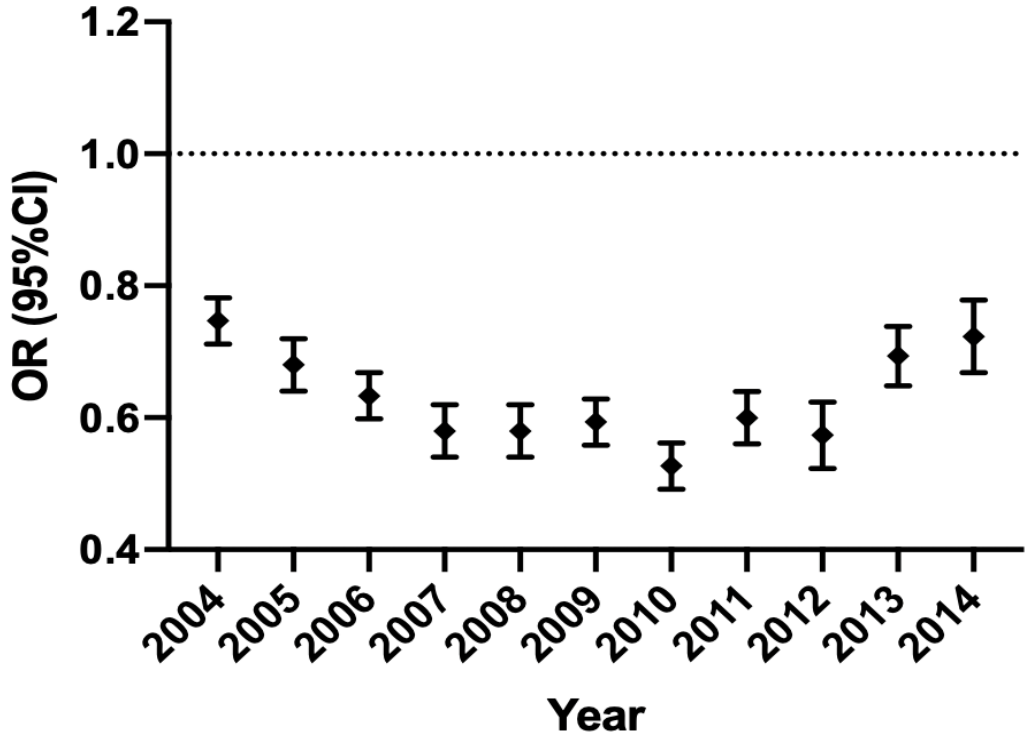
Table 4.2. Multivariable analysis of predictors of receipt of CRT-D Device*

Predictor	**OR [95% CI]**	**p-value**
Female sex	0.66 [0.64, 0.67]	<0.001
Age (Years)		
≤60 (reference)	-	-
61-70	0.77 [0.74, 0.80]	<0.001
71-80	0.52 [0.50, 0.54]	<0.001
>80	0.22 [0.21, 0.23]	<0.001
Primary payer		
Medicare (reference)	-	-
Medicaid	1.03 [0.98, 1.09]	0.304
Private Insurance	0.94 [0.91, 0.97]	<0.001
Self-pay	0.92 [0.84, 1.00]	0.057
No charge	1.33 [0.99, 1.78]	0.059
Shock	1.01 [0.93, 1.08]	0.887
Cardiac Arrest	1.09 [1.01, 1.18]	0.027
Ventricular Tachycardia	4.09 [3.97, 4.22]	<0.001
Ventricular Fibrillation	4.37 [3.99, 4.79]	<0.001
Dyslipidaemia	1.04 [1.02, 1.06]	<0.001
Atrial Fibrillation	0.53 [0.52, 0.54]	<0.001
Thrombocytopenia	0.82 [0.74, 0.90]	<0.001
Previous AMI	1.56 [1.52, 1.61]	<0.001
Previous PCI	0.95 [0.92, 0.98]	<0.001
Previous CABG	1.21 [1.17, 1.24]	<0.001
Previous CVA	0.89 [0.85, 0.93]	<0.001
Family history of CAD	1.01 [0.95, 1.07]	0.771
Alcohol abuse	0.97 [0.89, 1.05]	0.417
Deficiency anaemias	0.84 [0.82, 0.87]	<0.001
Chronic blood loss anaemia	0.85 [0.76, 0.95]	0.006
RA/collagen vascular diseases	0.81 [0.76, 0.86]	<0.001
Chronic pulmonary disease	0.94 [0.91, 0.96]	<0.001
Coagulopathy	1.00 [0.92, 1.09]	<0.001
Depression	0.87 [0.83, 0.91]	<0.001
Diabetes	1.11 [1.09, 1.14]	<0.001
Diabetes with complications	1.04 [0.99, 1.09]	0.129

Drug abuse	1.06 [0.93, 1.20]	0.413
Hypertension	0.94 [0.92, 0.96]	<0.001
Hypothyroidism	0.89 [0.86, 0.91]	<0.001
Liver disease	0.88 [0.80, 0.97]	0.008
Lymphomas	0.65 [0.59, 0.72]	<0.001
Fluid and electrolyte disturbances	0.83 [0.81, 0.85]	<0.001
Metastatic cancer	0.52 [0.44, 0.62]	<0.001
Other neurological disorders	0.80 [0.76, 0.84]	<0.001
Obesity	0.91 [0.88, 0.94]	<0.001
Paralysis	0.89 [0.81, 0.99]	0.024
Peripheral vascular disease	0.99 [0.96, 1.03]	0.726
Psychoses	0.82 [0.75, 0.89]	<0.001
Pulmonary circulation disorder	0.54 [0.47, 0.62]	<0.001
Renal failure (chronic)	0.89 [0.85, 0.96]	0.002
Solid tumour without metastases	0.76 [0.70, 0.83]	<0.001
Valvular heart disease	0.81 [0.74, 0.90]	<0.001
Weight loss	0.64 [0.60, 0.69]	<0.001
Dementia	0.53 [0.47, 0.60]	<0.001
Hospital bed size		
Small (reference)	-	-
Medium	1.19 [1.15, 1.23]	<0.001
Large	1.26 [1.23, 1.31]	<0.001
Hospital Region		
Northeast (reference)	-	-
Midwest	0.65 [0.63, 0.67]	<0.001
South	0.66 [0.64, 0.68]	<0.001
West	0.74 [0.72, 0.77]	<0.001
Location/ Teaching status		
Rural (reference)	-	-
Urban non-teaching	1.96 [1.87, 2.05]	<0.001
Urban- teaching	1.72 [1.65, 1.80]	<0.001

*Indicator is receipt of CRT-P adjusting for the above variables and calendar year.
As an example, odds ratio of 0.56 favours receipt of CRT-P over CRT-D; CI: Confidence Interval; **OR:** Odds ratio; **CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively; **IQR:** interquartile range; **AMI:** acute myocardial infarction; **CABG:** coronary artery bypass graft; **PCI:** percutaneous coronary intervention; **CAD:** coronary artery disease.

Figure 4.4. Odds ratios (OR) of receipt of CRT-D (vs. CRT-P) in females*



Legend: *reference is male sex; **CI:** confidence interval; **CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively; p>0.05 (non-significant for trend)

5. Discussion

My analysis is the first to examine patient-related predictors of the choice of CRT device type offered to patients undergoing *de novo* implantation. Among these patient predictors was sex, with females shown to be independently associated with increased likelihood of receipt of CRT-P (vs. CRT-D) as were older age (>60 years), history of malignancy, anaemia and renal failure. I also identify sociodemographic differences in the type of CRT device offered to patients, with those in certain regions (e.g., North-East of the US), urban and larger bed hospitals more likely to receive CRT-D than CRT-P.

In my analysis several factors were predictive of receipt of CRT-D over CRT-P in a contemporary cohort of hospitalizations. Some of these showed similarity to the findings from the ESC Survey II which also reported factors such as male sex and admission to a university hospital as favouring a CRT-D device as well as AF favouring a CRT-P device.

[8] However, their study did not examine many variables that were included in my analysis and was also based on a modest number of patients (approximately 11% of all European patients undergoing the procedure), making their findings less reflective of the wider practice amongst operators. Furthermore, younger patients (≤75 years) were more likely to receive a CRT-P device in the ESC survey, whereas my findings demonstrate that the odds of receipt of CRT-D decline from the age of 60 years. Several other factors were shown to inversely correlate with the odds of receipt of CRT-D in my analysis that were not systematically examined in the ESC Survey or other previous literature such as history of malignancy, renal failure and anaemia. I also demonstrate regional differences in the practice of operators in the US, where patients managed in regions other than the Northeast, and those admitted to smaller and rural hospitals were significantly less likely to receive CRT-D devices. Furthermore, my findings suggest that those privately insured were less likely to be offered a CRT-D device whereas no difference was found in choice between other primary payer groups.

While the disparity in receipt of CRT-D between sexes has been previously reported in some studies, [41, 103] these were subject to certain limitations (e.g., selected population, unadjusted analyses) and, therefore, insufficiently powered to ascertain whether such differences do exist. Furthermore, it was unclear whether such differences, if any, have persisted over the years. The ESC Survey II reported lower utilisation of CRT-D (vs. CRT-P) in females compared with males in their survey of more than 10000 CRT implantations in Europe.[8] Similarly, in a study more than 300,000 CRT-D implantation procedures (2006-2012), females were also shown to be less likely to receive CRT-D.[104] However, their trend analysis only included crude rates without adjustment for any differences in patient or procedural characteristics between sexes. My study examines trends over a longer period (2004-2014) and demonstrates that females persistently less likely to receive a CRT-D

device compared to CRT-P over an eleven-year horizon, even after adjustment for baseline differences between the sexes. Several reasons could justify the lower rate of utilisation of CRT-D in females compared with males, including the overall lower rate of referral for CRT in females as well as their more superior response to CRT therapy with higher levels of reverse LV remodelling, making them at a lower risk of ventricular arrhythmias that would require defibrillation.[105-107] Furthermore, lower utilisation of CRT-D therapy in females may be related to patient preference, with females more likely to be concerned about their body image, especially that CRT-D devices are bulkier and more obvious in the chest region, as well as their greater fear of shock therapy compared with males as demonstrated in one study.[108]

Limitations

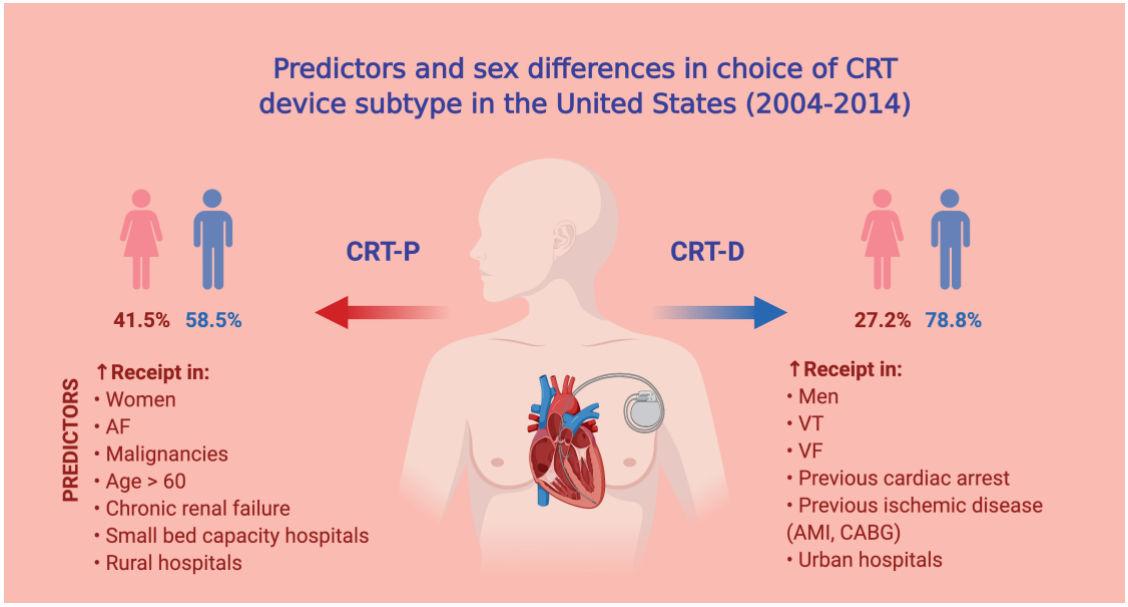
There are several limitations to my analysis. First, the analysis was derived from a large administrative clinical dataset that is coded according to the ICD-9 manual. Coding inaccuracies are possible, although the use of ICD-9 codes have been previously shown to in particular has been previously validated studies in studies examining cardiovascular and specifically CIED cohorts.[109-111] Second, I was unable to capture the following variables as they are coded in ICD-9: LV ejection fraction, aetiology of heart failure, and QRS duration, meaning that they were not adjusted for in my models. Finally, information on patient preference for device type as well as operator experience were not available, and these could have played a role in the choice of device implanted.

6. Summary

My analysis shows that age and female sex negatively correlate with the likelihood of receipt of CRT-D (vs. CRT-P). Several other patient comorbidities such as atrial fibrillation, malignancies, renal failure favour the receipt of CRT-P over CRT-D while a history of ischemic heart disease, cardiac arrest or ventricular arrhythmias favour the

receipt of CRT-D. These findings inform operators of the current practice in choice of CRT type, as well as highlight the disparity in receipt of CRT-D between sexes in a real-world national procedural cohort of de novo CRT implantations.

Graphical illustration of the summary of analysis findings



Chapter 5. Sex differences in de novo CIED implantation outcomes

The work in this chapter relates to the second phase of my thesis and is based on my study published in the Canadian Journal of Cardiology (Appendix 2). [112]

1. Introduction

There has been a growing interest in the study of sex differences in outcomes of cardiovascular procedures in recent years. Previous studies in procedures such as percutaneous coronary intervention, coronary artery bypass grafting and transcatheter aortic valve replacement have shown a disparity in clinical outcomes between sexes. [113-117]

Females undergoing CIED implantation are believed to be at a higher baseline risk of procedure-related complications, compared to males, due to anatomical differences such as their smaller chest wall size, smaller and thinner vasculature, thinner right ventricular walls, and lower body weight, all of which have been previously described as risk factors for procedure-related complications. [53, 118-120] However, these risks could be higher in patients receiving more complex devices such as cardiac resynchronisation therapy with defibrillator (CRT-D) or pacemaker (CRT-P) and implantable cardioverter defibrillators (ICD) than those receiving simple permanent pacemakers (PPM). While some previous studies have examined sex differences in procedural outcomes of cardiac implantable electronic device (CIED) implantations, their analyses lacked sufficient granularity to allow generalizability of their findings to the entire target population.[44, 55, 63, 91, 121] For example, some studies compared gender outcomes in specific device cohorts (e.g., ICD only) or examined the effect of sex in the overall CIED implantation cohort without differentiation between CIED types despite the difference in risk profiles of patients undergoing each type of device. Furthermore, there has been no temporal analysis of the trends of procedural outcomes according to sex.

2. Objectives

My main objectives of this chapter were to study the following:

a) Sex differences in in-hospital procedural outcomes of de novo CIED implantation procedure stratified by type of implanted device.

b) The trends of these sex differences over an 11-year period.

3. Methods

A full description of the methodology relating to all chapters of my thesis is provided in Chapter 3.

a) Data Source

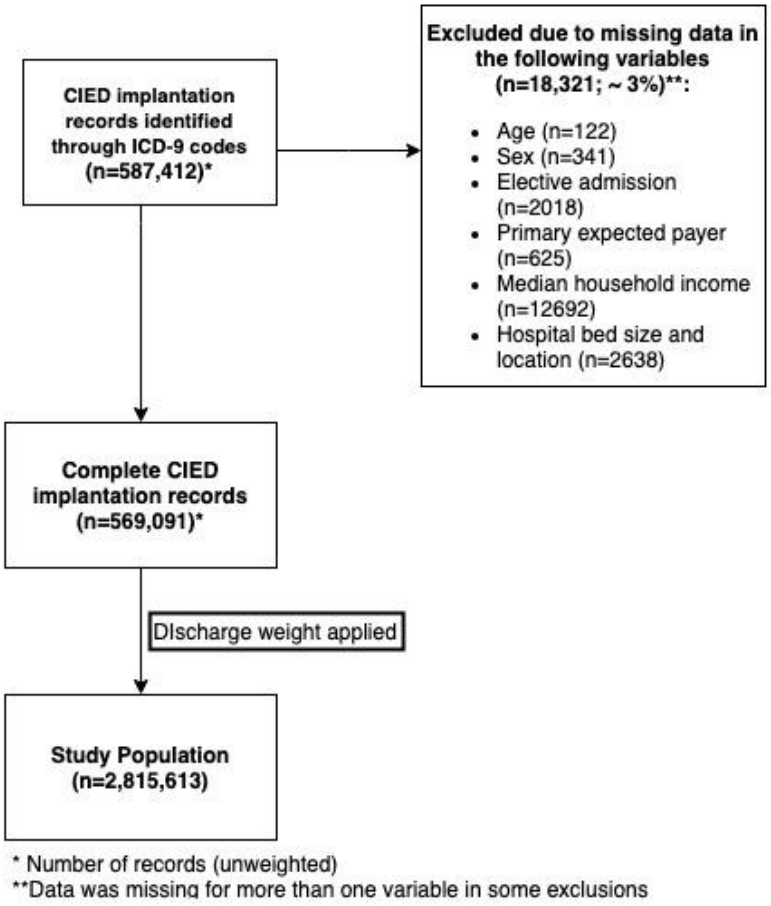
The data source for this study was the National Inpatient Sample (NIS). Further information on its structure and validation has been provided in Chapter 3 and also described in Chapter 4 under the same heading.

b) Study Design and Population

I included all adults (≥18 years) undergoing *de novo* CIED implantation procedures between 2004 and 2014 (PPM, CRT-P, CRT-D, and ICD) in my analysis. I excluded any records with missing data for the following variables: age, sex, elective (vs. urgent) admission, primary payer, median household income, and hospital bed size/location (Flow diagram in **Figure 5.1**). Missing records that were excluded represented less than 3% (n=18,321) of the original dataset. The final study cohort was stratified according to sex and further by CIED type.

All procedural information and patient characteristics other than Elixhauser comorbidities, as well as clinical outcomes were extracted using the International Classification of Diseases, ninth revision (ICD-9) procedure and diagnosis codes provided in **Table 3.1**.

Figure 5.1 Study Flow Diagram



c) Outcomes

The primary outcomes were in-hospital major acute cardiovascular events (MACE), all-cause mortality and procedural-related complications (bleeding, thoracic and cardiac). MACE was defined as a composite of all-cause mortality, cardiac complications, thoracic complications and device-related infection. Procedure-related bleeding was defined as any post-procedural haemorrhage or post haemorrhagic anaemia according to ICD-9 diagnosis codes (998.11 and 285.1). Cardiac complications were defined as a composite of cardiac tamponade, hemopericardium, pericardial effusion and pericardiocentesis while thoracic complications included any acute pneumothorax or haemothorax (with or without chest drainage drainage) or thoracic vascular injury.

d) Statistical analysis

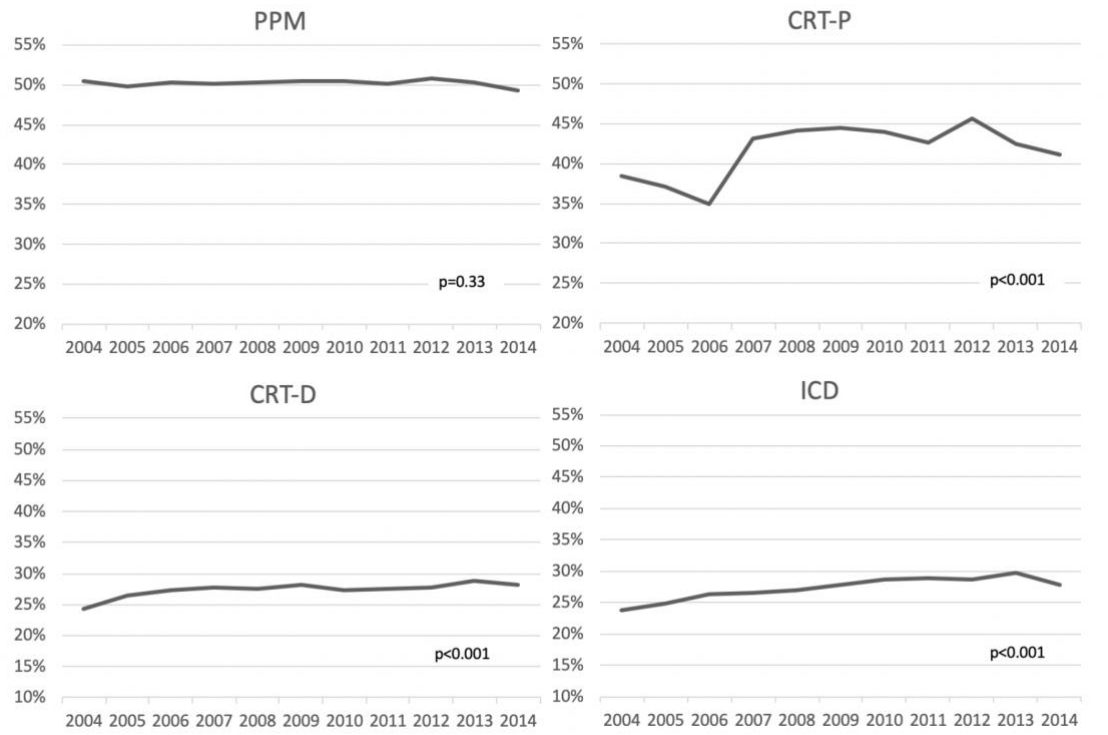
Descriptive statistics were performed as previously explained in Chapter 3. Sampling weights provided by the AHRQ were applied to all analyses. All statistical analyses were performed using SPSS version 24 (IBM Corp, Armonk, NY).

I performed trend analysis using linear regression models with the inclusion of time (in years) for assessing sex differences in outcomes over time. I also performed multivariable logistic regression modelling to examine the adjusted odds ratio (aOR [95% confidence interval]) of in-hospital adverse outcomes in females using males as the reference category, adjusting for the following variables: age, weekend admission, primary expected payer, median household income, dyslipidaemia, smoking status, previous acute myocardial infarction (AMI), previous coronary artery bypass graft (CABG), history of ischemic heart disease (IHD), previous percutaneous coronary intervention (PCI), previous cerebrovascular accidents including stroke and transient ischemic attacks (CVA), family history of coronary artery disease (CAD), thrombocytopenia, history of cardiac arrest, atrial fibrillation (AF), ventricular tachycardia and fibrillation (VF and VT respectively), all-cause infection and Elixhauser comorbidities (acquired immune deficiency syndrome, alcohol abuse, deficiency anaemias, chronic blood loss anaemia, rheumatoid arthritis/collagen vascular diseases, congestive heart failure, chronic pulmonary disease, coagulopathy, depression, diabetes (uncomplicated), diabetes with chronic complications, drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurological disorders, obesity, peripheral vascular disorders, psychoses, pulmonary circulation disorders, renal failure, solid tumour without metastasis, valvular heart disease, weight loss, bed size of hospital, location/teaching status of hospital, hospital volume, year of admission (except in trend analysis).

4. Results

There was a total of 2,815,613 hospitalization records for *de novo* CIED implantation in the United States between 2004 and 2014. Females represented 41.9% (n=1,178,492) of the cohort and their prevalence increased over the study period in all device groups other than PPM (PPM: 49.5% in 2004 to 50.7% in 2014). (**Figure 5.2**).

Figure 5.2 Proportion of females undergoing CIED implantation procedures according to type of CIED (2004-2014)



Legend: p-values are for trends

There were several baseline differences in patient characteristics between males and females in the total CIED cohort (**Table 5.1**). Females were older (median 77 vs. 73 years), less likely to be admitted electively, with a lower prevalence of cardiac risk factors including dyslipidaemia, history of IHD, previous AMI and PCI, VF, VT, renal failure and shock. In contrast, males had a lower prevalence of AF, hypothyroidism, hypertension, previous CVA and deficiency anaemias. The pattern of differences in characteristics between sexes was consistent across the different device groups (PPM, CRT-P, CRT-D and ICD). (**Tables 5.2 and 5.3**)

Table 5.1 Patient characteristics according to sex

Variable/Group (%)	Male (58.1)	Female (41.9)	Total	p-value
Number of weighted discharges	1637121	1178492	2815613	<0.001
Type of CIED, %				<0.001
PPM	53.2	74.7	62.2	
CRT-P	2.4	2.3	2.3	
CRT-D	16.7	8.7	13.3	
ICD	27.7	14.2	22.1	
Age (years), median (IQR)	73 (63, 81)	77 (68,84)	75 (65,82)	<0.001
Ethnicity, %				<0.001
White	79.9	77.6	78.9	
Black	8.8	10.8	9.6	
Hispanic	6.4	6.6	6.5	
Asian/Pacific Islander	1.8	2.1	1.9	
Native American	0.5	0.5	0.5	
Other	2.6	2.3	2.5	
Elective Admission, %	33.5	26.9	30.8	<0.001
Weekend admission, %	14.1	16.6	15.1	<0.001
Primary expected payer, %				<0.001
Medicare	71.2	78.6	74.3	
Medicaid	4.2	4.5	4.4	
Private Insurance	20.4	14.2	17.9	
Self-pay	1.9	1.3	1.7	
No charge	0.2	0.2	0.2	
Other	2.0	1.1	1.6	
Median Household Income (Percentile), %				<0.001
0-25th	24.9	27.0	25.8	
26-50th	26.3	26.9	26.6	
51-75th	24.8	24.0	24.5	
76-100th	24.0	22.1	23.2	
Shock, %	1.5	1.2	1.4	<0.001
All-cause infection, %*	2.5	2.4	2.5	0.198
Cardiac Arrest, %	3.7	3.7	3.7	0.612
Ventricular Tachycardia, %	20.1	10.2	16.0	<0.001
Ventricular Fibrillation, %	3.8	2.5	3.2	<0.001
Comorbidities, %				
Dyslipidaemia	43.9	39.7	42.1	<0.001
Smoking	8.8	5.5	7.4	<0.001
Atrial Fibrillation	36.0	41.3	38.2	<0.001
Thrombocytopaenia	3.7	2.8	3.3	<0.001
Previous AMI	16.9	8.8	13.5	<0.001
History of IHD	57.6	37.5	49.2	<0.001
Previous PCI	11.7	7.1	9.8	<0.001

Variable/Group (%)	Male (58.1)	Female (41.9)	Total	p-value
Previous CABG	18.5	7.5	13.9	<0.001
Previous CVA	4.1	4.9	4.5	<0.001
Family history of CAD	2.8	2.5	2.7	<0.001
AIDS	0.1	0.0	0.1	<0.001
Alcohol abuse	2.8	0.6	1.9	<0.001
Deficiency anaemias	11.3	15.4	13.0	<0.001
Chronic Blood loss anaemia	0.6	0.9	0.7	<0.001
RA/collagen vascular diseases	1.2	3.2	2.1	<0.001
Heart Failure	46.3	40.2	43.8	<0.001
Chronic pulmonary disease	19.1	19.1	19.1	0.103
Coagulopathy	4.8	4.0	4.5	<0.001
Depression	4.3	8.0	5.8	<0.001
Diabetes	25.7	23.9	24.9	<0.001
Diabetes with complications	4.6	4.4	4.5	<0.001
Drug abuse	1.1	0.6	0.9	<0.001
Hypertension	62.5	67.0	64.3	<0.001
Hypothyroidism	7.6	20.0	12.8	<0.001
Liver disease	1.2	1.0	1.1	<0.001
Lymphomas	0.7	0.6	0.6	<0.001
Fluid and electrolyte disturbances	15.3	20.7	17.5	<0.001
Metastatic cancer	0.5	0.4	0.5	<0.001
Other neurological disorders	5.4	6.9	6.0	<0.001
Obesity	8.2	9.4	8.7	<0.001
Paralysis	1.5	1.6	1.5	<0.001
Peripheral vascular disease	9.8	7.6	8.9	<0.001
Psychoses	1.5	2.1	1.8	<0.001
Pulmonary circulation disorder	0.5	0.8	0.6	<0.001
Renal failure (chronic)	17.0	14.7	16.0	<0.001
Solid tumour without metastases	1.5	0.9	1.2	<0.001
Valvular heart disease	1.2	1.7	1.4	<0.001
Weight loss	1.9	2.3	2.0	<0.001
Dementia	1.7	2.7	2.1	<0.001
Hospital bed size, %				<0.001
Small	8.5	9.2	8.8	
Medium	21.3	22.6	21.8	
Large	70.2	68.2	69.4	
Hospital Region, %				<0.001
Northeast	21.5	21.1	21.4	
Midwest	23.3	24.0	23.6	
South	37.0	37.8	37.3	
West	18.1	17.1	17.7	

Variable/Group (%)	Male (58.1)	Female (41.9)	Total	p-value
Location/ Teaching status, %				<0.001
Rural	6.0	7.4	6.6	
Urban non-teaching	40.1	41.8	40.8	
Urban- teaching	53.9	50.8	52.6	

* **All-cause infection**: Composite of septicaemia, viraemia and bacteraemia

Table 5.2 Patient characteristics of patients undergoing permanent pacemaker (PPM) and implantable cardioverter defibrillator (ICD) implantation

	PPM				ICD			
Variable/Group (%)	**Male (49.8)**	**Female (50.2)**	**Total**	**p-value**	**Male (73.1)**	**Female (26.9)**	**Total**	**p-value**
Number of weighted discharges	873600	881748	1755438	<0.001	452788	166801	619589	<0.001
Age (years), median (IQR)	77 (69, 83)	80 (72, 85)	78 (70, 84)	<0.001	66 (57, 75)	65 (54, 75)	66 (56, 75)	
Ethnicity, %				<0.001				<0.001
White	82.9	80.3	81.6		74.1	66.6	72.1	
Black	6.4	8.4	7.4		13.2	20.6	15.2	
Hispanic	6.0	6.3	6.1		7.5	7.7	7.6	
Asian/Pacific Islander	2.0	2.3	2.2		1.7	1.6	1.7	
Native American	0.4	0.5	0.5		0.6	0.5	0.6	
Other	2.3	2.1	2.2		3.0	2.9	3.0	
Elective Admission, %	25.6	22.0	23.8	<0.001	38.0	35.4	37.3	<0.001
Weekend admission, %	16.7	18.2	17.4	<0.001	12.6	13.7	12.9	<0.001
Primary expected payer, %				<0.001				<0.001
Medicare	78.0	83.5	80.8		57.8	57.4	57.7	
Medicaid	2.6	3.1	2.9		7.1	10.7	8.1	
Private Insurance	16.2	11.4	13.7		29.0	26.9	28.4	
Self-pay	1.4	1.0	1.2		3.1	2.8	3.0	
No charge	0.1	0.1	0.1		0.4	0.3	0.4	
Other	1.7	0.9	1.3		2.6	1.8	2.4	
Median Household Income (Percentile), %				<0.001				<0.001
0-25th	23.8	26.0	24.9		26.5	30.3	27.5	
26-50th	26.5	27.0	26.7		26.0	26.1	26.1	
51-75th	24.8	24.2	24.5		24.4	23.2	24.1	
76-100th	24.9	22.7	23.8		23.1	20.4	22.4	

	PPM				ICD			
Variable/Group (%)	**Male (49.8)**	**Female (50.2)**	**Total**	**p-value**	**Male (73.1)**	**Female (26.9)**	**Total**	**p-value**
Shock, %	0.9	0.8	0.9	0.016	2.5	2.6	2.5	**0.014**
All-cause infection, %*	2.7	2.5	2.6	<0.001	2.4	2.8	2.5	<0.001
Cardiac Arrest, %	2.9	3.0	3.0	0.137	6.3	8.4	6.8	<0.001
Ventricular Tachycardia, %	4.1	3.0	3.6	<0.001	46.3	41.2	44.9	<0.001
Ventricular Fibrillation, %	0.5	0.4	0.4	<0.001	10.3	12.8	10.9	<0.001
Comorbidities, %								
Dyslipidaemia	43.8	40.2	42.0	<0.001	45.4	38.0	43.4	<0.001
Smoking	7.2	4.5	5.9	<0.001	12.4	10.5	11.9	<0.001
Atrial Fibrillation	39.8	45.7	42.7	<0.001	27.2	23.2	26.2	<0.001
Thrombocytopenia	4.1	3.0	3.5	<0.001	3.0	2.6	2.9	<0.001
Previous AMI	9.1	6.1	7.6	<0.001	28.3	19.1	25.8	<0.001
History of IHD	45.7	32.4	39.0	<0.001	71.9	54.5	67.2	<0.001
Previous PCI	9.4	6.1	7.7	<0.001	15.5	10.8	14.2	<0.001
Previous CABG	14.6	6.1	10.3	<0.001	21.6	11.7	18.9	<0.001
Previous CVA	4.8	5.3	5.1	<0.001	3.1	3.4	3.2	<0.001
Family history of CAD	2.5	2.4	2.4	<0.001	3.6	3.2	3.5	<0.001
Alcohol abuse	2.4	0.5	1.4	<0.001	3.9	1.5	3.2	<0.001
Deficiency anaemias	13.3	16.2	14.8	<0.001	8.7	13.5	10.0	<0.001
Chronic Blood loss anaemia	0.8	0.9	0.9	<0.001	0.5	0.8	0.6	<0.001
RA/collagen vascular diseases	1.4	3.3	2.3	<0.001	1.0	3.1	1.5	<0.001
Heart Failure	24.1	28.8	26.4	<0.001	60.0	62.8	60.8	<0.001
Chronic pulmonary disease	18.1	17.8	17.9	<0.001	19.9	23.3	20.8	<0.001
Coagulopathy	5.3	4.1	4.7	<0.001	4.2	3.9	4.1	<0.001
Depression	4.8	8.2	6.5	<0.001	3.8	7.9	4.9	<0.001
Diabetes	24.1	22.7	23.4	<0.001	26.7	26.6	26.7	0.579
Diabetes with complications	4.9	4.3	4.6	<0.001	4.4	5.0	4.6	<0.001

	PPM				ICD			
Variable/Group (%)	**Male (49.8)**	**Female (50.2)**	**Total**	**p-value**	**Male (73.1)**	**Female (26.9)**	**Total**	**p-value**
Drug abuse	0.7	0.4	0.5	<0.001	2.0	1.7	1.9	<0.001
Hypertension	66.6	70.3	68.5	<0.001	58.8	57.3	58.4	<0.001
Hypothyroidism	9.0	21.9	15.5	<0.001	5.2	13.3	7.4	<0.001
Liver disease	1.1	0.9	1.0	<0.001	1.3	1.2	1.3	<0.001
Lymphomas	0.8	0.6	0.7	<0.001	0.5	0.6	0.5	<0.001
Fluid and electrolyte disturbances	16.5	21.7	19.1	<0.001	14.2	19.3	15.6	<0.001
Metastatic cancer	0.7	0.5	0.6	<0.001	0.2	0.2	0.2	0.054
Other neurological disorders	7.4	7.9	7.6	<0.001	3.5	4.5	3.8	<0.001
Obesity	7.6	8.8	8.2	<0.001	9.1	11.9	9.9	<0.001
Paralysis	1.9	1.8	1.9	<0.001	1.1	1.2	1.1	<0.001
Peripheral vascular disease	10.0	7.7	8.8	<0.001	9.6	7.7	9.1	<0.001
Psychoses	1.8	2.2	2.0	<0.001	1.3	2.3	1.6	<0.001
Pulmonary circulation disorder	0.6	0.9	0.7	<0.001	0.3	0.5	0.4	<0.001
Renal failure (chronic)	16.7	14.5	15.6	<0.001	15.5	14.2	15.1	<0.001
Solid tumour without metastases	2.1	0.9	1.5	<0.001	0.9	0.7	0.8	<0.001
Valvular heart disease	1.6	1.9	1.8	<0.001	0.8	1.2	0.9	<0.001
Weight loss	2.2	2.4	2.3	<0.001	1.6	2.1	1.7	<0.001
Dementia	2.9	3.4	3.2	<0.001	0.4	0.5	0.4	<0.001
Hospital bed size, %				<0.001				<0.001
Small	9.5	9.7	9.6		6.6	6.8	6.7	
Medium	23.4	23.7	23.6		19.2	19.6	19.3	
Large	67.1	66.6	66.9		74.2	73.6	74.1	
Hospital Region, %				<0.001				<0.001
Northeast	21.5	21.5	21.5		22.9	21.6	22.6	
Midwest	22.7	23.5	23.1		23.5	24.6	23.8	
South	36.4	37.3	36.9		37.5	38.3	37.7	

	PPM				ICD			
Variable/Group (%)	**Male (49.8)**	**Female (50.2)**	**Total**	**p-value**	**Male (73.1)**	**Female (26.9)**	**Total**	**p-value**
West	19.4	17.6	18.5		16.0	15.5	15.9	
Location/ Teaching status, %				<0.001				<0.001
Rural	8.0	8.5	8.3		3.6	3.4	3.5	
Urban non-teaching	44.7	44.5	44.6		34.8	33.9	34.5	
Urban- teaching	47.3	47.0	47.1		61.6	62.8	61.9	

*__All-cause infection__: Composite of septicaemia, viremia and bacteraemia

Table 5.3 Patient Characteristics of the cardiac resynchronization therapy implantation groups

	CRT-P				CRT-D			
Variable/Group (%)	**Male (58.5)**	**Female (41.5)**	**Total**	**p-value**	**Male (72.8)**	**Female (27.2)**	**Total**	**p-value**
Number of weighted discharges	38597	27539	66136	<0.001	272136	102404	374540	<0.001
Age (years), median (IQR)	77 (68, 83)	78 (69, 84)	77 (69, 83)		71 (62, 78)	71 (62, 78)	71 (62, 78)	
Ethnicity, %				<0.001				<0.001
White	84.1	81.5	83.0		80.2	72.3	78.0	
Black	6.4	8.9	7.4		9.3	15.8	11.1	
Hispanic	5.3	5.4	5.3		6.1	7.4	6.5	
Asian/Pacific Islander	1.2	1.4	1.3		1.3	1.3	1.3	
Native American	0.7	0.7	0.7		0.5	0.6	0.5	
Other	2.3	2.0	2.2		2.6	2.6	2.6	
Elective Admission, %	44.7	43.1	44.0	<0.001	50.4	50.3	50.4	0.718
Weekend admission, %	11.1	10.7	10.9	0.07	9.0	8.9	9.0	0.543
Primary expected payer, %				<0.001				<0.001
Medicare	78.3	82.6	80.1		71.9	71.4	71.7	
Medicaid	2.9	3.1	3.0		4.4	6.5	5.0	
Private Insurance	16.0	12.3	14.5		20.3	19.3	20.1	
Self-pay	1.1	1.0	1.0		1.5	1.5	1.5	
No charge	0.0	0.1	0.1		0.2	0.2	0.2	
Other	1.6	0.9	1.3		1.7	1.2	1.5	
Median Household Income (Percentile), %				<0.001				<0.001
0-25th	23.2	27.1	24.8		25.4	29.4	26.5	
26-50th	26.2	27.2	26.6		26.3	26.8	26.4	
51-75th	26.6	24.9	25.9		25.4	23.5	24.9	

	CRT-P				CRT-D			
Variable/Group (%)	**Male (58.5)**	**Female (41.5)**	**Total**	**p-value**	**Male (72.8)**	**Female (27.2)**	**Total**	**p-value**
76-100th	24.0	20.9	22.7		23.0	20.2	22.2	
Shock, %	1.7	1.4	1.6	0.017	1.9	1.6	1.8	<0.001
All-cause infection, %*	2.5	1.8	2.2	<0.001	1.8	1.6	1.7	<0.001
Cardiac Arrest, %	1.6	1.4	1.5	<0.001	2.1	2.5	2.2	<0.001
Ventricular Tachycardia, %	10.2	6.0	8.4	<0.001	29.3	22.1	27.4	<0.001
Ventricular Fibrillation, %	0.8	0.8	0.8	0.663	3.9	4.1	3.9	**0.003**
Comorbidities, %								
Dyslipidaemia	39.6	38.4	39.1	0.002	42.7	38.6	41.6	<0.001
Smoking	5.1	3.7	4.5	<0.001	7.7	6.1	7.2	<0.001
Atrial Fibrillation	52.0	58.5	54.7	<0.001	36.8	29.4	34.8	<0.001
Thrombocytopenia	4.9	3.1	4.1	<0.001	3.1	2.0	2.8	<0.001
Previous AMI	13.3	9.0	11.5	<0.001	24.0	15.5	21.7	<0.001
History of IHD	59.0	41.3	51.6	<0.001	72.2	52.2	66.7	<0.001
Previous PCI	10.3	8.1	9.4	<0.001	13.0	9.5	12.1	<0.001
Previous CABG	19.7	8.8	15.2	<0.001	26.2	12.5	22.4	<0.001
Previous CVA	4.4	5.3	4.8	<0.001	3.6	3.5	3.5	0.452
Family history of CAD	2.2	2.7	2.4	<0.001	2.7	2.9	2.7	<0.001
Alcohol abuse	1.9	0.4	1.3	<0.001	2.2	0.6	1.7	<0.001
Deficiency anaemias	12.6	15.0	13.6	<0.001	9.0	11.4	9.7	<0.001
Chronic Blood loss anaemia	0.5	0.9	0.7	<0.001	0.5	0.5	0.5	0.018
RA/collagen vascular diseases	1.6	3.5	2.4	<0.001	1.1	2.9	1.6	<0.001
Heart Failure	76.0	75.0	75.6	0.002	90.7	92.1	91.1	<0.001
Chronic pulmonary disease	21.8	21.0	21.5	0.029	21.0	22.5	21.4	<0.001
Coagulopathy	6.3	4.1	5.4	<0.001	4.2	3.0	3.8	<0.001

	CRT-P				CRT-D			
Variable/Group (%)	**Male (58.5)**	**Female (41.5)**	**Total**	**p-value**	**Male (72.8)**	**Female (27.2)**	**Total**	**p-value**
Depression	3.8	7.5	5.3	<0.001	3.5	6.4	4.3	<0.001
Diabetes	24.8	23.6	24.3	<0.001	29.1	29.7	29.2	<0.001
Diabetes with complications	4.4	3.6	4.0	0.001	4.4	4.4	4.4	0.197
Drug abuse	0.6	0.3	0.5	<0.001	0.9	0.5	0.8	<0.001
Hypertension	57.1	61.4	58.9	<0.001	56.3	56.4	56.4	0.600
Hypothyroidism	8.8	21.1	13.9	<0.001	7.1	15.2	9.3	<0.001
Liver disease	1.1	0.9	1.0	0.003	1.1	0.8	1.0	<0.001
Lymphomas	1.1	0.8	1.0	0.001	0.5	0.6	0.6	0.025
Fluid and electrolyte disturbances	16.2	19.3	17.5	<0.001	12.8	14.6	13.3	<0.001
Metastatic cancer	0.4	0.4	0.4	0.549	0.1	0.2	0.1	0.337
Other neurological disorders	4.0	4.1	4.0	0.368	2.5	2.8	2.5	<0.001
Obesity	7.3	9.1	8.1	<0.001	8.3	10.5	8.9	<0.001
Paralysis	1.0	0.8	0.9	0.001	0.8	0.9	0.8	0.012
Peripheral vascular disease	9.5	6.7	8.3	<0.001	9.7	6.7	8.9	<0.001
Psychoses	1.1	1.4	1.2	0.01	0.9	1.4	1.0	<0.001
Pulmonary circulation disorder	0.6	0.8	0.7	0.011	0.3	0.3	0.3	0.02
Renal failure (chronic)	22.0	18.6	20.6	<0.001	20.3	15.9	19.1	<0.001
Solid tumour without metastases	1.4	0.8	1.2	<0.001	0.8	0.5	0.7	<0.001
Valvular heart disease	1.1	1.4	1.2	<0.001	0.6	0.8	0.6	<0.001
Weight loss	2.5	2.5	2.5	0.752	1.3	1.4	1.3	0.047
Dementia	1.0	1.1	1.1	0.404	0.3	0.3	0.3	0.256
Hospital bed size, %				<0.001				<0.001

	CRT-P				CRT-D			
Variable/Group (%)	**Male (58.5)**	**Female (41.5)**	**Total**	**p-value**	**Male (72.8)**	**Female (27.2)**	**Total**	**p-value**
Small	9.4	10.9	10.0		8.5	8.0	8.4	
Medium	19.7	19.1	19.4		18.3	19.7	18.7	
Large	70.9	70.1	70.6		73.1	72.3	72.9	
Hospital Region, %				<0.001				<0.001
Northeast	15.7	14.2	15.1		20.8	19.7	20.5	
Midwest	28.8	29.4	29.1		25.1	25.9	25.3	
South	39.0	40.3	39.5		37.3	38.9	37.8	
West	16.5	16.2	16.4		16.7	15.5	16.4	
Location/ Teaching status, %				<0.001				<0.001
Rural	5.3	6.4	5.8		3.2	3.2	3.2	
Urban non-teaching	32.6	33.1	32.8		35.4	34.1	35.0	
Urban- teaching	62.1	60.6	61.4		61.4	62.8	61.8	

*__All-cause infection__: Composite of septicaemia, viremia and bacteraemia

In-hospital adverse outcomes

Overall, the crude rates of all in-hospital adverse events were higher in females than males (MACE: 5.6% vs. 4.5%; all-cause mortality: 1.0% vs. 0.9%; procedure-related bleeding: 3.2% vs. 2.7%; thoracic complications: 3.8% vs. 2.4%; and cardiac complications: 0.5% vs. 0.3%) with the exception of device-related infections, which were higher in males (1.1% vs. 0.6%). (**Table 5.4**, **Figure 5.3**) Similar differences in outcomes were observed between males and females in all device subgroups, with the exception of certain outcomes in the CRT groups. The rates of certain adverse outcomes were lower in females in the CRT-P group (MACE: 6.6% vs. 7.3%, all-cause mortality: 1.0% vs. 1.6%, procedure-related bleeding: 3.3% vs. 3.6%) as well as in the CRT-D group (all-cause mortality: 0.6% vs. 0.8%). (**Table 5.5, Figure 5.4**)

Table 5.4 In-hospital clinical outcomes of total cohort according to sex

	Male (58.1)	**Female (41.9)**	**Total**	**p-value**
MACE, %*	4.5	5.6	5.0	<0.001
All-cause mortality, %	0.9	1.0	1.0	<0.001
Procedure-related bleeding, %	2.7	3.2	2.9	<0.001
Thoracic complications, %	2.4	3.8	3.0	<0.001
Cardiac complications, %	0.3	0.5	0.4	<0.001
Device-related infection, %	1.1	0.6	0.9	<0.001

*MACE: Composite of mortality, thoracic complications, cardiac complications, and device-related infection.

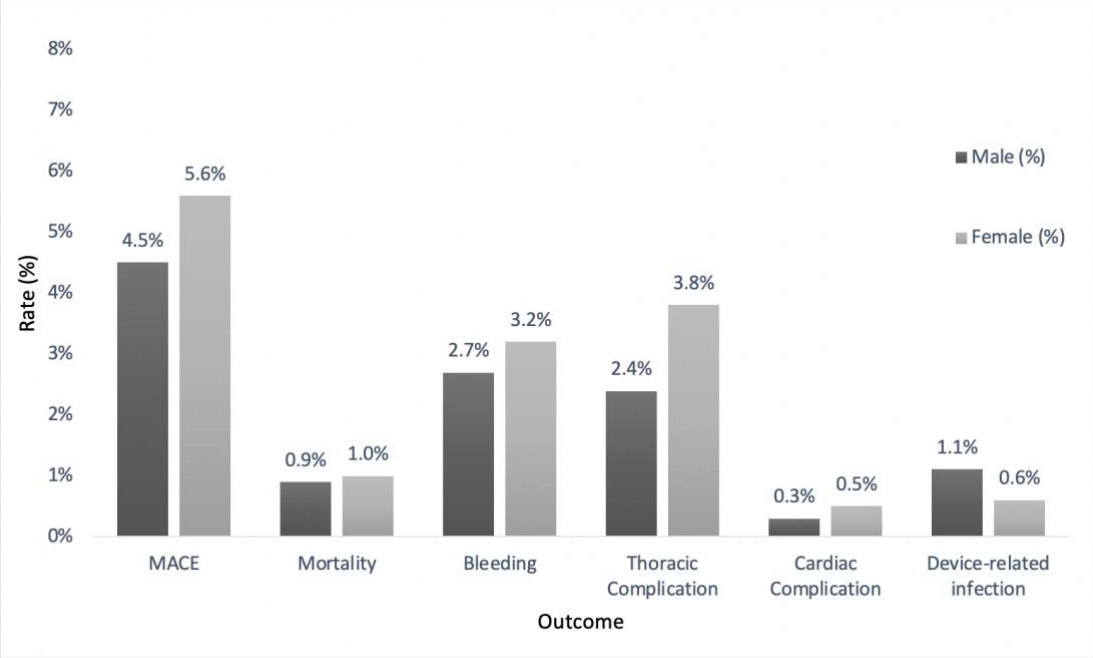
Table 5.5 In-hospital clinical Outcomes according to sex and type of CIED

Outcome/Study Group	Male	Female	Total	p-value
MACE, %*				
PPM	4.6	5.8	5.2	<0.001
CRT-P	7.3	6.6	7.0	0.001
CRT-D	4.7	5.1	4.8	<0.001
ICD	4.0	4.8	4.2	<0.001
All-cause mortality, %				
PPM	1.0	1.2	1.1	<0.001
CRT-P	1.6	1.0	1.4	<0.001
CRT-D	0.8	0.6	0.8	<0.001
ICD	0.6	0.7	0.6	<0.001
Procedure-related bleeding, %				
PPM	3.3	3.4	3.4	<0.001

Outcome/Study Group	Male	Female	Total	p-value
CRT-P	3.6	3.3	3.4	0.041
CRT-D	1.8	2.1	1.9	<0.001
ICD	2.0	2.5	2.2	<0.001
Thoracic complications, %				
PPM	2.6	4.0	3.3	<0.001
CRT-P	4.1	4.4	4.2	0.090
CRT-D	2.3	3.3	2.6	<0.001
ICD	2.0	2.9	2.2	<0.001
Cardiac complications, %				
PPM	0.3	0.4	0.4	<0.001
CRT-P	0.4	0.6	0.5	0.026
CRT-D	0.3	0.6	0.3	<0.001
ICD	0.3	0.6	0.4	<0.001
Device-related infection, %*				
PPM	0.9	0.5	0.7	<0.001
CRT-P	1.8	1.1	1.5	<0.001
CRT-D	1.6	0.9	1.4	<0.001
ICD	1.3	0.8	1.2	<0.001

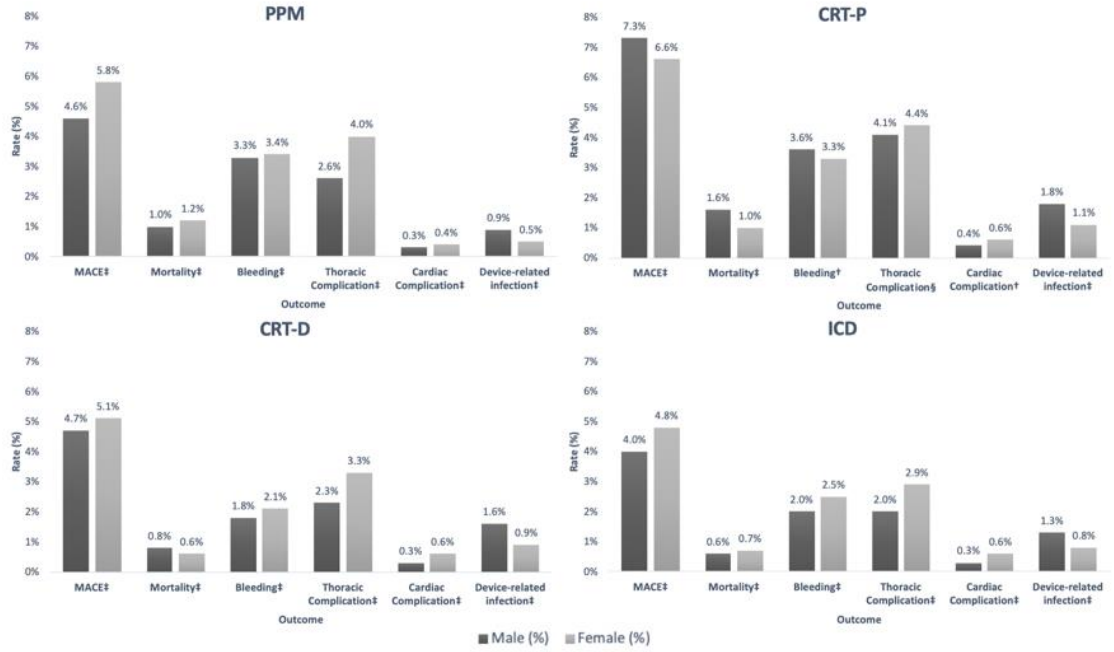
*MACE: Composite of mortality, thoracic complications, cardiac complications and device-related infection; ICD: implantable cardioverter-defibrillator; CRT-P & CRT-D: cardiac resynchronization therapy with pacemaker or defibrillator, respectively; PPM: permanent pacemaker

Figure 5.3 In-hospital outcomes of total CIED cohort according to sex



Legend: p<0.001 for all outcomes; **MACE**: Composite of mortality, thoracic and cardiac complications, and device-related infection

Figure 5.4 In-hospital outcomes of CIED subtypes according to sex

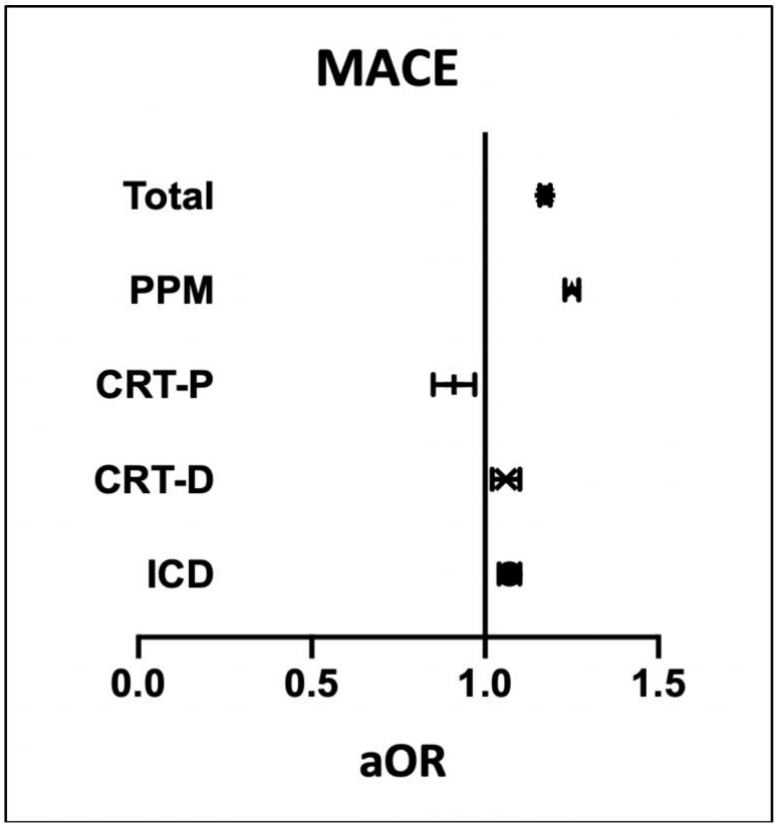


Legend: § non-significant; † p<0.05; ‡ p<0.001; **ICD**: automated implantable cardioverter-defibrillator; **CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively; **MACE**: Composite of all-cause mortality, thoracic and cardiac complications, and device-related infection; **PPM:** permanent pacemaker.

After adjustment for baselines differences, females were associated with increased odds of MACE (1.17 [1.16, 1.19]) and procedure-related complications (bleeding: 1.13 [1.12, 1.15], thoracic: 1.42 [1.40, 1.44] and cardiac: 1.44 [1.38, 1.50]), but no difference in mortality (0.96 [0.94, 1.00]). **(Table 5.6, Figures 5.5 and 5.6)** Within the individual device groups, female sex was generally associated with increased odds of MACE and procedure-related complications (bleeding, cardiac and thoracic) but not mortality. One exception was the CRT-P group where females experienced reduced odds of MACE (aOR 0.91 [0.85, 0.97]) and no statistically significant different odds of procedure-related complications (aOR bleeding: 1.01 [0.92, 1.11], thoracic: 1.04 [0.95, 1.12] and cardiac: 1.06 [0.84, 1.35]).

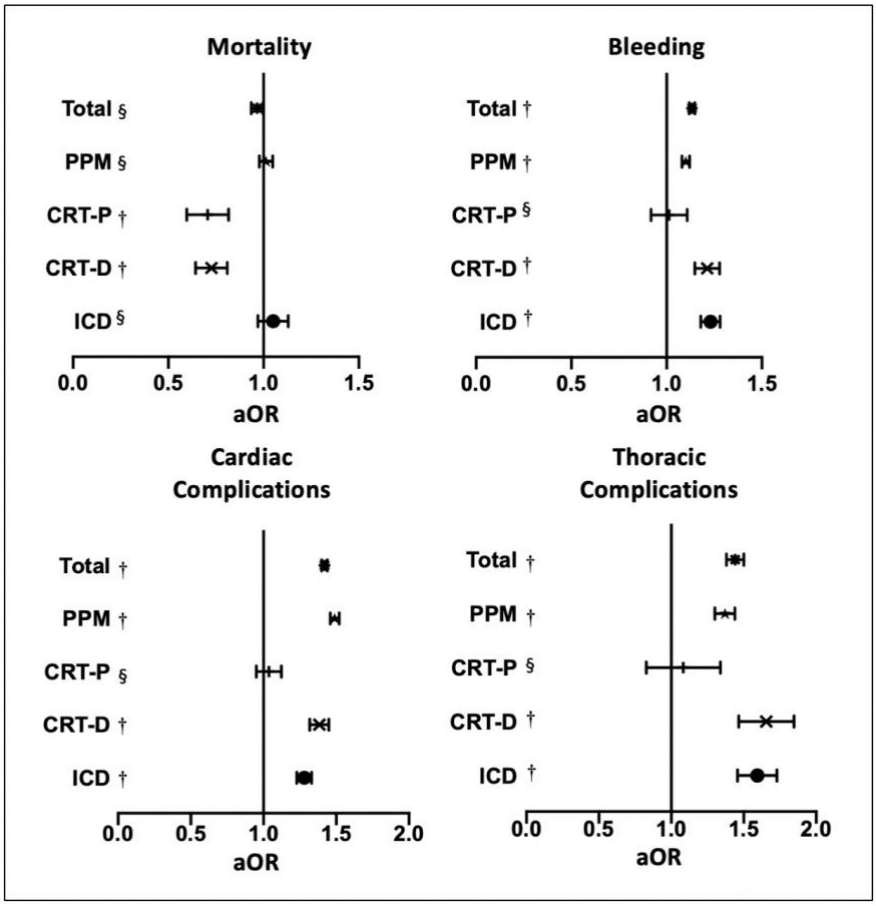
Trend analyses demonstrated persistently increased or worsening odds of MACE and procedure-related complications (bleeding, thoracic and cardiac) in females compared with males between 2004 and 2014. (**Figures 5.7 and 5.8**, p<0.001) However, the odds of all-cause mortality remained insignificant between sexes throughout the study period.

Figure 5.5 Adjusted odds ratio (aOR) of major adverse cardiovascular events (MACE) in females (reference is males)



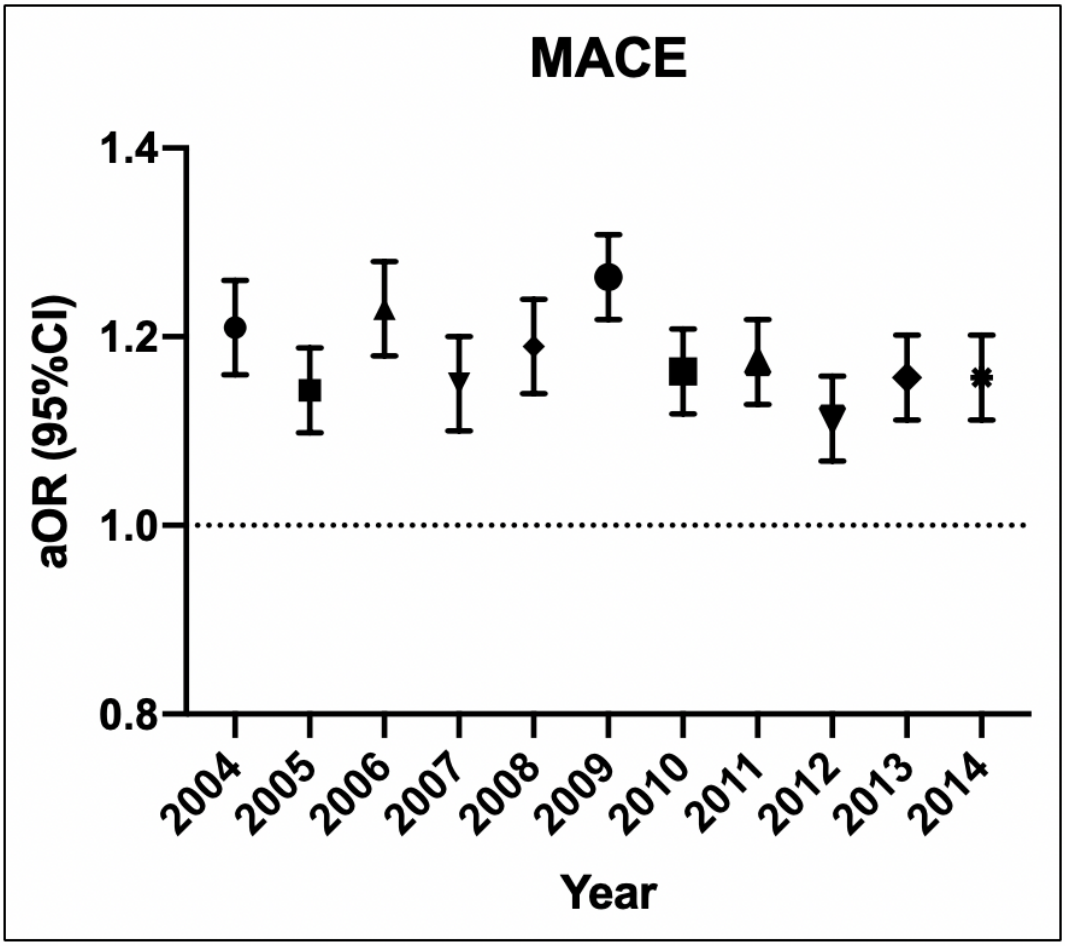
Legend: ***p<0.01; † p<0.001; ICD**: automated implantable cardioverter-defibrillator; **CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively; **MACE**: Composite of all-cause mortality, thoracic and cardiac complications, and device-related infection; **PPM:** permanent pacemaker.

Figure 5.6 Adjusted odds ratios (aOR) of all-cause mortality and procedure-related complications in females (reference is males)



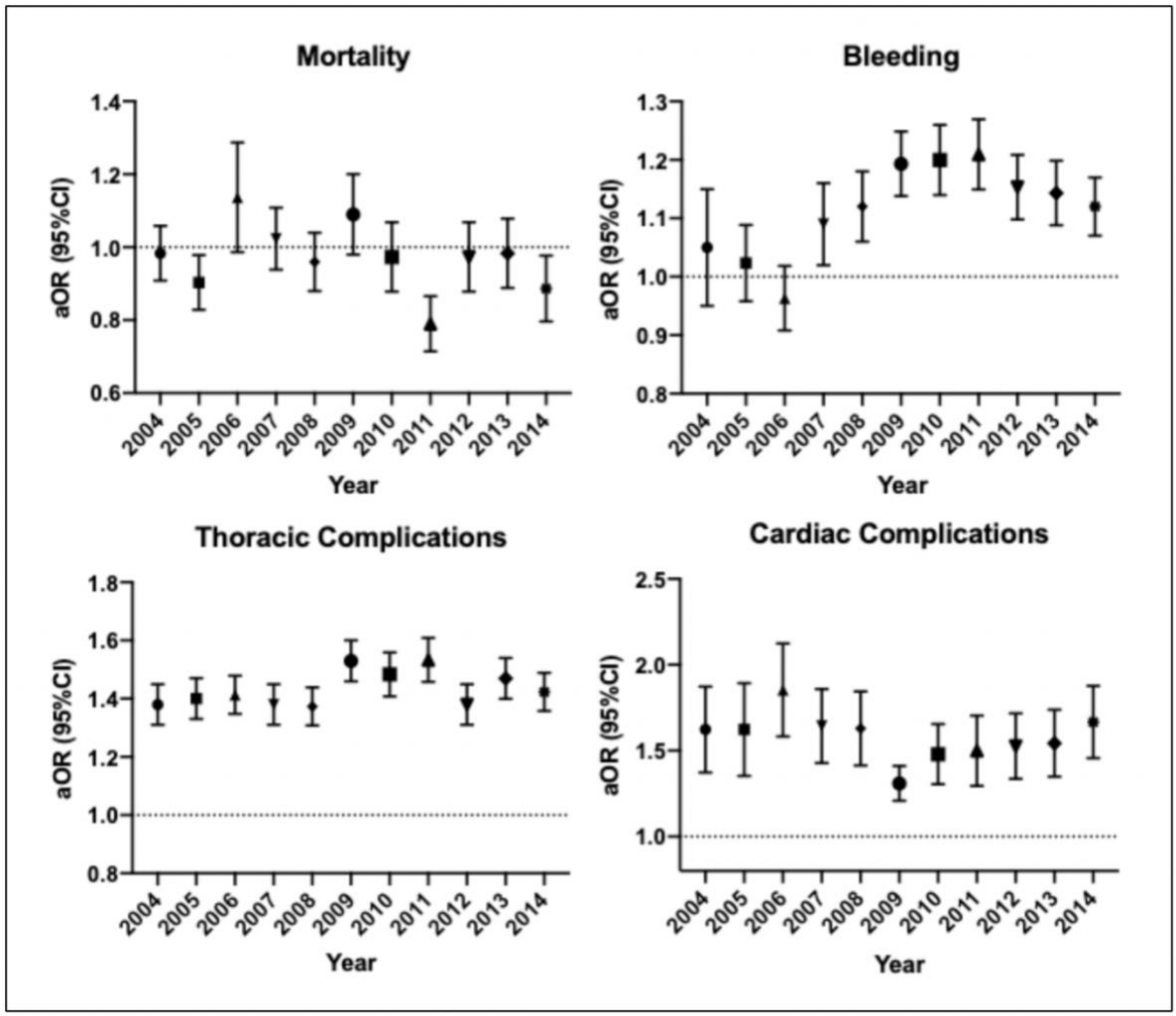
Legend: † p<0.001**; §** non-significant**; ICD**: automated implantable cardioverter-defibrillator; **CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively; **PPM:** permanent pacemaker

Figure 5.7 Trend of adjusted odds ratios (aOR) of MACE in females compared with males (2004-2014)*



Legend: *p<0.001 for trend; **MACE**: Composite of all-cause mortality, thoracic and cardiac complications, and device-related infection

Figure 5.8 Trend of adjusted odds ratios (aOR) of all-cause mortality and procedure-related complications in females compared with males (2004-2014)*



Legend: *p<0.001 for all trends

Table 5.6 Adjusted odds of adverse outcomes in females

Group/ Outcome	**MACE***		**All-cause Mortality**		**Procedure-related Bleeding**		**Thoracic Complications**		**Cardiac Complications**	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Total										
Male**	-	-	-	-	-	-	-	-	-	-
Female	1.17 [1.16, 1.19]	<0.001	0.96 [0.94, 1.00]	0.198	1.13 [1.12, 1.15]	<0.001	1.42 [1.40, 1.44]	<0.001	1.44 [1.38, 1.50]	<0.001
PPM										
Male**	-	-	-	-	-	-	-	-	-	-
Female	1.25 [1.23, 1.27]	<0.001	1.01 [0.98, 1.05]	0.367	1.10 [1.08, 1.12]	<0.001	1.49 [1.46, 1.52]	<0.001	1.37 [1.30, 1.44]	<0.001
CRT-P										
Male**	-	-	-	-	-	-	-	-	-	-
Female	0.91 [0.85, 0.97]	0.005	0.70 [0.60, 0.82]	<0.001	1.01 [0.92, 1.11]	0.872	1.04 [0.95, 1.12]	0.424	1.06 [0.84, 1.35]	0.610
CRT-D										
Male**	-	-	-	-	-	-	-	-	-	-
Female	1.06 [1.02, 1.10]	0.003	0.72 [0.66, 0.80]	<0.001	1.21 [1.15, 1.28]	<0.001	1.38 [1.32, 1.45]	<0.001	1.65 [1.47, 1.85]	<0.001
ICD										
Male**	-	-	-	-	-	-	-	-	-	-
Female	1.07 [1.04, 1.10]	<0.001	1.05 [0.97, 1.13]	0.252	1.23 [1.18, 1.28]	<0.001	1.28 [1.23, 1.33]	<0.001	1.59 [1.46, 1.73]	<0.001

*__MACE:__ Composite of mortality, thoracic complications, cardiac complications and device-related infection; **ICD**: implantable cardioverter-defibrillator; **CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively. **PPM:** permanent pacemaker.

5. Discussion

My national-level analysis of de novo CIED implantation procedures in the US is the largest to investigate differences in in-hospital outcomes between sexes. I conclude several important findings. First, I show that, overall, females are at an increased risk of major acute cardiovascular events as well as procedure-related complications after CIED implantation, including bleeding and thoracic and cardiac complications. These findings were observed across all device groups other than CRT-P, where the odds of MACE were lower in females and no difference in postprocedural complications (bleeding, thoracic and cardiac) was observed between sexes. Second, I found no difference in all-cause mortality between sexes in the overall cohort as well as in the PPM and ICD device groups, whereas females were at a lower risk of mortality in the CRT-P and CRT-D groups. Finally, my analysis demonstrates that the increased risk of procedure-related complications in females has persisted, or for some outcomes worsened, over the eleven-year study period.

While previous studies have examined the risk of adverse outcomes in females undergoing CIED implantation, the current evidence is conflicting, with some studies suggesting an increased risk of adverse outcomes in females and some suggesting no difference between sexes.[23, 55, 59, 60, 62-64, 84, 87, 90] Furthermore, these studies were limited by the inclusion of specific cohorts (e.g. heart failure patients) or device types (e.g. ICD only), or the analysis of older procedural cohorts, making them less generalisable to current practice. [55, 63, 122-126] Additionally, there is a significant variation in procedural outcomes examined in many studies with some looking at a composite of any hospital complication or specific complications (e.g., mortality) at various timepoints (e.g., 1 year). For example, an analysis of more than 77,000 CIED implantation procedures between 2010 and 2014 from the Japanese Diagnosis Procedure Combination database showed no difference in in-hospital complications between sexes in the overall cohort (OR 1.09 (0.99-1.21)) and those

undergoing non-PPM device implantations (OR 0.88 (0.63-1.23)), with a slight increase in the odds of any complication in those receiving PPM (OR 1.12 (1.01-1.25)). [64] However, their analysis did not look at individual CIED subtypes other than PPM, nor did it examine individual complications (e.g., thoracic or cardiac). In contrast, a study of more than 160,000 ICD and CRT implantations between 2006 and 2007 from the US National Cardiovascular Data Registry (NCDR) ICD registry showed increased odds of in-hospital complications among females (OR 1.71 (1.57-1.86)).[63] However, these conclusions were derived from an outdated cohort that precedes many advances in CIED implantation techniques. My national-level analysis of de novo CIED procedures shows an increased risk of MACE as well as individual complications (bleeding, thoracic and cardiac) in females in the overall CIED cohort. When stratified by device type, I observed similar sex differences in the odds of procedure-related complications except in the CRT-P group where there were no differences in procedure-related complications between sexes. Furthermore, the odds of any in-hospital complication (MACE) in that group was lower in females, driven by their lower rates of mortality. One possible explanation for the lack of sex differences in this device group is the relatively small sample size compared with other device groups, making it insufficiently powered to detect any obvious sex differences in that group, especially that there was a signal of increased odds among females for cardiac, thoracic and bleeding complications that did not reach statistical significance.

A limited number of studies have systematically examined sex differences in in-hospital mortality after CIED implantation across difference CIED groups. My study demonstrates no difference in mortality between sexes across all device groups except CRT, where females were associated with a lower risk of mortality compared with males. My findings confirm those in previous studies, although many of these did not stratify their analyses according to CIED type. In an analysis by Moore et al. no difference was observed

in in-hospital was observed between sexes (OR 0.99 (0.80-1.22)) in over 81,000 procedures.[91] Similarly, in a study of ~8500 patients aged >65 years undergoing ICD implantation from a stratified (5%) sample of the Medicare dataset showed no difference in the hazard ratio (HR) of 1-year mortality between sexes (0.97 (0.84–1.12)).[59] However, this study examined mortality in a specific elderly patient group undergoing implantation of a specific type of CIED, making its findings less generalisable to younger patients as well as those undergoing implantation of different device types. It is possible that the reduced mortality in females undergoing CRT implantation is attributable to their favourable response to resynchronisation therapy as demonstrated in previous studies.[127] The lack of difference in mortality between sexes across all other device groups, despite a higher risk of procedure-related complications in females as shown in my analysis, suggests that mortality is unlikely to be related to the procedure.

My analysis of in-hospital outcomes after CIED implantation demonstrates a rising trend of post-procedural complications (bleeding, thoracic and cardiac) in females over an 11-year period, which is a finding of concern in light of the significant technical advancements in recent years. Several anatomical factors increase the risk of thoracic and cardiac complications in females including their smaller thoracic cavities and subclavian/axillary vein diameters compared with males, which increase the risk pneumothorax, as well as their thinner right ventricle walls which makes the risk of cardiac perforation more likely. [53, 118-120] These findings highlight the inherent risk of procedural complications in females that warrants further research into technical strategies to neutralise the risk. For example, routine ultrasound guided vascular access as well as cephalic vein cut down could help reduce these complications in females, as would fluoroscopy or ultrasound-guided true septal placement (vs. apical or coronary sinus) of right ventricular leads. In a select group of patients, the use of subcutaneous or intracardiac

pacemakers could also help reduce these risks, although these are only proposed strategies that require validation in future studies.

Limitations

The first limitation of my analysis relates to the administrative nature of the dataset from which it was performed, which is subject to coding inaccuracies as mentioned in the limitations section in **Chapter 4**. Second, the NIS dataset does not provide information on the indication for CIED implantation as well as operator experience. Furthermore, my findings should be interpreted as associations and not causal given the observational nature of this analysis. Finally, my analysis only focused on in-hospital outcomes and it is possible that sex differences in longer-term outcomes may be more pronounced or insignificant.

6. Summary

In my analysis of 2.8 million hospitalisations for *de novo* CIED implantations in the United States, I show that female sex is an independent predictor of in-hospital adverse outcomes, but not mortality, and that this disparity in outcomes between sexes persisted over an 11-year period. These findings warrant further research on new technical and technological approaches to mitigate the inherent risk of procedural complications in females undergoing *de novo* CIED implantation.

Chapter 6. De novo CIED implantation outcomes in patients with cancer

The work in this chapter relates to the second phase of my thesis and is based on my study published in Europace journal (Appendix 3).[128]

1. Introduction

The incidence of cancer remains high both in developed countries and worldwide. More than 360,000 new cases of cancer were diagnosed in the United Kingdom (UK) alone between 2015 and 2017, making the nation's incidence rank higher than 90% of the rest of the world.[129]

There has been a significant evolution in cancer treatments over the years, including chemotherapeutics and radiotherapy, which has reflected on the rates of cancer survival. However, such therapies are not free from side effects, one of which is cardiotoxicity which results in heart failure (HF), cancer-treatment induced arrhythmias (CTIA) and myocardial ischaemia. [130-132] These adverse events are more likely to occur in patients with pre-existing cardiac disease which is a substrate for cardiotoxicity and could persist for years even after withdrawal of the cancer treatment. [131, 133] Although the mainstay for the management of CTIA and HF remains pharmacological, a number of patients will require a cardiac implantable electronic device (CIED) to manage their conduction system disease, arrhythmias or advanced heart failure. Depending on the indication, CIED options include permanent pacemakers (PPM), implantable cardioverter-defibrillators (ICD), and cardiac resynchronization therapy (CRT).[134, 135] However, it is unclear the number of patients with previous or current cancer who require CIED implantation continues to grow over the years, and whether their cancer diagnosis influences their procedural outcomes. This drives

the need for outcomes data for this population who are often excluded from major studies and clinical trials.[136]

2. Objectives

My main objectives of this chapter were to study the following:

c) The prevalence of cancer patients undergoing *de novo* CIED implantation from a national perspective over a 12-year period

d) Compare in-hospital procedural outcomes of de novo CIED implantation procedure between patients with and without (historical and current) cancer, stratified by type of implanted device.

3. Methods

A full description of the methodology relating to all chapters of my thesis is provided in Chapter 3.

a) Data Source

The data source for this study was the United States (US) National Inpatient Sample (NIS). Further information on its structure and validation has been provided in Chapter 3 and also described in Chapter 4 under the same heading.

b) Study Design and Population

I included all hospitalizations between January 2004 and September 2015 in the US during which *de novo* CIED implantation procedures were performed. I used the International Classification of Diseases, ninth revision (ICD-9) to extract patient diagnoses and procedural data as described in Chapter 3 (codes listed in **Table 3.1**). ICD-9 and Clinical Classification Software (CCS) codes were used to identify patients with a historical or current cancer diagnosis (**Table 6.1**). I excluded patients with any missing records for the following variables: age, sex, length of stay and mortality (total n=19,155, ~3% of dataset), as well as hospitalisations during which the following procedures were performed:

coronary angiography, percutaneous coronary intervention, and coronary artery bypass grafting. (see **Figure 6.1** for study flow diagram) Furthermore, I excluded patients with more than one historical or current cancer diagnosis.

Patients were stratified based on the presence or absence of cancer and further by type of prevalent cancer in to 5 groups (haematological, prostate, colon, breast and lung). Haematological malignancies included leukaemia, lymphoma (Hodgkin's and non-Hodgkin's), and multiple myeloma.

Figure 6.1. Flow chart of study population selection process

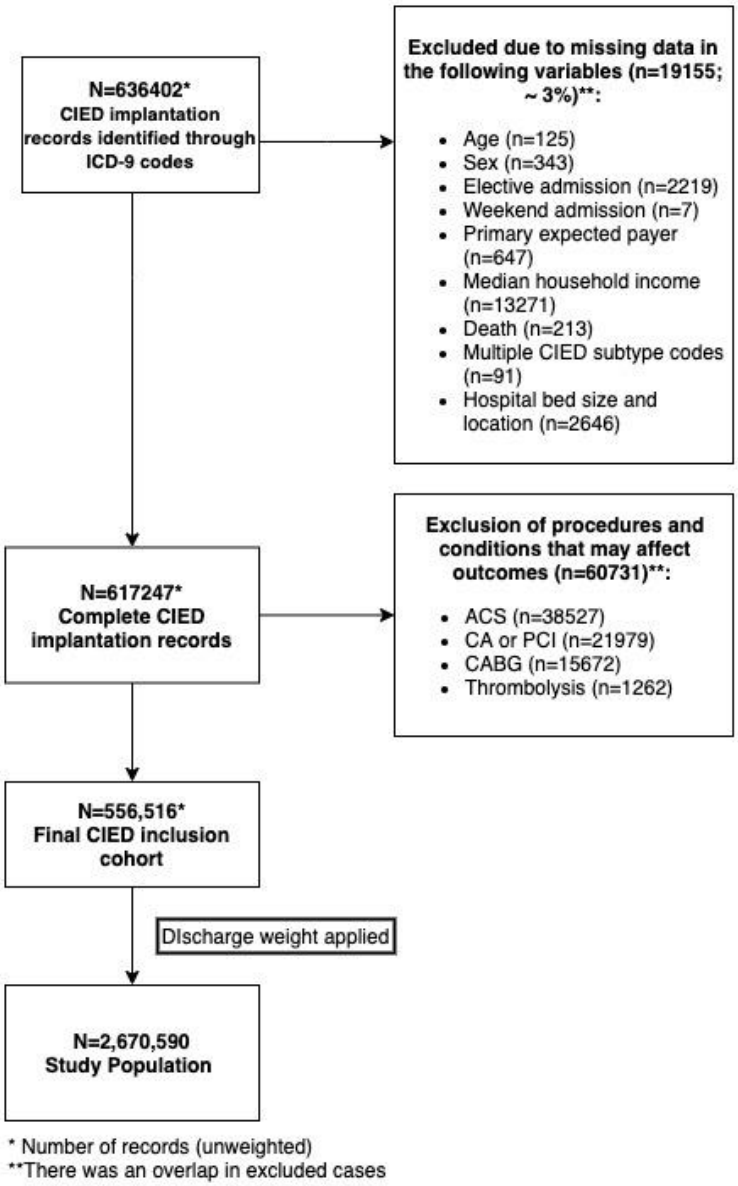


Table 6.1. Cancer codes

Variable	Source	Diagnostic (D)/ Procedural (P)	Codes
Cancer of head and neck	CCS	D	11
History of cancer of head and neck	ICD-9	D	V1001 V1002 V1021
Cancer of oesophagus	CCS	D	12
History of cancer of the oesophagus	ICD-9	D	V1003
Cancer of stomach	CCS	D	13
History of cancer of stomach	ICD-9	D	V1004
Cancer of colon	CCS	D	14
History of cancer of colon	ICD-9	D	V1005
Cancer of rectum and anus	CCS	D	15
History of cancer of the rectum and anus	ICD-9	D	V1006
Cancer of liver and intrahepatic bile duct	CCS	D	16
History of cancer of the liver and intrahepatic bile duct	ICD-9	D	V1007
Cancer of pancreas	CCS	D	17
Cancer of other GI organs, peritoneum	CCS	D	18
History of cancer of other GI organs, peritoneum	ICD-9	D	V1000 V1009
Cancer of bronchus, lung	CCS	D	19
History of cancer of bronchus, lung	ICD-9	D	V1011
Cancer, other respiratory and intra thoracic	CCS	D	20
History of cancer, other respiratory and intra thoracic	ICD-9	D	V1012 V1020 V1022
Cancer of bone and connective tissue	CCS	D	21
Melanomas of skin	CCS	D	22
History of melanoma of skin	ICD-9	D	V1082
Other non-epithelial cancer of skin	CCS	D	23
Cancer of breast	CCS	D	24
History of cancer of breast	ICD-9	D	V103
Cancer of uterus	CCS	D	25
History of cancer of uterus	ICD-9	D	V1042
Cancer of cervix	CCS	D	26
History of cancer of cervix	ICD-9	D	V1041
Cancer of ovary	CCS	D	27
History of cancer of ovary	ICD-9	D	V1043
Cancer of other female genital organs	CCS	D	28
History of cancer of other female genital organs	ICD-9	D	V1040 V1044
Cancer of prostate	CCS	D	29
History of cancer of prostate	ICD-9	D	V1046
Cancer of testis	CCS	D	30
History of cancer of testis	ICD-9	D	V1047

Cancer of other male genital organs	CCS	D	31
History of cancer of other male genital organs	ICD-9	D	V1045 V1048 V1049
Cancer of bladder	CCS	D	32
History of bladder cancer	ICD-9	D	V1051
Cancer of kidney and renal pelvis	CCS	D	33
History of cancer of kidney and renal pelvis	ICD-9	D	V1052 V1053
Cancer of other urinary organs	CCS	D	34
History of cancer of other urinary organs	ICD-9	D	V1050 V1059
Cancer of brain and nervous system	CCS	D	35
History of cancer of brain and nervous system	ICD-9	D	V1085 V1086
Cancer of thyroid	CCS	D	36
History of cancer of thyroid	ICD-9	D	V1087
Hodgkin's disease	CCS	D	37
History of Hodgkin's disease	ICD-9	D	V1072
Non-Hodgkin's lymphoma	CCS	D	38
History of non-Hodgkin's lymphoma	ICD-9	D	V1071 V1079
Leukaemia	CCS	D	39
History of leukaemia's	ICD-9	D	V1060 V1061 V1062 V1063 V1069
Multiple myeloma	CCS	D	40
Cancer, other and unspecified	CCS	D	41
Secondary malignancies	CCS	D	42
Neoplasms of unspecified site	CCS	D	43
History of cancer, other and unspecified	ICD-9	D	V1029 V1081 V1084 V1088 V1089 V1090 V1091 V711
Chemotherapy	ICD-9	D/P	Diagnoses: V58.11-12, V66.2, or V67.2, V87.41, 285.3 and procedures: 99.25, 00.10
Radiotherapy	ICD-9	D/P	Diagnoses: V58.0, V66.1 and V67.1 and procedures: 92.2-92.39

CCS: Clinical classification Software; ICD-9: International Classification of Diseases, Ninth Revision

c) Outcomes

The main outcomes were in-hospital major acute cardiovascular events (MACE) all-cause mortality and procedural-related complications (major bleeding, thoracic and cardiac complications, and device-related infection). MACE was defined as a composite of mortality, thoracic complications, cardiac complications and device-related infection. All analyses were stratified by type of CIED that was implanted. Major bleeding was defined

as any intracranial, gastrointestinal or post-procedural haemorrhage. Thoracic complications were defined as a composite of acute pneumothorax or haemothorax, with or without drainage, or thoracic vascular injury whereas cardiac complications were defined as a composite of cardiac tamponade, hemopericardium and pericardiocentesis.

d) Statistical Analysis

Descriptive statistics were performed as previously explained in Chapter 3. Sampling weights provided by the AHRQ were applied to all analyses. All statistical analyses were performed using SPSS version 26 (IBM Corp, Armonk, NY).

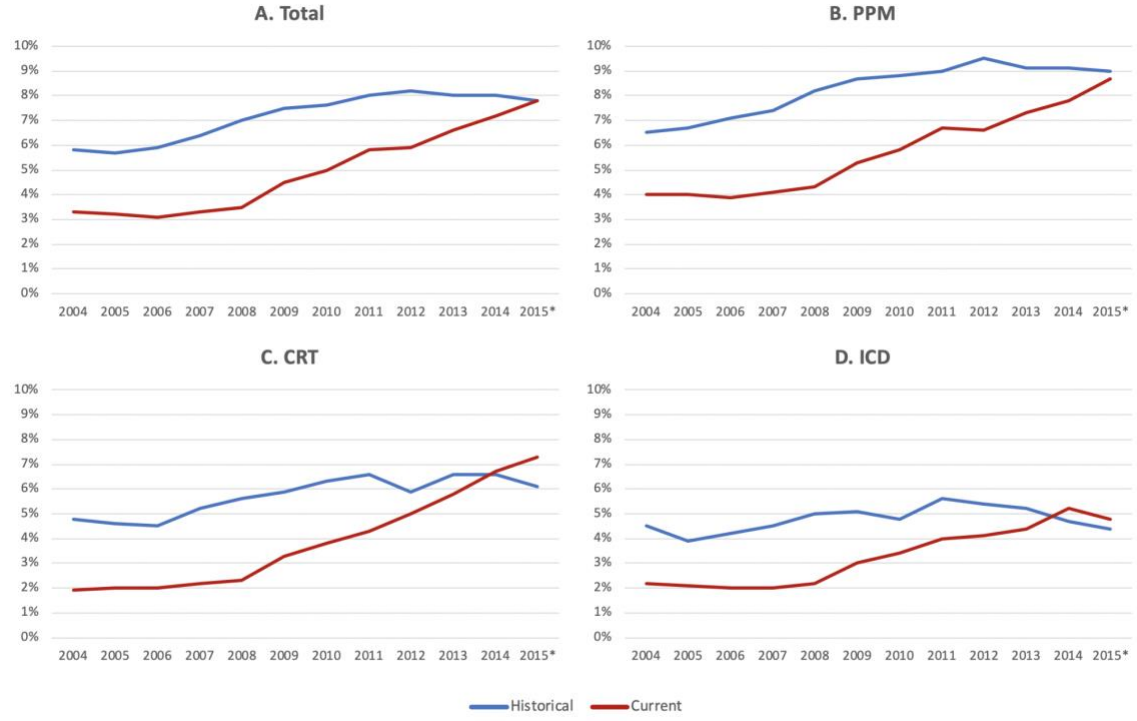
Multivariable logistic regression models were constructed to examine the following associations using the no-cancer group as the reference 1) cancer diagnosis timing groups (historical and current) and in-hospital outcomes, 2) prevalent current cancer types and each in-hospital outcome. All associations are presented as odds ratios (95% confidence intervals). The following variables were adjusted for in all models: age, sex, weekend admission, primary expected payer, median household income, dyslipidaemia, smoking status, cardiac previous acute myocardial infarction, previous CABG, history of ischemic heart disease (IHD), previous percutaneous coronary intervention (PCI), previous cerebrovascular accidents (CVA) including stroke or transient ischemic attacks, family history of CAD, bed size of hospital, region of hospital, location/teaching status of hospital, year of admission, history of cardiac arrest, ventricular tachycardia (VDT) and ventricular fibrillation (VF), atrial fibrillation (AF), cardiogenic shock and the Elixhauser comorbidities: acquired immune deficiency syndrome, rheumatoid arthritis/collagen vascular diseases, heart failure (HF), chronic pulmonary disease, coagulopathy, diabetes (uncomplicated), diabetes with chronic complications, hypertension, hypothyroidism, liver disease, metastasis status, other neurological disorders, obesity, peripheral vascular disorders, valvular heart disease, and weight loss.

Trend analyses was performed by assessing the interaction term between each cancer type and year in my logistic regression models.

4. Results

A total of 2,670,590 *de novo* CIED implantations were included in my analysis of which 187,387 (7.0%) patients had a historical cancer diagnosis and 122,620 (4.6%) patients had current cancer. The number of cancer patients (historical and current) undergoing any CIED implantation increased between 1.5 to 2-fold over the study period (current: 3.3% to 7.8%; historical: 5.8% to 7.8%), a pattern that was consistent across all device groups (**Figure 6.2**). The rate of utilisation of PPM compared with other CIED types (CRT and ICD) was higher among the cancer groups (historical: 73.6%, current: 75%) than the no-cancer group (62%).

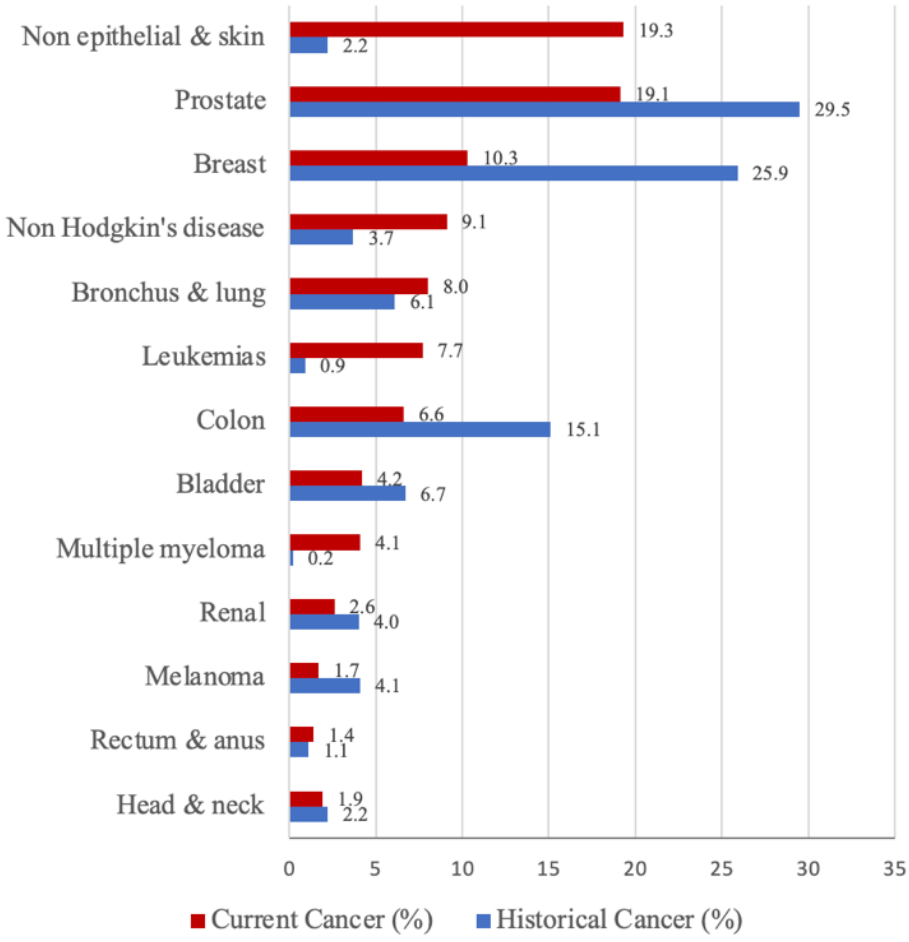
Figure 6.2. Prevalence of cancer over the study period in A) total cohort and B) individual CIED subgroups



Legend: *2015 only includes admissions from 1st January through 30th September; p_{trend} <0.001 for all except ICD: p=0.07; ICD: implantable cardioverter-defibrillator; CRT: cardiac resynchronization therapy; PPM: permanent pacemaker

The most prevalent current cancer types were non-epithelial and skin (19.3%), prostate (19.1%), haematological (Hodgkin's and non-Hodgkin's lymphoma, leukaemia and multiple myeloma, total: 17.1%), breast (10.3%), bronchus and lung (8.0%), and colon (4.2%) malignancies whereas the most common historical cancers. included prostate (29.5%), breast (25.9%), colon (15.1%), bladder (6.7%), and bronchus and lung malignancies (6.0). (**Figure 6.3**)

Figure 6.3. Prevalence of most common cancer diagnoses



Patient characteristics

Compared to those without cancer, patients with historical and current cancer were older, more likely to undergo an emergent (non-elective) procedure and were more likely to be of white ethnic background. (**Table 6.2**) The highest prevalence of males was among those with current cancer (62.7%) followed by those without cancer (57.1%) and those with

historical cancer (55.9%). Overall, the prevalence of HF was lower in the cancer groups (historical and current) compared with the no cancer group whereas the prevalence of risk factors such as AF, hypertension and dyslipidaemia were higher in the cancer groups. Specifically, the current cancer group had the highest prevalence of comorbidities such as coagulopathies (including thrombocytopaenia and anaemia), renal failure, chronic pulmonary disease, AF, and fluid and electrolyte disturbances.

Table 6.2. Sociodemographic data of the study groups

Variable/Group (%)	No cancer (88.4)	Historical cancer (7.0)	Current cancer (4.6)	p-value
Number of weighted discharges	2360583	187387	122620	-
Device type, %				<0.001
PPM	62.0	73.6	75.0	
CRT	16.4	12.7	11.8	
ICD	21.6	13.8	13.2	
Age (years), median (IQR)	75 (65,82)	79 (72,85)	78 (71,84)	<0.001
Males, %	57.1	55.9	62.7	<0.001
Ethnicity, %				<0.001
White	78.2	85.3	84.3	
Black	10.1	7.5	7.0	
Hispanic	6.8	3.8	4.8	
Asian/Pacific Islander	2.0	1.1	1.7	
Native American	0.5	0.4	0.2	
Other	2.4	1.8	2.1	
LOS, days (median (IQR))	3 (1,7)	3 (2,6)	5 (2,9)	<0.001
Elective Admission, %	31.9	27.1	24.3	<0.001
Weekend admission, %	14.7	16.1	17.5	<0.001
Primary expected payer, %				<0.001
Medicare	73.5	85.7	83.3	
Medicaid	4.7	1.5	2.2	
Private Insurance	18.3	11.4	12.6	
Self-pay	1.6	0.5	0.7	
No charge	0.2	0.1	0.1	
Other	1.6	0.9	1.1	
Median Household Income (Percentile), %				<0.001
0-25th	26.2	22.1	21.8	
26-50th	26.6	25.3	25.5	
51-75th	24.5	25.2	25.2	
76-100th	22.7	27.5	27.5	
Hospital bed size, %				0.002
Small	9.1	9.1	9.1	
Medium	22.3	22.5	23.0	

Variable/Group (%)	No cancer (88.4)	Historical cancer (7.0)	Current cancer (4.6)	p-value
Large	68.6	68.4	67.8	
Hospital Region, %				<0.001
Northeast	21.1	25.9	20.6	
Midwest	23.5	23.6	25.1	
South	37.8	34.4	32.9	
West	17.6	16.1	21.4	
Location/ Teaching status, %				<0.001
Rural	6.6	6.4	6.3	
Urban non-teaching	40.6	40.0	39.1	
Urban- teaching	52.8	53.6	54.6	
Shock, %	0.9	0.4	1.1	<0.001
Cardiac Arrest, %	1.4	0.7	1.9	<0.001
Ventricular Tachycardia, %	3.5	2.0	3.8	<0.001
Ventricular Fibrillation, %	2.7	1.3	2.3	<0.001
Comorbidities, %				
Dyslipidaemia	41.8	45.8	44.7	<0.001
Smoking	15.5	20.4	15.6	<0.001
Atrial Fibrillation	38.3	40.4	44.0	<0.001
Thrombocytopenia	2.1	1.9	4.7	<0.001
Previous AMI	11.0	10.6	9.5	<0.001
History of IHD	43.9	41.0	42.3	<0.001
Previous PCI	8.2	9.5	6.4	<0.001
Previous CABG	12.4	12.8	9.0	<0.001
Previous CVA	3.6	5.8	3.6	<0.001
Family history of CAD	2.2	2.2	1.5	<0.001
AIDS	0.1	0.0	0.1	<0.001
Alcohol abuse	1.9	1.1	1.7	<0.001
Anaemia	12.9	13.9	23.0	<0.001
RA/collagen vascular diseases	2.1	2.3	2.6	<0.001
Heart Failure	43.7	34.7	39.9	
Chronic pulmonary disease	18.7	18.6	23.0	<0.001
Coagulopathy	3.9	3.6	7.6	<0.001
Depression	5.9	6.3	7.9	<0.001
Diabetes	29.3	26.4	28.8	<0.001
Drug abuse	1.0	0.3	0.6	<0.001
Hypertension	64.2	69.5	67.2	<0.001
Hypothyroidism	13.0	16.5	16.3	<0.001
Liver disease	1.1	0.7	1.5	<0.001
Fluid and electrolyte disturbances	16.8	14.0	25.2	<0.001
Obesity	9.0	6.1	8.8	<0.001
Peripheral vascular disease	8.4	8.0	11.0	<0.001
Psychoses	1.9	1.3	1.9	<0.001
Pulmonary circulation disorder	0.6	0.4	1.3	<0.001
Renal failure (chronic)	15.7	14.7	22.9	<0.001

Variable/Group (%)	No cancer (88.4)	Historical cancer (7.0)	Current cancer (4.6)	p-value
Valvular heart disease	1.4	1.1	3.0	<0.001
Weight loss	1.9	1.2	4.4	<0.001
Dementia	1.9	2.0	2.1	<0.001

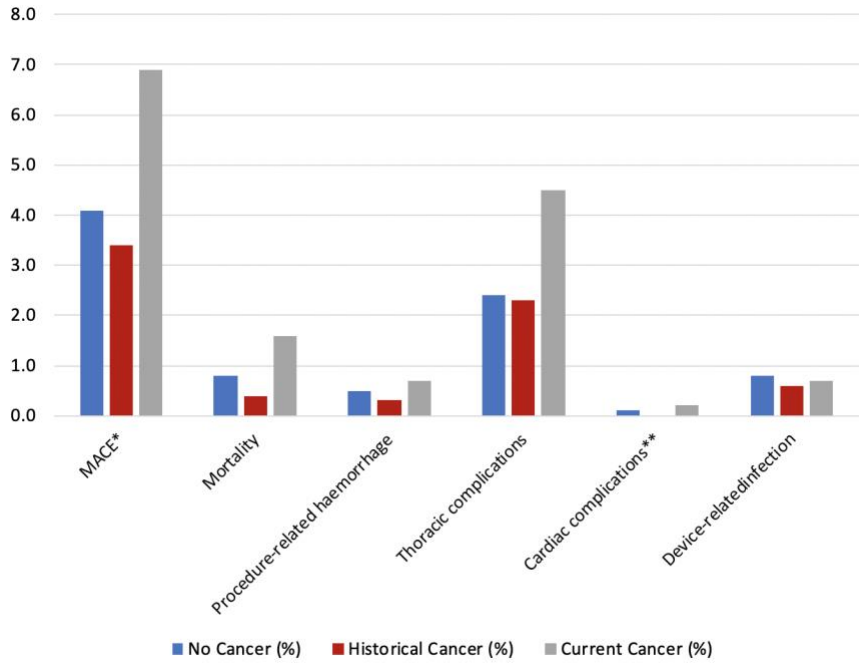
CRT: cardiac resynchronization; IQR: interquartile range; PPM: permanent pacemaker; ICD: Implantable cardioverter-defibrillator

In-hospital outcomes

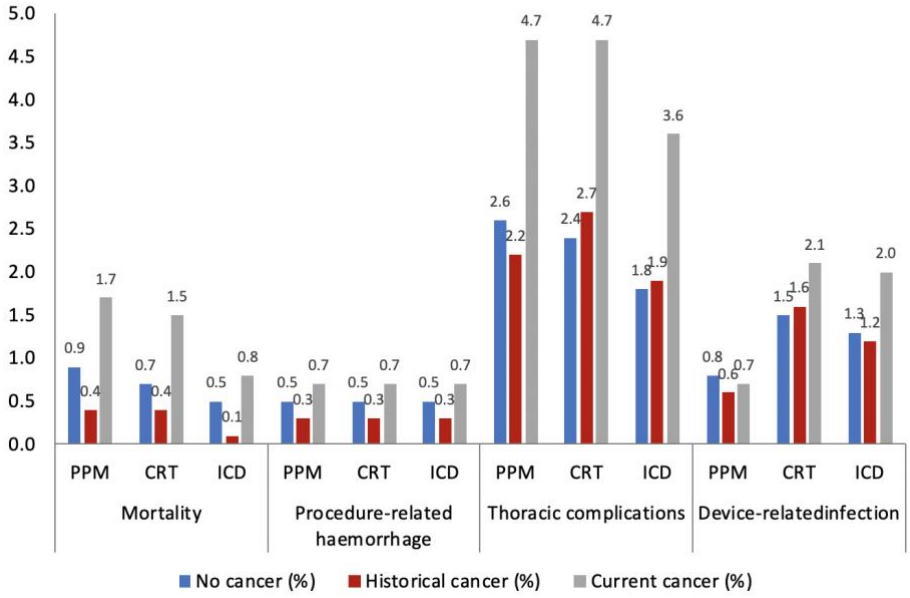
The rates of in-hospital mortality and post-procedure complications were significantly (1.5 to 2-fold) higher among patients with current cancer compared with those without cancer (MACE: 6.9% vs. 4.1%; mortality: 1.6% vs. 0.8%; major bleeding: 2.0% vs. 1.1%; thoracic complications: 4.5% vs. 2.4%; cardiac complications: 0.2% vs. 0.1%), except for device related infection which was similar in both groups (1.1 vs. 1.0%). (**Figure 6.4, Table 6.3**). However, patients with a historical cancer diagnosis experienced similar or lower rates of adverse events to those without cancer. Similar findings were observed in the individual CIED groups. (**Figure 6.4**)

Figure 6.4. In-hospital adverse events in A) overall cohort and B) individual CIED subgroups according to timing of cancer diagnosis

A)



B)



Legend: *MACE: Composite of mortality, thoracic complications, cardiac complications and device-related infection; **Cardiac complications occurred at a frequency less than 0.05% in the historical cancer groups; ICD: implantable cardioverter-defibrillator; CRT: cardiac resynchronization therapy; PPM: permanent pacemaker

Table 6.3. In-hospital adverse event rates

Outcome/ Study Group (% of cohort)	No cancer (88.4)	Historical cancer (7.0)	Current cancer (4.6)	p-value
MACE, %*				
Total, %	4.1	3.4	6.9	<0.001
PPM, %	4.2	3.3	6.8	<0.001
CRT, %	4.6	4.6	7.9	<0.001
ICD, %	3.6	3.3	6.3	<0.001
All-cause mortality, %				
Total, %	0.8	0.4	1.6	<0.001
PPM, %	0.9	0.4	1.7	<0.001
CRT, %	0.7	0.4	1.5	<0.001
ICD, %	0.5	0.1	0.8	<0.001
Major bleeding, %				
Total, %	1.1	0.8	2.0	<0.001
PPM, %	1.2	0.8	2.0	<0.001
CRT, %	1.1	0.8	1.5	<0.001
ICD, %	1.1	0.8	1.9	<0.001
Thoracic complications, %				
Total, %	2.4	2.3	4.5	<0.001
PPM, %	2.6	2.2	4.7	<0.001
CRT, %	2.4	2.7	4.7	<0.001
ICD, %	1.8	1.9	3.6	<0.001
Cardiac complications, %**				

Outcome/ Study Group (% of cohort)	No cancer (88.4)	Historical cancer (7.0)	Current cancer (4.6)	p-value
Total, %	0.1	0.0	0.2	<0.001
PPM, %	0.1	0.0	0.2	<0.001
CRT, %	0.1	0.0	0.1	<0.001
ICD, %	0.1	0.0	0.2	<0.001
Device-related infection, %*				
Total, %	1.0	0.8	1.1	<0.001
PPM, %	0.8	0.6	0.7	0.002
CRT, %	1.5	1.6	2.1	<0.001
ICD, %	1.3	1.2	2.0	<0.001

*MACE: Composite of mortality, thoracic complications, cardiac complications and device-related infection; **Cardiac complications occurred at a frequency less than 0.05% in the historical cancer groups; ICD: implantable cardioverter-defibrillator; CRT: cardiac resynchronization therapy; PPM: permanent pacemaker.

After adjustment for baseline differences between the no cancer and cancer groups, there were no increased odds of MACE, mortality or procedure-related complications between patients with historical cancer and those without cancer in the total cohort (**Table 6.4, Figure 6.5).** However, patients with current cancer were association with increased odds of all mortality and procedure-related complications compared with patients without cancer. Although similar findings were observed in the individual CIED subgroups, there were two exceptions. The odds of thoracic complications were increased in patients with historical and current cancer in the CRT group (1.16 95% CI 1.07, 1.26 and 1.34 95% CI 1.23, 1.46, respectively), whereas mortality was similar between patients with current cancer and no caner in the ICD group (OR 1.01 95% CI 0.83, 1.22, p=0.922).

Most prevalent current cancer types

The five most prevalent cancer types among those undergoing de novo CIED implantation included haematological, breast, lung, colon and prostate malignancies. The highest rates of MACE (15.7%), all-cause mortality (3.6%) and thoracic complications (12.4%) were observed among lung cancer patients while the highest rates of major bleeding (4.0%) and cardiac complications (0.3%) were in the colon and breast cancer groups, respectively. (**Table 6.5, Figure 6.6**) These findings were similar in the individual

CIED subgroups, with the exception of all-cause mortality and cardiac complications in the CRT group, which were highest in the colon and lung cancer subgroups, respectively.

Figure 6.5. Adjusted odds ratios (OR) of adverse events in total cohort and according to device subtype

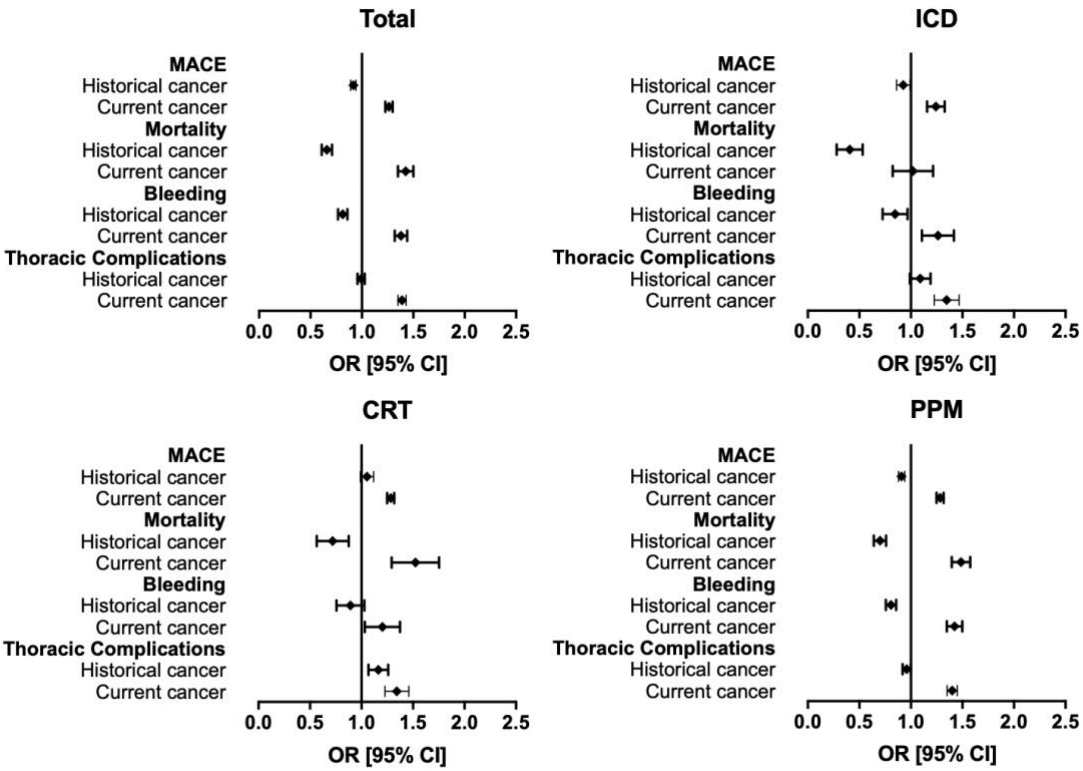


Figure 6.6 In-hospital adverse events according in most prevalent cancer groups

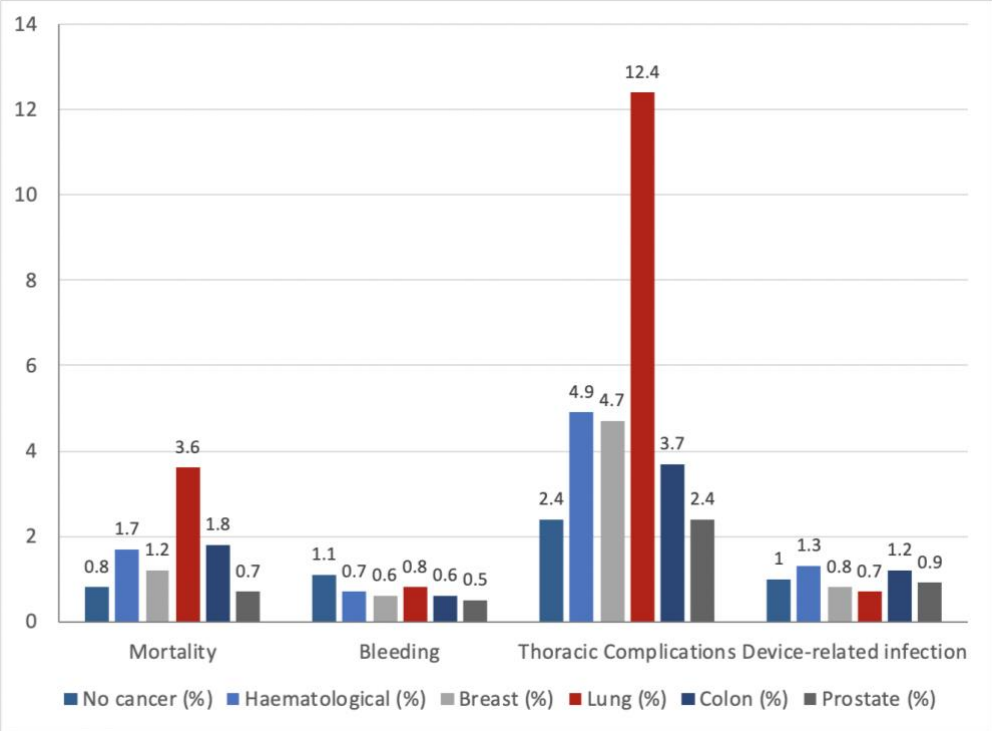


Table 6.4. Adjusted odds of in-hospital adverse events*

Study Group/ Outcome	MACE**		Mortality		Major Bleeding		Thoracic Complications	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Total								
No cancer*	-	-	-	-	-	-	-	-
Historical cancer	0.92 [0.89, 0.94]	<0.001	0.66 [0.61, 0.71]	<0.001	0.81 [0.77, 0.86]	<0.001	0.99 [0.96, 1.03]	0.763
Current cancer	1.26 [1.23, 1.30]	<0.001	1.43 [1.35, 1.50]	<0.001	1.38 [1.32, 1.44]	<0.001	1.39 [1.35, 1.43]	<0.001
PPM								
No cancer*	-	-	-	-	-	-	-	-
Historical cancer	0.91 [0.88, 0.94]	<0.001	0.70 [0.64, 0.76]	<0.001	0.80 [0.76, 0.86]	<0.001	0.96 [0.92, 1.00]	0.051
Current cancer	1.28 [1.25, 1.32]	<0.001	1.48 [1.40, 1.58]	<0.001	1.42 [1.35, 1.50]	<0.001	1.40 [1.35, 1.45]	<0.001
CRT								
No cancer*	-	-	-	-	-	-	-	-
Historical cancer	1.05 [0.99, 1.12]	0.135	0.71 [0.57, 0.88]	0.002	0.89 [0.76, 1.03]	0.118	1.16 [1.07, 1.26]	<0.001
Current cancer	1.18 [1.10, 1.26]	<0.001	1.51 [1.30, 1.76]	<0.001	1.19 [1.04, 1.38]	0.014	1.34 [1.23, 1.46]	<0.001
ICD								
No cancer*	-	-	-	-	-	-	-	-
Historical cancer	0.93 [0.86, 0.99]	0.032	0.39 [0.29, 0.54]	<0.001	0.84 [0.73, 0.97]	0.016	1.09 [0.99, 1.19]	0.078
Current cancer	1.24 [1.16, 1.33]	<0.001	1.01 [0.83, 1.22]	0.922	1.26 [1.11, 1.42]	<0.001	1.34 [1.23, 1.47]	<0.001

*reference group for each outcome, **MACE: Composite of mortality, thoracic and cardiac complications and device-related infection. ICD: implantable cardioverter-defibrillator; CRT: cardiac resynchronization therapy; PPM: permanent pacemaker

Table 6.5. In-hospital crude adverse event rates in most prevalent current cancer groups

Outcome/ Study Group (% of total cohort)	No cancer (88.4)	Haematological (0.9)	Breast (0.5)	Lung (0.4)	Colon (0.3)	Prostate (0.9)	p-value
MACE, %*							
Total, %	4.1	7.5	6.5	15.7	6.5	4.0	<0.001
PPM, %	4.2	7.5	6.5	16.6	6.3	3.3	<0.001
CRT, %	4.6	7.9	9.8	11.0	7.8	5.3	0.002
ICD, %	3.6	7.3	3.3	12.1	6.7	6.1	<0.001
All-cause mortality, %							
Total, %	0.8	1.7	1.2	3.6	1.8	0.7	<0.001
PPM, %	0.9	2.1	1.4	4.2	1.7	0.6	<0.001
CRT, %	0.7	1.5	0.8	0.6	3.3	0.5	0.022
ICD, %	0.5	0.6	**	1.4	1.1	1.2	<0.001
Major bleeding, %							
Total, %	1.1	1.8	1.1	2.2	4.0	1.7	<0.001
PPM, %	1.2	1.9	1.3	2.3	3.6	1.8	<0.001
CRT, %	1.1	1.3	**	1.8	5.5	1.5	<0.001
ICD, %	1.1	1.5	1.0	1.8	5.5	1.6	<0.001
Thoracic complications, %							
Total, %	2.4	4.9	4.7	12.4	3.7	2.5	<0.001
PPM, %	2.6	4.9	4.8	13.2	3.8	2.2	<0.001
CRT, %	2.4	4.8	6.2	9.8	4.7	3.3	<0.001
ICD, %	1.8	4.9	2.3	8.0	2.3	3.0	<0.001
Cardiac complications, %							
Total, %	0.1	0.2	0.3	0.2	0.1	0.1	<0.001
PPM, %	0.1	0.2	0.3	0.2	0.1	0.1	<0.001
CRT, %	0.1	0.1	**	0.6	**	**	0.612

Outcome/ Study Group (% of total cohort)	No cancer (88.4)	Haematological (0.9)	Breast (0.5)	Lung (0.4)	Colon (0.3)	Prostate (0.9)	p-value
ICD, %	0.1	**	0.6	**	0.5	0.1	<0.001
Device-related infection, %*							
Total, %	1.0	1.3	0.8	0.7	1.2	0.9	<0.001
PPM, %	0.8	1.0	0.5	0.5	1.0	0.6	<0.001
CRT, %	1.5	2.0	2.8	0.6	1.3	1.6	<0.001
ICD, %	1.3	1.9	0.7	2.7	2.7	2.0	<0.001

*MACE: Composite of mortality, thoracic complications, cardiac complications and device-related infection; **No or fewer than 10 events occurred; ICD: implantable cardioverter-defibrillator; CRT: cardiac resynchronization therapy; PPM: permanent pacemaker.

Table 6.6. Adjusted odds of in-hospital adverse events in most prevalent current cancer groups*

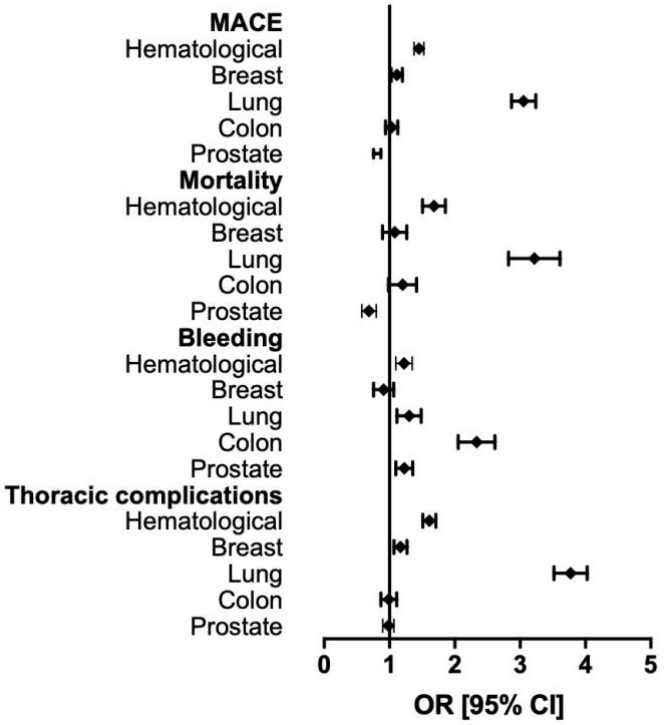
Study Group/ Outcome	MACE**		Mortality		Major Bleeding		Thoracic Complications	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Total								
No cancer*	-	-	-	-	-	-	-	-
Haematological	1.45 [1.38, 1.53]	<0.001	1.67 [1.51, 1.86]	<0.001	1.22 [1.10, 1.35]	<0.001	1.61 [1.51, 1.71]	<0.001
Breast	1.11 [1.03, 1.20]	0.005	1.07 [0.90, 1.27]	0.441	0.90 [0.76, 1.07]	0.229	1.17 [1.07, 1.27]	<0.001
Lung	3.05 [2.87, 3.24]	<0.001	3.20 [2.83, 3.62]	<0.001	1.29 [1.12, 1.49]	<0.001	3.77 [3.52, 4.03]	<0.001
Colon	1.03 [0.94, 1.13]	0.529	1.19 [0.99, 1.42]	0.062	2.32 [2.06, 2.62]	<0.001	0.99 [0.87, 1.11]	0.832
Prostate	0.81 [0.76, 0.87]	<0.001	0.68 [0.58, 0.80]	<0.001	1.22 [1.10, 1.36]	<0.001	0.98 [0.90, 1.07]	0.670
PPM								
No cancer*	-	-	-	-	-	-	-	-
Haematological	1.45 [1.38, 1.53]	<0.001	1.83 [1.62, 2.06]	<0.001	1.32 [1.17, 1.48]	<0.001	1.57 [1.45, 1.69]	<0.001
Breast	1.11 [1.03, 1.20]	0.005	1.18 [0.99, 1.42]	0.068	1.03 [0.86, 1.24]	0.733	1.20 [1.09, 1.32]	<0.001
Lung	3.05 [2.87, 3.24]	<0.001	3.14 [2.75, 3.59]	<0.001	1.25 [1.07, 1.47]	0.005	3.82 [3.55, 4.12]	<0.001
Colon	1.03 [0.94, 1.13]	0.529	1.05 [0.85, 1.30]	0.639	2.04 [1.77, 2.35]	<0.001	1.00 [0.87, 1.14]	0.992
Prostate	0.81 [0.76, 0.87]	<0.001	0.62 [0.51, 0.75]	<0.001	1.24 [1.10, 1.40]	<0.001	0.89 [0.80, 0.99]	0.028
CRT								
No cancer*	-	-	-	-	-	-	-	-
Haematological	1.31 [1.15, 1.48]	<0.001	1.54 [1.17, 2.02]	0.002	0.95 [0.72, 1.27]	0.749	1.54 [1.32, 1.80]	<0.001
Breast	1.54 [1.27, 1.87]	<0.001	0.86 [0.42, 1.77]	0.688	†	†	1.48 [1.17, 1.89]	0.001
Lung	1.76 [1.38, 2.23]	<0.001	0.85 [0.35, 2.09]	0.730	1.61 [0.95, 2.75]	0.079	2.90 [2.25, 3.73]	<0.001
Colon	1.05 [0.80, 1.38]	0.740	2.98 [1.93, 4.62]	<0.001	3.99 [2.87, 5.56]	<0.001	1.18 [0.84, 1.67]	0.339
Prostate	0.75 [0.63, 0.89]	<0.001	0.41 [0.24, 0.70]	0.001	1.09 [0.80, 1.48]	0.592	1.02 [0.83, 1.26]	0.828
ICD								
No cancer*	-	-	-	-	-	-	-	-
Haematological	1.48 [1.30, 1.68]	<0.001	0.84 [0.55, 1.27]	0.394	1.02 [0.79, 1.33]	0.859	1.91 [1.64, 2.23]	<0.001
Breast	0.61 [0.45, 0.82]	0.001	†	†	0.65 [0.38, 1.12]	0.117	0.66 [0.46, 0.95]	0.023
Lung	2.39 [1.96, 2.91]	<0.001	2.00 [1.17, 3.42]	0.011	0.97 [0.61, 1.55]	0.907	2.79 [2.20, 3.53]	<0.001

Study Group/ Outcome	MACE**		Mortality		Major Bleeding		Thoracic Complications	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Colon	1.04 [0.79, 1.38]	0.761	1.09 [0.56, 2.10]	0.806	2.84 [2.07, 3.90]	<0.001	0.66 [0.42, 1.04]	0.075
Prostate	1.22 [1.05, 1.42]	0.008	1.71 [1.23, 2.37]	0.001	1.13 [0.86, 1.50]	0.379	1.30 [1.05, 1.60]	0.014

*reference group for each outcome, **MACE: Composite of mortality, thoracic and cardiac complications and device-related infection; ICD: implantable cardioverter-defibrillator; CRT: cardiac resynchronization therapy; PPM: permanent pacemaker; †: no or fewer than 10 events occurred

In multivariable analysis, lung cancer patients were associated with a significant increase in odds of MACE (OR 3.05 95% CI 2.87, 3.24), all-cause mortality (OR 3.20 95% CI 2.83, 3.62), thoracic complications (OR 3.77 95% CI 3.52, 4.03) and major bleeding (OR 1.29 95% CI 1.12, 1.49). (**Table 6.6, Figure 6.7**) Patients with haematological malignancies were at increased odds of MACE (OR 1.45 95% CI 1.38, 1.53), mortality (OR 1.67 95% CI 1.51, 1.86) and post-procedure complications (major bleeding: OR 1.22 95% CI 1.10, 1.35, thoracic complications: OR 1.61 95% CI 1.51, 1.71). The only in-hospital complication that was increased in patients with colon and prostate cancer was major bleeding (OR colon: 2.32 95% CI 2.06, 2.62, prostate: 1.22 95% CI 1.10, 1.36), while mortality and other in-hospital complications were similar to those without cancer. Similarly, patients with breast cancer were only associated with increased odds of thoracic complications (OR 1.17 95% CI 1.07, 1.27) while all other outcomes were similar to, or lower than, patients without cancer.

Figure 6.7 Odds ratios (OR) of in-hospital adverse events in most prevalent cancer groups*



The above findings were found to be similar in the PPM subgroup. However, in the CRT subgroup only patients with lung, haematological, and breast malignancies were associated with increased odds of MACE and thoracic complications compared to those without cancer. (**Table 6.6, Figure 6.7**) The odds of mortality were only increased in patients with haematological and colon malignancies, while the odds of major bleeding were only increased in patients with colon cancer. In patients undergoing ICD implantation, the odds of MACE and thoracic complications were only increased in patients with haematological, lung and prostate malignancies. Only patients with lung and prostate malignancy were associated with increased odds of mortality while colon cancer patients were the only subgroup associated with increased odds of bleeding.

5. Discussion

My national-level analysis is the first to systematically examine in-hospital outcomes of patients with cancer undergoing de novo CIED implantation according to cancer timing (current or historical) and CIED type. I demonstrate several important findings. First, I show that the prevalence of patients with current and historical cancers has significantly increased among those undergoing CIED implantation over a 12-year period and are more likely to undergo implantation of PPM than CRT or ICD. Second, I show that patients with current cancer were associated with an increased risk of in-hospital mortality and adverse outcomes after CIED implantation compared to those without cancer, a finding that was consistent across individual CIED subtypes, while no risk of complications was observed in those with historical cancer except thoracic complications in patients undergoing CRT implantation. Furthermore, I report differences in outcomes between patients with prevalent current cancer types, with lung and haematological malignancies being associated with the highest risk of mortality and thoracic complications while

prostate and colon cancers had the highest odds of major bleeding compared to those without cancer.

Cancer survival has increased over the past two decades, commensurate with advancements in cancer therapeutics (e.g. anthracyclines, anti-HER2 and anti-VEGF agents as well as radiotherapy). [137] However, such therapies, as well as other factors such as direct metastases to the heart (including the conduction tissue) and the fluid/electrolyte abnormalities in cancer patients are also associated with cardiotoxicity in the form of conduction system disease, CTIA as well as heart failure, which may require CIED implantation as part of their management.[131, 138] Furthermore, cancer patients often have significant comorbidities at baseline.[139, 140] While there have been many studies examining the impact of comorbidities on CIED procedural outcomes, there has been limited evidence for cancer patients who are often excluded from clinical trials despite their high prevalence as demonstrated in my current study.[141] Furthermore, there have been no studies looking comparing outcomes according to device type. This drives the need for outcomes data for this frequently encountered population in clinical practice to inform operators and patients of procedural outcomes in this high-risk patient group and guide operators' decision making when choosing the type of CIED offered to patients with specific cancer types.

My findings suggest that the prevalence of (historical and current) cancer patients is high among those undergoing CIED implantation, representing one in six patients in 2015, which is commensurate with the overall increase in cancer survivors reported in national surveys. [137, 142, 143] Moreover, the most prevalent cancer types in those undergoing CIED implantation are similar to those of the background population (non-melanoma skin cancers, bronchus, lung and bronchus, breast, colon, prostate and haematological malignancies).[142, 143]

In my analysis patients with current cancer were associated with worse outcomes after de novo CIED implantation (MACE, mortality and procedure-related complications) in patients with current cancer compared with those without cancer, even after adjustment for baseline differences between the groups, while patients with historical cancer experienced a similar risk of mortality and complications. These findings were generally consistent across individual CIED types despite variations in their procedural complexity. One exception was the increased risk of thoracic complications in historical cancer patients in the CRT group, which could possibly be explained by their susceptibility to vascular injuries due to previous radiation and central venous access for chemotherapy.

Further differences were noted between current cancer patients according to the type of cancer; patients with lung and haematological malignancies were associated with the highest odds of MACE and mortality whereas colon and prostate cancers groups were associated with increased odds of major bleeding but not MACE or mortality. Similar differences were observed within the individual CIED subgroups. Despite the limited evidence to date, I postulate several reasons that may lead to worse outcomes in cancer patients and specifically in those with prevalent cancer types. The most obvious cause of mortality and major bleeding in those with current cancer is likely due to their primary cancer (e.g. metastases, tumour angiogenesis, cancer-associated coagulopathies) or even the associated cancer therapies (including chemotherapeutic agents and anticoagulation).[144] [145] Furthermore, direct tumour invasion as well as chest irradiation may increase the incidence of thoracic and vascular complications.

While CIED implantation may be unavoidable and lifesaving in many cancer patients, several strategies may be employed to help neutralise the inherent risk of complications in these patients. For example, the use of ultrasound-guided venous access and cephalic vein approach, as well as echocardiography guided septal-pacing may help

minimise their risks. Furthermore, there may be a role for intracardiac (leadless) or subcutaneous pacemakers in patients who are in need of PPM or ICD therapy, respectively, and who are at a high-risk of complications after a standard transvenous CIED implantation. Additionally, the use of antimicrobial envelopes routinely in cancer patients may minimise their risk of device-related infection, to which they may be more prone due to their impaired immunity and delayed tissue healing. [146]

Limitations

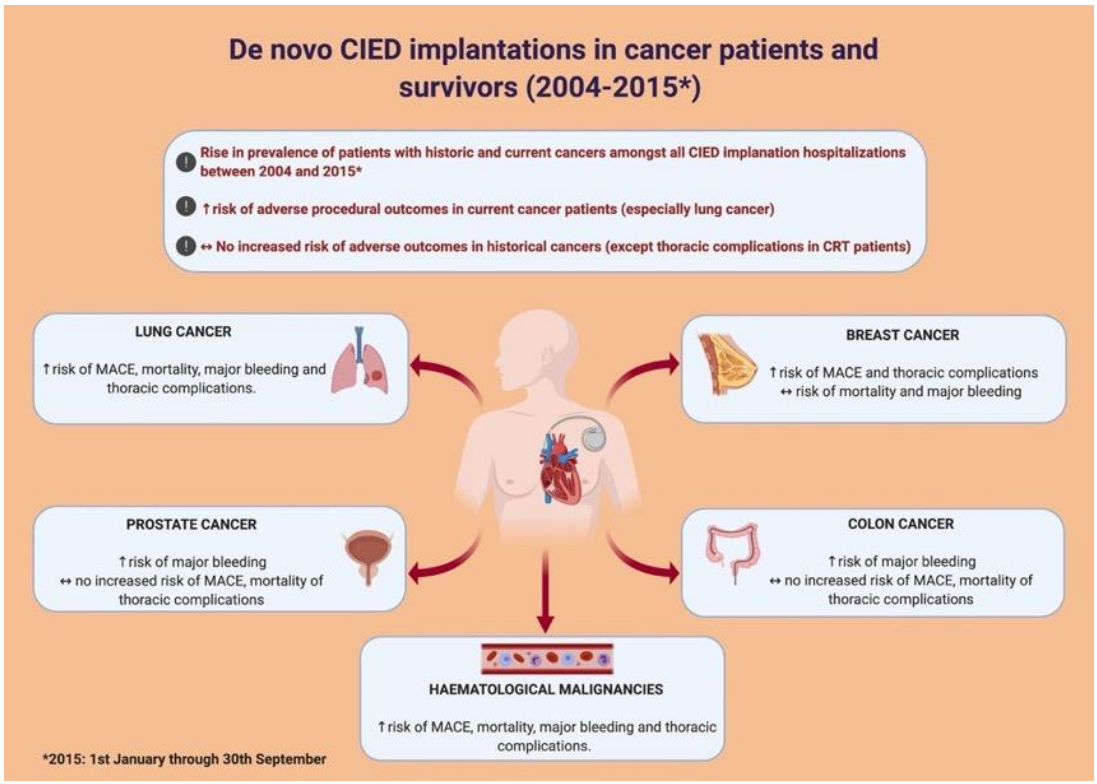
There are several limitations to my study. As mentioned in previous chapters, the NIS is an administrative dataset that is coded according to the ICD-9 manual and the quality of coding is reliant on those managing the dataset. Second, the NIS does not include information on pharmacotherapy (e.g., cancer therapeutics and anticoagulation) as well as indication of CIED implantation and type of PPM device (e.g., VVI or DDD) and, therefore, these were not adjusted for in my analysis. Furthermore, the NIS only captures in-hospital outcomes and does not specify the exact cause of death, although a previous national study has shown that the majority of procedure-related complications have been shown to occur in the peri-procedural phase and the majority of deaths in the context of CIED implantation were not procedure-related. [55] Finally, the severity and extent of active malignancy was only judged based on metastases and it is possible that certain unmeasurable markers of overall frailty in cancer patients would have led to them being offered specific device types (e.g., PPM or ICD only), with only the healthier cancer offered more complex device groups.

6. Summary

My national analysis of de novo CIED implantation procedures in the United States demonstrates an increased risk of mortality and procedure-related complications among those with a current cancer diagnosis, especially lung, haematological and colon subtypes.

Furthermore, a historical diagnosis of cancer was not associated with worse outcomes in my study. My findings add to the body of literature on outcomes of cancer patients undergoing CIED implantation, who have become increasingly encountered over a 12-year study period and identify specific cancer subtypes that are associated with an increased risk of mortality and procedural outcomes.

Graphical illustration of the main study findings



Chapter 7. The impact of frailty on de novo CIED procedural outcomes

The work in this chapter relates to the second phase of my thesis and is based on my study published in the Canadian Journal of Cardiology (Appendix 4).[147]

1. Introduction

Frailty is defined as "a clinically recognizable state of increased vulnerability resulting from aging-associated decline in reserve and function across multiple physiologic systems such that the ability to cope with every day or acute stressors is compromised".[148] While frailty is often used to describe older adults or those with multiple comorbidities, patients with neither characteristic could still be considered biologically frail as demonstrated in previous studies. [76, 77, 149] Although frailty has been shown to be a marker of adverse cardiovascular outcomes in previous studies, the prevalence and outcomes of frail patients undergoing *de novo* implantation of different CIED types has not been systematically examined. [150-152] Many of these patients have significant comorbidities which excludes them from randomised trials. Very few studies have examined the relationship between frailty and CIED implantation outcomes, they used non-objective measures as a surrogate of frailty such as number of comorbidities and old age, excluding younger biologically frail patients. [149, 152, 153]

Although several scoring systems for frailty have been previously described, none is considered to be a gold standard.[154] One recently described score is the Hospital Frailty Risk Score (HFRS) which is derived from electronic health records and based on International Classification of Diseases, Tenth Revision (ICD-10) codes. [155] The HFRS was validated against two well-established scores: The Fried Frailty Phenotype score and the Rockwood Frailty Index.

2. Objectives

My main objectives of this chapter were to study the following:

a) The distribution of frailty amongst patients undergoing *de novo* CIED implantation.
b) The relationship between frailty and in-hospital procedural outcomes of CIED implantation, stratified by CIED type.

3. Methods

A full description of the methodology relating to all chapters of my thesis is provided in Chapter 3.

a) Data Source

The data source for this study was the United States (US) National Inpatient Sample (NIS). Further information on its structure and validation has been provided in Chapter 3 and also described in Chapter 4 under the same heading.

b) Study Design and Population

All de novo CIED implantation procedures in the US NIS between 2004 and 2014 were included in my analysis, including permanent pacemakers (PPM), implantable cardioverter-defibrillators (ICD), and cardiac resynchronization therapy (CRT) with pacemaker (CRT-P) or defibrillator (CRT-D). All procedures, patient characteristics and clinical outcomes other than death were extracted using the International Classification of Diseases, ninth revision (ICD-9) procedure and diagnosis codes provided in **Table 3.1** in Chapter 3. Furthermore, ICD-9 equivalents of the ICD-10 codes in the HFRS were used to calculate the overall frailty score (full list in **Table 7.1**). Patients were groups in to 3 groups based on their frailty score: Low-Risk Frailty (LRF; <5), Intermediate-Risk Frailty (IRF; 5-15) and High-Risk Frailty (HRF; >15). Records with missing data for the following variables were excluded (total n=18,321, 3% of dataset): age, gender, admission or discharge date, length of stay and mortality. Furthermore, procedures for device upgrades

or generator replacements were excluded so as to only include *de novo* procedures. (see **Figure 7.1** for study flow diagram)

Figure 7.1. Flow chart of cohort selection

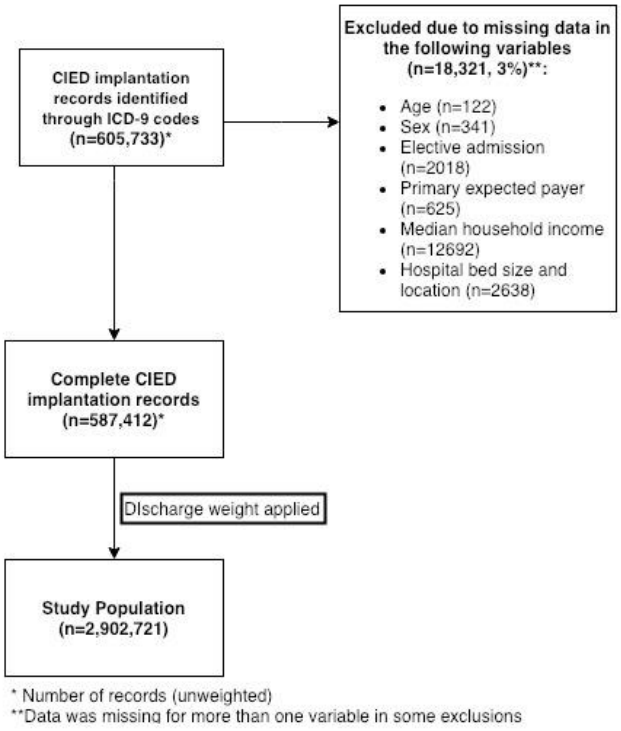


Table 7.1. List of Hospital Frailty Score ICD-10 variables and their ICD-9 conversions

ICD-10	Weight	ICD-9 equivalent
F00	7.1	331.0
G81	4.4	342*
G30	4	331.0
I69	3.7	438.9, 438.89, 438.82, 438.81, 438.1*
R29	3.6	781.9*,7817,7816,7961,71965,7814,71960,71961,71962,71963 ,71964,71966,71967, 71968,71969,72989
N39	3.2	599* except 599.0 and 599.7*
F05	3.2	293.0 290.41 293.89 290.11 290.3 293.1
W19	3.2	E888*
S00	3.2	910.0, 910.1, 910.8 910.9 918.0 920 910.2 910.6
R31	3	599.7*
B96	2.9	041*
R41	2.7	799.5* 780.93 781.8
R26	2.6	781.2 719.7
I67	2.6	437* 436
R56	2.6	780.3*
R40	2.5	780.0*

T83	2.4	997.70
S06	2.4	850* 851* 852* 853* 854* 80010 80011 80019 80060 80061 80069 80110 80111 80119 80160 80161 80169 80310 80311 80319 80360 80361 80369 80410 80411 80419 80460 80461
S42	2.3	810 811 812
E87	2.3	276* except 276.5
M25	2.3	719*
E86	2.3	276.5
R54	2.2	797
Z50	2.1	V57
F03	2.1	294.2 290.0* 290.1* 290.2* 290.3* 290.8* 290.9*
W18	2.1	E885 E886 E917.7 E917.8 E884.6
Z75	2	V63.2 V63.8 V63.9 Actually V63* and V60.5
F01	2	290.4*
S80	2	916*
L03	2	681* 682*
H54	1.9	369*
E53	1.9	266*
Z60	1.8	V62.9
G20	1.8	332*
R55	1.8	780.2
S22	1.8	807.0* 807.1* 807.2 807.3 807.4 805.2 805.4
K59	1.8	564.89
N17	1.8	584
L89	1.7	707.0*
Z22	1.7	V02*
B95	1.7	041.0* and 041.1*
L97	1.6	707.10
R44	1.6	781.1 782.0
K26	1.6	532*
I95	1.6	458*
N19	1.6	586
A41	1.6	038.9
Z87	1.5	V12.60 V12.69 V1260 V1269 V137 V139 V219 V470 V499 V1582 V1261 V1260 V1269 V1271 V1270 V1279 V133 V1351 V1352 V134 V1359 V1322 V1323 V1324 V1329 V1302 V1303 V1301 V1300 V1309 V1321 V131 V1329 V1361 V1362 V1364 V1363 V1364 V1367 V1365 V1366 V1368 V1369 V1551
J96	1.5	518.81 518.84 518.51 518.83
X59	1.5	E928.9
M19	1.5	715*
G40	1.4	345*
M81	1.4	733.0*

S72	1.4	820* 821*
S32	1.4	805.4 805.5 808* 806.4 806.5
E16	1.4	251*
R94	1.4	794*
N18	1.4	585*
R33	1.3	788.2*
R69	1.3	799.9
N28	1.3	593*
R32	1.2	788.30
G31	1.2	331.11 331.19 331.2 330.8 331.82 331.83 331.6 331.89 331.9
Y95	1.2	136.9
S09	1.2	959.01
R45	1.2	308.0
G45	1.2	435*
Z74	1.1	V60.9
M79	1.1	729.99
W06	1.1	E884.4
S01	1.1	870* 871* 872* 873* 8541* 8531*8525*8523*8521* 8519 8517* 8515* 8513* 8511*
A04	1.1	008.43, 008.0*, 0081, 0082, 0083, 00841, 00842, 00846,00847,00849, 0085, 008.44, 008.45
A09	1.1	009.3
J18	1.1	486*, 485*, 514, 481
J69	1	507.0
R47	1	784.59
E55	1	268*
Z93	1	V44
R02	1	785.4
R63	0.9	783.9
H91	0.9	389.9
W10	0.9	E880.9
W01	0.9	E885
E05	0.9	242*
M41	0.9	737.3*
R13	0.8	787.2
Z99	0.8	V46
U80	0.8	V09.1
M80	0.8	733.0* AND 733.1 V13.51
K92	0.8	570 579*
I63	0.8	434.91 434.11 434.01 V12.54 997.02
N20	0.7	592*
F10	0.7	291* 303*
Y84	0.7	E878 E879
R00	0.7	785.1
J22	0.7	519.8
Z73	0.6	V695 V4985

R79	0.6	790.6
Z91	0.5	V15*
S51	0.5	881.00
R32	0.5	296.20/296.26 296.30/296.36
M48	0.5	724.0* 723.0
E83	0.4	275
M15	0.4	716.5*
D64	0.4	285.8 285.9
L08	0.4	686
R11	0.3	787.0*
K52	0.3	558*
R50	0.1	780.60

c) Outcomes

The primary outcome measures were in-hospital major acute cardiovascular events (MACE), all-cause mortality and procedural-related complications (bleeding, thoracic and cardiac complications). In-hospital MACE was a composite of all-cause mortality, thoracic and cardiac complications, device-related infection and reoperation. Procedure-related bleeding was defined as any post-procedural haemorrhage. Thoracic complications included any acute pneumothorax or haemothorax, with or without drainage, or thoracic vascular injury, while cardiac complications were defined as a composite of cardiac tamponade, hemopericardium, pericardiocentesis.

d) Statistical Analysis

Descriptive statistics were performed as previously explained in Chapter 3. Exploratory analyses were performed to compare the rates of in-hospital complications between the frailty groups. Sampling weights provided by the AHRQ were applied to all analyses. All statistical analyses were performed using SPSS version 26 (IBM Corp, Armonk, NY).

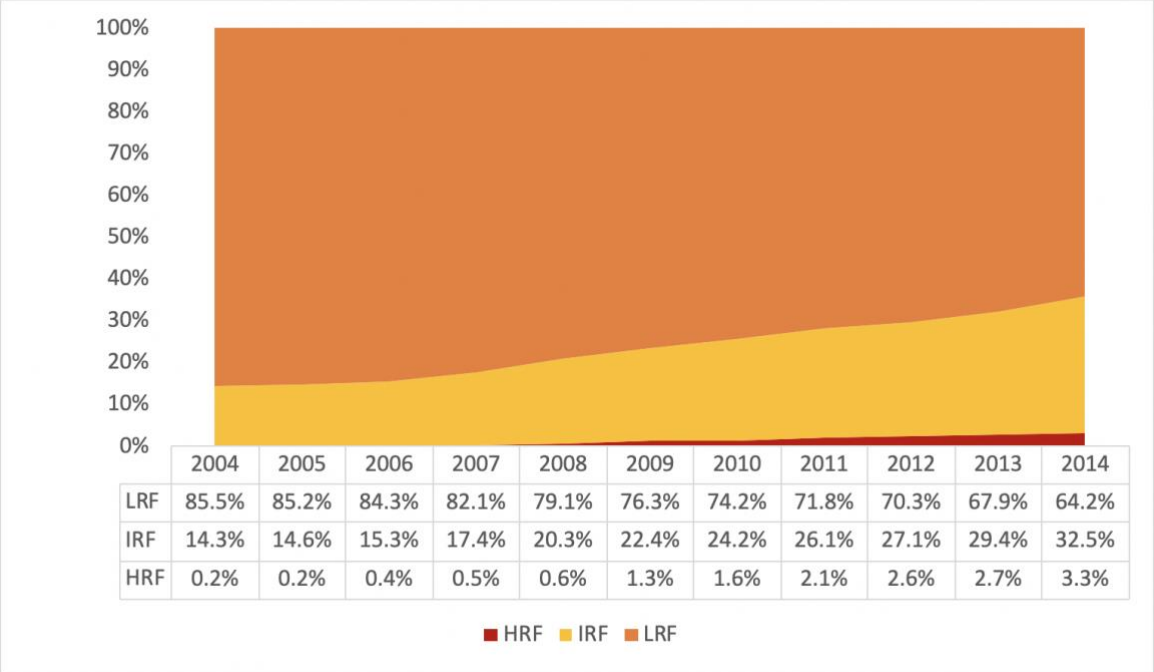
Multivariable logistic regression modelling was employed, using maximum likelihood estimation, to examine the association between frailty and in-hospital outcome in the higher risk frailty groups (IRF and HRF) using the low-risk category (LRF) as the

reference. All associations are expressed as odds ratios with corresponding 95% confidence intervals (CI). To account for baseline differences between the groups, I adjusted for all variables that were not part of HFRS (to avoid collinearity), including age, sex, weekend admission, primary expected payer, median household income, dyslipidaemia, smoking status, previous acute myocardial infarction, previous CABG, history of ischemic heart disease (IHD), previous percutaneous coronary intervention (PCI), previous cerebrovascular accidents (CVA) including stroke or transient ischemic attacks, family history of CAD, bed size of hospital, region of hospital, location/teaching status of hospital, history of cardiac arrest, ventricular tachycardia and ventricular fibrillation, acquired immune deficiency syndrome, rheumatoid arthritis/collagen vascular diseases, congestive heart failure, chronic pulmonary disease, coagulopathy, diabetes, hypertension, hypothyroidism, liver disease, lymphoma, metastatic cancer, other neurological disorders, obesity, peripheral vascular disorders, solid tumour without metastasis, valvular heart disease, weight loss and year of admission.

4. Results

The total number of de novo CIED implantations between 2004 and 2014 were 2,902,721 hospitalizations, of which the proportion of patients with low, intermediate and high frailty risk were 77.6%, 21.2% and 1.2%, respectively. The prevalence of patients with intermediate and high-risk frailty has risen between 2004 and 2014 (IRF: 14.3% to 32.5% and HRF: 0.2% to 3.3%). (**Figure 7.2**) This pattern was consistent across all the CIED groups. (**Figure 7.3**) More complex device implantations (CRT and ICD) were implanted in HRF patients by the end of the study period. (**Figure 7.4**)

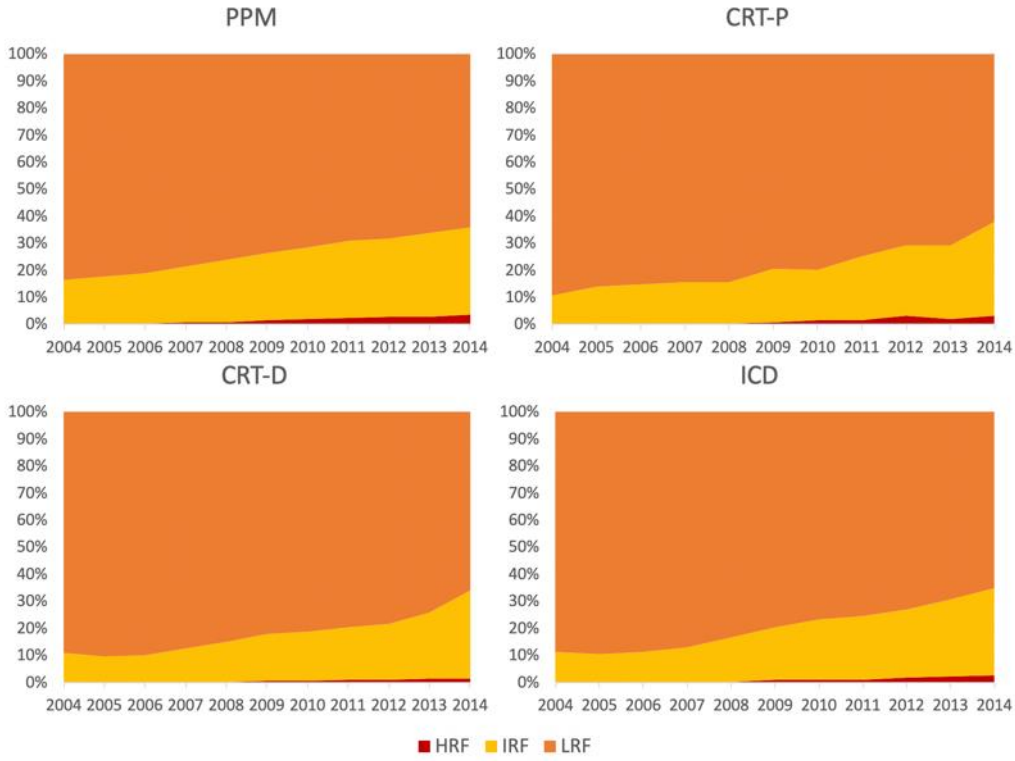
Figure 7.2. Prevalence of frailty amongst patients undergoing CIED implantations (2004-2014)



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
LRF	85.5%	85.2%	84.3%	82.1%	79.1%	76.3%	74.2%	71.8%	70.3%	67.9%	64.2%
IRF	14.3%	14.6%	15.3%	17.4%	20.3%	22.4%	24.2%	26.1%	27.1%	29.4%	32.5%
HRF	0.2%	0.2%	0.4%	0.5%	0.6%	1.3%	1.6%	2.1%	2.6%	2.7%	3.3%

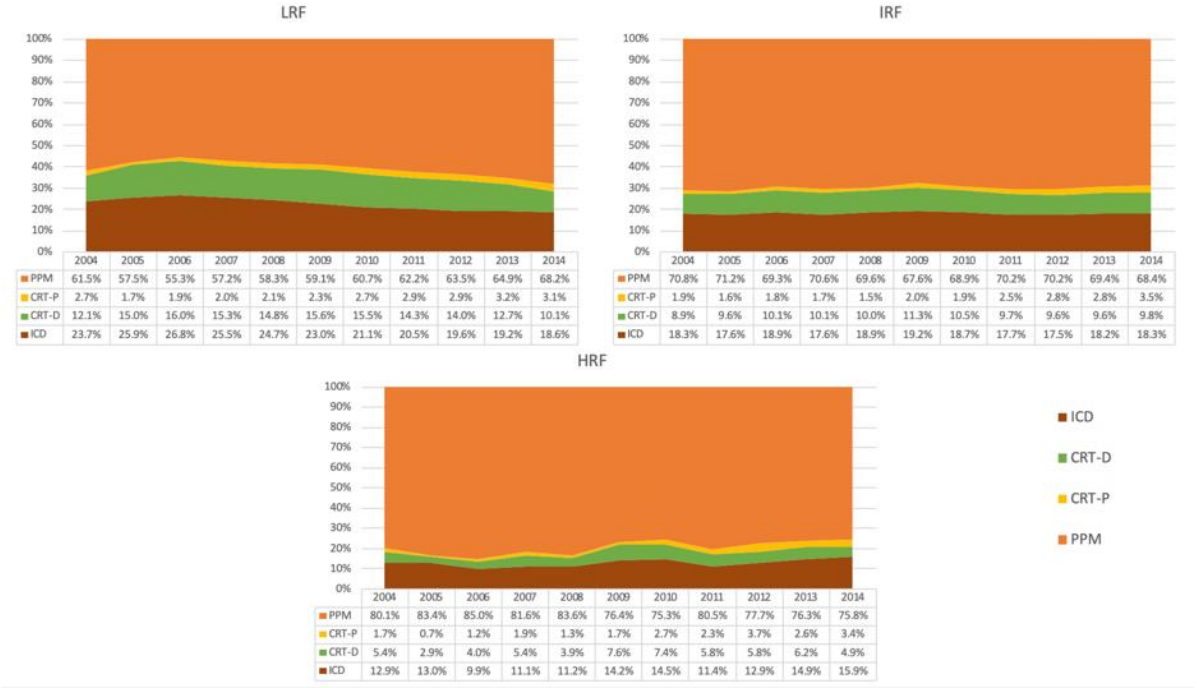
Legend: HRF: High-risk frailty; IRF: Intermediate-risk frailty; LRF: Low-risk frailty

Figure 7.3. Prevalence of frailty according to type of CIED



Legend: HRF: High-risk frailty; IRF: Intermediate-risk frailty; LRF: Low-risk frailty

Figure 7.4. Proportion of CIED types among frailty risk groups



Legend: HRF: High-risk frailty; IRF: Intermediate-risk frailty; LRF: Low-risk frailty

Overall, there was a linear relationship between frailty risk and age as well as sex, with higher frailty groups more likely to be older, females and of non-white ethnic background. (**Table 7.2**) Patients with higher frailty risk (IRF and HRF) also had a higher prevalence of arrhythmias (ventricular and atrial fibrillation), history of cardiac arrest, diabetes with complications, previous cerebrovascular accidents (including stroke and transient ischaemic attacks), hypertension and valvular heart disease. However, they also had a lower prevalence of previous AMI or coronary revascularisation (percutaneous coronary intervention or coronary artery bypass grafting).

Table 7.2. Patient characteristics according to frailty risk group

Variable/Frailty risk (%)	LRF (77.6)	IRF (21.2)	HRF (1.2)	p-value
Number of weighted discharges	2252144	614774	35804	
PPM, %	59.9	69.5	78.0	-
CRT-P, %	2.4	2.2	2.6	-
CRT-D, %	14.4	10.0	5.8	-
ICD, %	23.3	18.3	13.6	-
Age (years), median (IQR)	74 (64,82)	78 (68,84)	80 (71,86)	<0.001
Males, %	60.3	51.7	43.0	<0.001
Ethnicity, %				<0.001

Variable/Frailty risk (%)	LRF (77.6)	IRF (21.2)	HRF (1.2)	p-value
White	79.7	76.3	75.1	
Black	9.1	11.3	11.6	
Hispanic	6.3	7.0	7.8	
Asian/Pacific Islander	1.8	2.2	2.6	
Native American	0.5	0.5	0.4	
Other	2.5	2.6	2.4	
Elective Admission, %	36.0	13.0	7.3	<0.001
Weekend admission, %	13.2	21.7	23.6	<0.001
Primary expected payer, %				<0.001
Medicare	72.7	79.6	83.1	
Medicaid	4.3	4.6	4.7	
Private Insurance	19.4	12.7	9.6	
Self-pay	1.7	1.6	1.4	
No charge	0.2	0.2	0.1	
Other	1.7	1.5	1.2	
Median Household Income (Percentile), %				<0.001
0-25th	72.7	79.6	83.1	
26-50th	4.3	4.6	4.7	
51-75th	19.4	12.7	9.6	
76-100th	1.7	1.6	1.4	
Shock, %	0.6	4.0	5.6	<0.001
All-cause infection, %*	0.8	7.5	21.5	<0.001
Cardiac Arrest, %	2.5	7.5	11.4	<0.001
Ventricular Tachycardia, %	16.0	15.9	13.6	<0.001
Ventricular Fibrillation, %	2.7	5.1	5.6	<0.001
Comorbidities, %				
Dyslipidaemia	43.2	38.6	37.8	<0.001
Smoking	7.7	6.4	5.1	<0.001
Atrial Fibrillation	36.9	42.5	46.5	<0.001
Thrombocytopenia	2.3	6.7	10.4	<0.001
Previous AMI	14.6	10.0	8.4	<0.001
History of IHD	50.1	46.5	41.8	<0.001
Previous PCI	10.5	7.2	5.4	<0.001
Previous CABG	15.0	10.3	7.7	<0.001
Previous CVA	3.8	6.4	9.7	<0.001
Family history of CAD	2.9	1.9	1.0	<0.001
AIDS	0.1	0.1	0.0	<0.001
Alcohol abuse	1.6	2.6	2.8	<0.001
Deficiency anaemias	9.1	25.7	39.9	<0.001
Chronic Blood loss anaemia	0.5	1.4	1.5	<0.001
RA/collagen vascular diseases	1.9	2.6	3.2	<0.001
Heart Failure	41.5	51.6	52.7	<0.001
Chronic pulmonary disease	17.8	23.4	24.4	<0.001
Coagulopathy	3.0	9.2	13.8	<0.001

Variable/Frailty risk (%)	LRF (77.6)	IRF (21.2)	HRF (1.2)	p-value
Depression	5.2	7.7	10.3	<0.001
Diabetes	24.6	25.8	26.5	<0.001
Diabetes with complications	3.2	8.9	10.4	<0.001
Drug abuse	0.8	1.2	1.1	<0.001
Hypertension	63.3	67.8	71.5	<0.001
Hypothyroidism	11.9	15.6	19.8	<0.001
Liver disease	0.9	1.8	2.0	<0.001
Lymphomas	0.6	0.9	1.0	<0.001
Fluid and electrolyte disturbances	8.9	45.5	77.8	<0.001
Metastatic cancer	0.4	0.7	0.8	<0.001
Other neurological disorders	3.0	15.8	25.3	<0.001
Obesity	8.1	10.4	13.4	<0.001
Paralysis	0.8	3.7	9.4	<0.001
Peripheral vascular disease	8.1	11.4	12.9	<0.001
Psychoses	1.4	3.0	4.8	<0.001
Pulmonary circulation disorder	0.3	1.6	3.7	<0.001
Renal failure (chronic)	10.2	35.5	48.4	<0.001
Solid tumour without metastases	1.2	1.6	1.7	<0.001
Valvular heart disease	0.8	3.2	5.6	<0.001
Weight loss	0.9	5.4	12.5	<0.001
Dementia	0.7	6.4	15.4	<0.001
Hospital bed size, %				<0.001
Small	8.8	8.7	9.0	
Medium	21.6	22.4	24.1	
Large	69.5	68.9	66.9	
Hospital Region, %				<0.001
Northeast	21.7	20.5	16.3	
Midwest	23.5	23.9	23.7	
South	37.4	37.0	38.8	
West	17.5	18.5	21.2	
Location/ Teaching status, %				<0.001
Rural	6.7	6.2	5.2	
Urban non-teaching	40.9	40.4	42.5	
Urban- teaching	52.4	53.4	52.4	

*__All-cause infection__: Composite of septicaemia, viremia and bacteraemia; **HRF:** High-risk frailty; **IRF:** Intermediate-risk frailty; **LRF:** Low-risk frailty.

In-hospital adverse outcomes

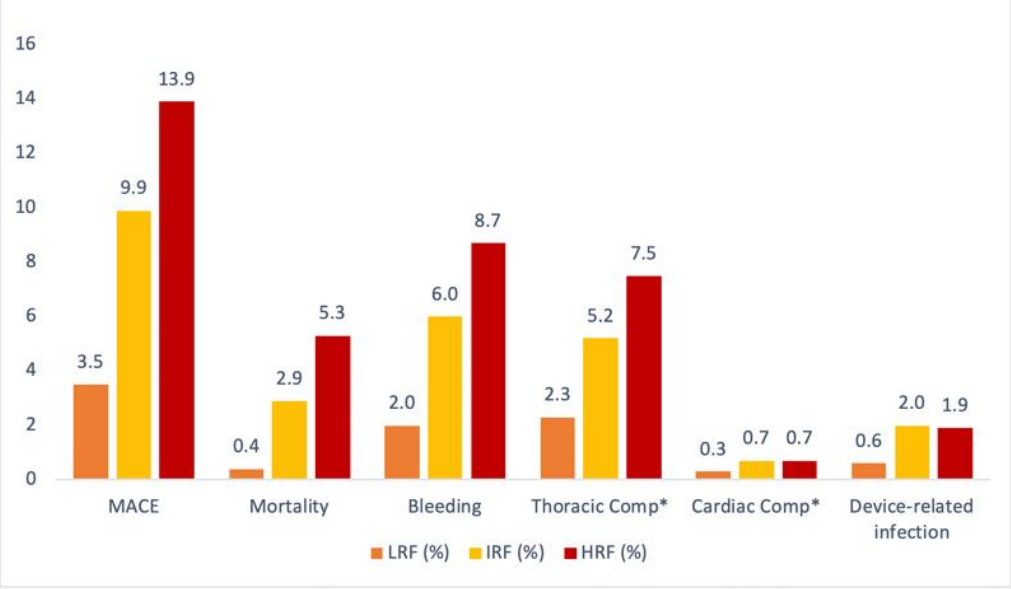
There was a positive correlation between frailty risk and the rates of MACE, all-cause mortality, thoracic complications and procedure-related bleeding (LRF vs. IRF vs. HRF; MACE: 3.5% vs. 9.9% vs. 13.9%; mortality: 0.4% vs. 2.9% vs. 5.3%; thoracic

complications: 2.3% vs. 5.2% vs. 7.5%; bleeding: 2.0% vs. 6.0% vs. 8.7%). (**Table 7.3, Figure 7.5**) Similar findings were observed in the individual CIED groups, with the highest rate of MACE in the CRT-P and CRT-D groups, especially in those with HRF (18.8% and 16.4%, respectively), driven by their high rates of procedure-relating bleeding and thoracic complications. (**Table 7.4, Figure 7.6**) Device-related infection and cardiac complications were also more than 2-fold higher in the IRF and HRF groups compared with LRF group in the total cohort as well as in the individual CIED subgroups.

Table 7.3. In-hospital clinical outcomes of total cohort according to frailty risk group

Variable/Frailty Risk (% of cohort)	LRF (77.6)	IRF (21.2)	HRF (1.2)	p-value
MACE, %	3.5	9.9	13.9	<0.001
All-cause mortality, %	0.4	2.9	5.3	<0.001
Procedure-related bleeding, %	2.0	6.0	8.7	<0.001
Thoracic complications, %	2.3	5.2	7.5	<0.001
Cardiac complications, %	0.3	0.7	0.7	<0.001
Device-related infection, %*	0.6	2.0	1.9	<0.001
Lead revision, %	1.6	1.5	1.4	0.003
Pocket revision, %	1.0	1.5	1.6	<0.001

Figure 7.5. In-hospital adverse events of frailty groups in total cohort



Legend: *Comp: complications; p<0.001 for all outcomes; **MACE**: Composite of mortality, thoracic and cardiac complications, device-related infection and reoperation.

Table 7.4. In-hospital clinical outcomes according to frailty risk group and type of CIED

Variable/Frailty Risk Group	LRF	IRF	HRF	p-value
MACE, %*				
PPM, %	3.7	9.4	13.5	<0.001
CRT-P, %	4.6	15.8	18.8	<0.001
CRT-D, %	3.3	12.5	16.4	<0.001
ICD, %	2.9	9.7	14.4	<0.001
All-cause mortality, %				
PPM, %	0.4	3.0	5.7	<0.001
CRT-P, %	0.6	4.3	5.4	<0.001
CRT-D, %	0.3	3.1	4.1	<0.001
ICD, %	0.2	2.1	3.7	<0.001
Procedure-related bleeding, %				
PPM, %	2.4	6.1	9.1	<0.001
CRT-P, %	2.3	7.7	12.2	<0.001
CRT-D, %	1.2	5.4	6.6	<0.001
ICD, %	1.4	5.5	7.1	<0.001
Thoracic complications, %				
PPM, %	2.6	5.1	7.4	<0.001
CRT-P, %	3.0	8.4	10.3	<0.001
CRT-D, %	2.0	5.6	7.0	<0.001
ICD, %	1.6	4.8	8.0	<0.001
Cardiac complications, %				
PPM, %	0.3	0.7	0.7	<0.001
CRT-P, %	0.3	1.1	1.0	<0.001
CRT-D, %	0.3	0.7	0.9	<0.001
ICD, %	0.3	0.8	0.5	<0.001
Device-related infection, %*				
PPM, %	0.5	1.4	1.4	<0.001
CRT-P, %	0.9	3.8	3.7	<0.001
CRT-D, %	0.9	4.1	5.3	<0.001
ICD, %	0.8	2.6	3.0	<0.001
Length of stay (days), median (IQR)				
PPM	3 (2,6)	7 (4,11)	10 (6,17)	<0.001
CRT-P	2 (1,6)	9 (6,14)	13 (8,19)	<0.001
CRT-D	2 (1,5)	9 (6,15)	15 (9,21)	<0.001
ICD	3 (1,6)	10 (6,15)	15 (9,23)	<0.001

MACE: Composite of mortality, thoracic and cardiac complications, device-related infection and reoperation; **LRF:** Low-risk frailty; **ICD**: automated implantable cardioverter-defibrillator; **CRT-P & CRT-D:** cardiac resynchronization therapy - pacemaker or - defibrillator, respectively; **PPM:** permanent pacemaker.

Figure 7.6. In-hospital adverse events in frailty groups according to type of CIED

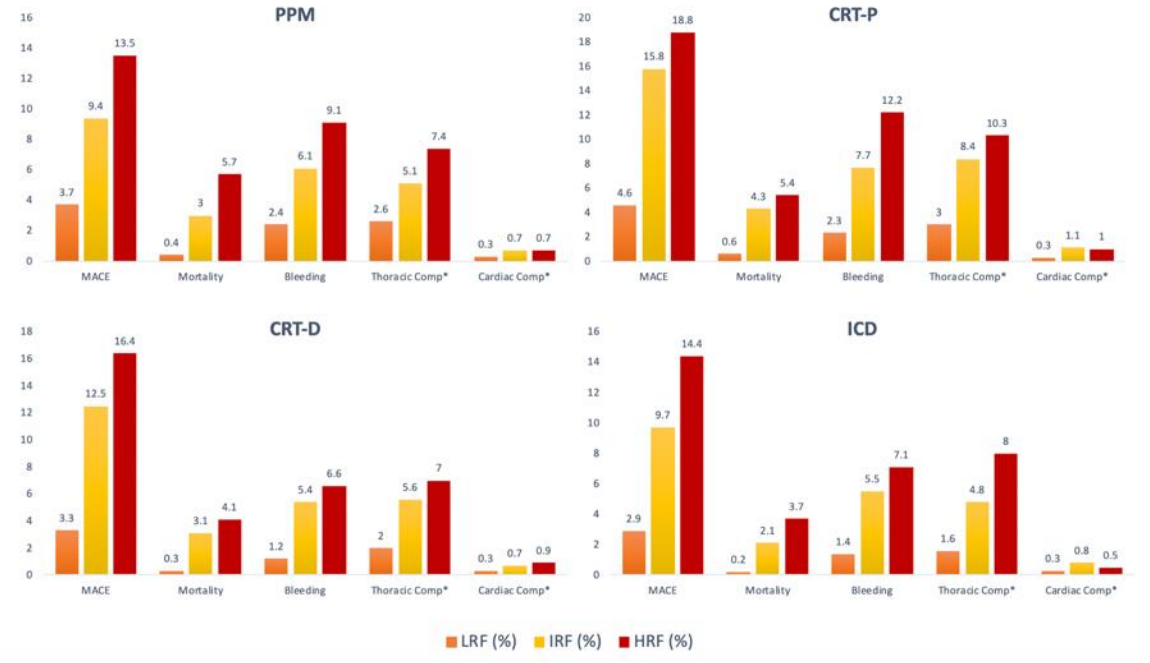
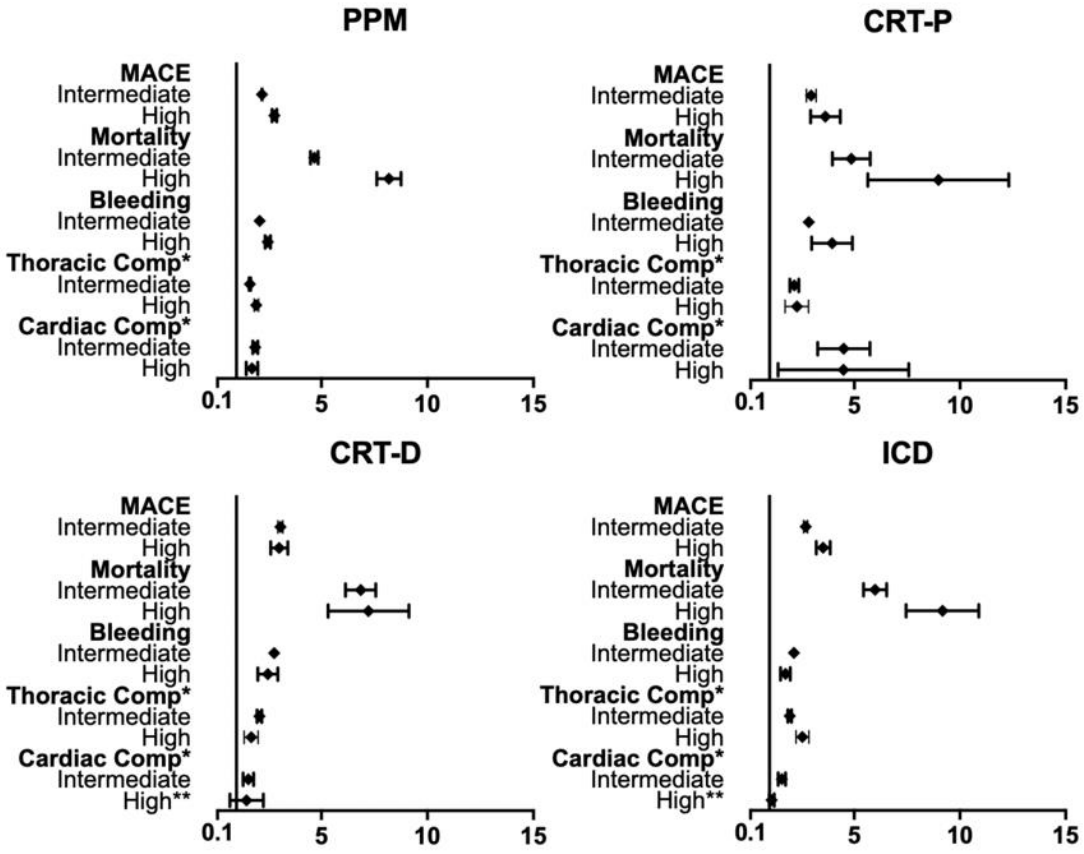


Figure 7.7. Adjusted relative risk (RR) and 95% confident intervals of adverse outcomes according to frailty risk group and type of CIED (reference is low-frailty risk group)



Legend: *p>0.05 (p<0.001 otherwise)

In multivariable analysis, the odds of MACE, all-cause mortality and complications (bleeding, thoracic and cardiac) were significantly increased (up to 8-fold) with higher frailty risk (IRF and HRF) in the overall cohort, compared to the LRF group. (**Table 7.5**) The highest odds were those of all-cause mortality which were 5 to 8-fold higher in the IRF and HRF groups, respectively (OR IRF: 5.01 [4.85, 5.18]; HRF: 8.32 [7.82, 8.84]). While this pattern was consistent across the device groups, the odds of cardiac complications were insignificant for HRF patients undergoing CRT-D and ICD compared with LRF patients in those device groups. (**Figure 7.7**)

5. Discussion

My national analysis of more than 2.9 million CIED implantation procedures in the US demonstrates a rise in the prevalence of frailty amongst those undergoing CIED implantation over an 11-year period, across all CIED subtypes, with patients classed as intermediate or high-risk frailty more than doubling during that period. My analysis also shows an incremental rise in the risk of mortality and procedural complications (bleeding, thoracic and cardiac, device-related infection) with increasing frailty risk, regardless of the type of CIED implanted. The odds of in-hospital mortality were as greater than 7-fold in patients with high-risk frailty in the overall cohort as well as in individual CIED groups.

There are limited data on the prevalence of frailty among those undergoing CIED implantation. Furthermore, the studies that have examined frailty used non-objective measures of frailty such as age or comorbidity burden, despite previous studies showing little correlation between the age and number of comorbidities and frailty. [76, 77, 149] My study is the first to examine the distribution of frailty risk (low, intermediate and high) in patients undergoing CIED implantation nationally and shows that one in three patients classed as intermediate or high-risk frailty in 2015, more than a two-fold over the 11-year study period. This is significantly higher than figures reported from several small studies,

although these were largely limited by their measures for frailty assessment and sample size. For example, a recent multicentre survey from 14 countries performed by the European Heart Rhythm Association (EHRA) reported that less than 10% of patients undergoing CIED implantations in Europe are classed as prefrail or frail, although the assessment of frailty was not objective and was based on the physicians' judgements. [156] Similarly, the prevalence of frailty was 12.8% in a single-centre study of 219 CIED implantations in the United States. [157] However, their analysis only included less than 50% of all their procedures during their 2-month study coverage.

My analysis shows a positive correlation between frailty risk and in-hospital mortality as well as procedure-related complications after CIED implantation, irrespective of the type of CIED and patients' comorbidities and age. The odds of mortality were increased by almost 5-fold in patients with intermediate-risk frailty and up to 9-fold in those with high-risk frailty, depending on the type of CIED, while the risk of other complications was between 50% and 200% higher in those with intermediate and high-risk frailty compared with low-risk frailty patients. Although few studies have looked at the impact of frailty on mortality and complications of CIED implantation, a study of 83,792 elderly patients (≥65 years) with heart failure undergoing de novo ICD implantation in the United States demonstrated higher mortality at one-year in those with frailty, as measured by the ACG System frailty marker, compared with this those without any conditions other than heart failure. [152] However, their analysis only included a specific cohort (elderly with heart failure) undergoing a specific device implantation (ICD), making their findings less generalisable to the overall CIED population. Another analysis of CIED procedures in the US between 1997 and 2004 demonstrated higher rates of in-hospital mortality and 'any complication' in frail patients, although this was judged by the authors according to age, comorbidity burden and urgency of admission, none of which are reliable surrogates of

frailty. [23] My study demonstrated that the impact of frailty risk on clinical outcomes is similar across the different device groups. The latter finding has important clinical implications as it may encourage operators to offer more complex devices (e.g., ICD or CRT) who may have been denied such therapy due to fears of worse complications rates. The lower utilisation of complex devices in frail patients has been previously demonstrated in a recent EHRA survey.[156]

The higher rates of device-related infection in patients with intermediate and high-risk frailty in my analysis, especially in those in receipt of complex devices (ICD and CRT) are unsurprising. Several reasons could explain these findings including the reduced immunity in frail patients who are often older and have reduced hose defence response. [158, 159] Furthermore, complex devices require a longer time to implant with more lead manipulation, all of which increase the likelihood of secondary inflammation and infection.[79, 80] I believe that my findings in the present study highlight the importance of an objective assessment of patient frailty status prior to cardiac device implantation to identify patients at a higher risk of adverse outcomes as well as explore strategies that may mitigate these risks including pre-habilitation prior to the procedure, shorter procedure time, operation by more skilled (non-trainee) implanters as well as the use of antimicrobial envelopes in more frailty patients and those receiving complex devices in view of the significant clinical and economic consequences of device-related infections.[160, 161]

Limitations

As mentioned in my previous Chapters (4 to 6), one of the inherent limitations of NIS is the reliance on coding according to the ICD-9 system which is subject to inaccuracies based on the technical abilities of those managing the dataset. However, administrative datasets such as NIS have been previously shown to have comparable capture of demographics and procedural information compared with electronic health

records of multistate registries in previous studies. [162] Another limitation previously mentioned in preceding chapters is the lack of capture of certain information relating to pharmacotherapy and device indication, meaning that these variables were not adjusted for in the present analysis. Nevertheless, the large sample size and extensive capture of many demographics may mitigate some of these limitations since the patterns of my findings were observed in a national procedural cohort. Finally, since my dataset only captures in-hospital outcomes, it is possible that the observed differences between frailty risk groups may become more pronounced on longer follow-up.

6. Summary

My analysis shows a rise in the number of frail patients undergoing de novo CIED implantation over an 11-year period in the United States, with many intermediate and high-risk frailty patients receiving more complex devices. A higher frailty risk as measured by the Hospital Frailty Risk Score is associated with higher rates of in-hospital mortality and worse procedural outcomes, irrespective of the type of CIED implanted as demonstrated in my study. My findings emphasise the need for the assessment of frailty in patients undergoing CIED implantation using objective scoring systems such as the HFRS to identify those at a high risk of postoperative mortality and adverse outcomes who may benefit from pre-habilitation prior to the procedure.

Chapter 8. Impact of comorbidity burden on de novo CIED procedural outcomes

The work in this chapter is based on a study I have conducted that has been accepted for publication in the Mayo Clinic Proceedings journal (currently in press).

1. Introduction

The overall rate utilisation of cardiac implantable electronic devices (CIED), including permanent pacemakers (PPM), implantable cardioverter defibrillators (ICD) and cardiac resynchronization therapy (CRT), has significantly increased in recent years on a global level, largely due to an increasingly ageing population who are more likely to experience conduction system disease and heart failure (HF). [6, 23-30] However, advancing age is also commensurate with comorbidities, meaning that patients undergoing CIED implantation are often multi-morbid. While the impact of many individual comorbidities on CIED procedural outcomes has previously been studied, many of these conditions co-exist, rendering the need for assessment of the impact of overall burden of comorbidities on CIED procedural outcomes as important as that of individual conditions. [163-168]

Several measures of comorbidity burden have been previously described, among which is the Charlson Comorbidity Index (CCI), utilises 17 conditions to measure comorbidity through a score based on the number as well as specific impact of each condition. [78, 169] The impact of CCI on outcomes such as mortality and hospital readmissions has been examined in many cardiovascular cohorts. [78, 165, 167] However, the few studies that have looked at the impact of comorbidity on procedural outcomes of CIED implantations have been subject to certain limitations including, but not limited to, the analysis of specific devices (e.g. ICD), small cohorts that are insufficiently powered to detect differences between difference comorbidity classes, as well as the inclusion of

upgrade/replacement as well as *de novo* procedures despite differences in the procedural complexity and risks of each.[23, 61, 65, 72-75] As such, there is limited data on the distribution and procedural outcomes of different comorbidity burden levels, as measured by validated comorbidity measures such as CCI, after CIED implantation, and whether differences in these outcomes are observed between CIED subtypes.

2. Objectives

My main objectives in this chapter were to study the following:

a) The distribution of comorbidity burden among different device procedural groups (PPM, CRT-P, CRT-D and ICD).
b) The association between comorbidity burden, as measured by CCI score, and de novo CIED procedural outcomes, with a comparison between different device types.

3. Methods

A full description of the methodology relating to all chapters of my thesis is provided in Chapter 3.

a) Data Source

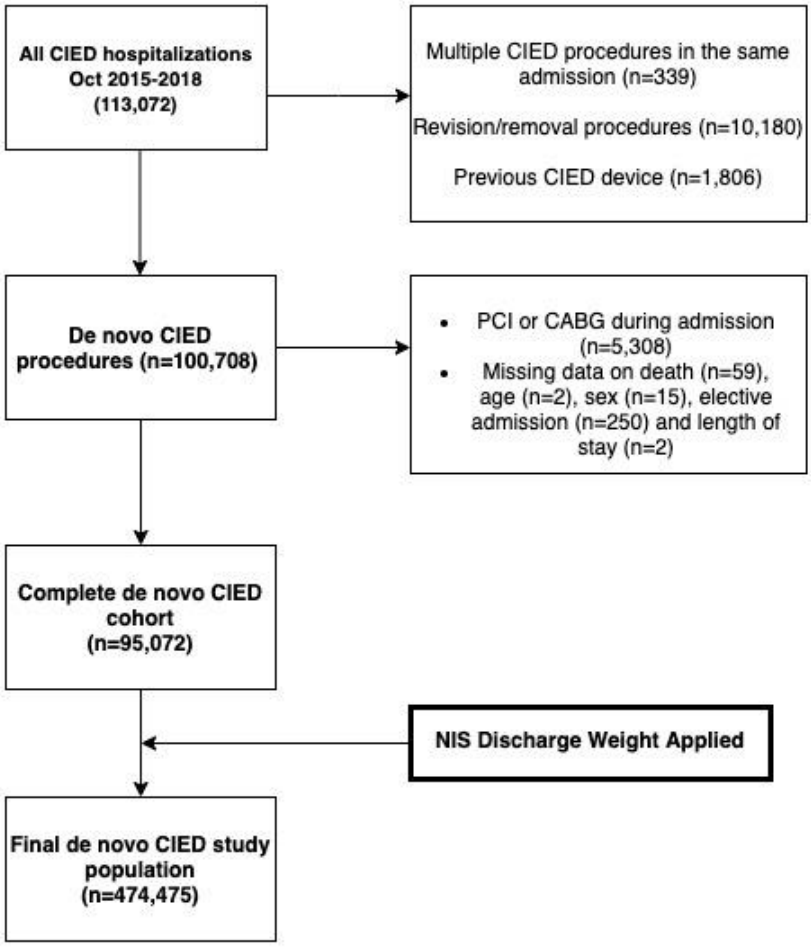
The data source for this study was the National Inpatient Sample (NIS). Further information on its structure and validation has been provided in Chapter 3 and also described in Chapter 4 under the same heading.

b) Study Design and Population

All *de novo* CIED implantations from September 2015 through December 2018 were retrospectively analysed. CIED procedures (Single and Dual Chamber PPM, CRT-P, CRT-D, and ICD), patient characteristics, comorbidities other than those in the CCI

score as well as data for other procedures, diagnoses and clinical outcomes were extracted from NIS using the International Classification of Diseases, tenth revision (ICD-10) procedure and diagnosis codes provided in Chapter 3 (Table 3.2). Missing records (n=328, 0.3% of dataset) for age, sex, procedure urgency (elective vs. urgent), length of stay and mortality were excluded from the analysis, as were any cases of device upgrades or generator replacements and patients undergoing multiple CIED procedures or PCI or CABG during the same admission. (Study flow diagram in **Figure 8.1**)

Figure 8.1. Study Flow Diagram



All 17 variables in the CCI score are listed in **Table 8.1** along with their assigned weights used to calculate the CCI score. All variables were extracted using the Charlson package in Stata 16 MP based on the algorithm previously described by the package authors.[169]

Table 8.1. Distribution of Charlson Comorbidity Index (CCI) components in the total cohort and individual CIED groups

Charlson Item	Allocated score	Single Chamber PPM (%)	Dual Chamber PPM (%)	CRT-P (%)	CRT-D (%)	ICD (%)	Total (%)
Congestive heart failure	1	53.2	32.5	83.1	96.8	81.6	48.8
Renal Disease	2	33.9	26.2	35.9	38.1	28.1	28.5
Diabetes (uncomplicated)	1	22	23.9	24.3	28.6	25.9	24.4
Chronic obstructive pulmonary disease	1	24.3	21.1	28.8	27.5	25.1	22.8
Previous Myocardial infarction	1	12.3	12.5	18.6	28.9	34	17.3
Diabetes with chronic complications	2	14.7	13.7	16.4	20.1	15.2	14.7
Peripheral vascular disease	1	11.3	10.1	11.5	14.5	11.4	10.8
Previous Cerebrovascular disease	1	10.4	8.4	7.2	5.7	6.2	8
Dementia	1	15.9	9.1	5.7	2.8	2.2	8
Any malignancy including leukaemia and lymphoma	2	4.3	3.6	3.8	2.7	2.5	3.5
Rheumatologic disease	1	3.2	3.1	3.1	2.3	2.1	2.9
Mild liver disease	1	2.2	2	2.3	2.5	3.2	2.2
Hemiplegia or paraplegia	2	1.9	1.3	1.1	0.7	1	1.3
Peptic ulcer	1	1.3	0.8	0.8	0.8	0.9	0.9
Metastatic solid tumour	6	1.1	0.7	0.6	0.3	0.4	0.7
Moderate or severe liver disease	3	0.7	0.4	0.4	0.5	0.5	0.4
AIDS	6	0	0.1	0	0.1	0.3	0.1

CIED: cardiac implantable electronic device; **CRT:** cardiac resynchronization therapy with defibrillator (CRT-D) or pacemaker (CRT-P), **ICD:** implantable cardioverter defibrillator; **PPM:** permanent pacemaker

c) Outcomes

The primary outcome measures were in-hospital all-cause mortality, major acute cardiovascular and cerebrovascular events (MACCE), and procedure-related complications (thoracic, cardiac and device-related). In-hospital MACCE was defined as a composite of

all-cause mortality, thoracic, cardiac and device-related complications. Thoracic complications were defined as a composite of pneumothorax, pleural drainage and thoracic vascular laceration while cardiac complications were a composite of hemopericardium, pericardial effusion or pericardiocentesis, cardiac tamponade, and cardiac laceration. Device-related complications were defined as a composite of wound disruption, device infection, lead revision and mechanical device complications.

d) Statistical Analysis

Descriptive statistics were performed as previously explained in Chapter 3. Data extraction and cleaning was performed using Stata 16 MP (College Station, TX, USA) while statistical analysis was performed using SPSS version 26 (IBM Corp, Armonk, NY). Sampling weights provided by the AHRQ were applied to all analyses. For exploratory analysis, the CCI groups were stratified into the following categories: CCI 0 (no comorbidity burden), CCI 1 (mild), CCI 2 (moderate) and CCI ≥3 (severe).

Multivariable logistic regression models were performed to examine the association between CCI (as a continuous scale) and in-hospital outcomes (MACCE, all-cause mortality and individual complications), expressed as odds ratios (OR) with corresponding 95% confidence intervals (CI), adjusting for covariates that were not part of CCI. The following variables were adjusted for: type of device, age, sex, elective admission, weekend admission, primary expected payer, median household income, hospital bed size, location and teaching status, pre-procedure cardiogenic shock, ventricular tachycardia and fibrillation, atrial fibrillation, dyslipidaemia, smoking status, thrombocytopenia, history of percutaneous coronary intervention and/or coronary artery bypass surgery, anaemias and coagulopathies, hypertension, and valvular heart disease.

4. Results

A total of 474,475 *de novo* CIED implantation procedures were included my analysis. Dual chamber PPM was the most frequently implanted device (n=305,705, 64.4%), followed by ICD (n=75,055, 15.8%), single chamber PPM (n=40,575, 8.6%), CRT-D (n=35,990, 7.6%) and CRT-P (n=17,150, 3.6%). The distribution of CCI score in the overall cohort was as follows: CCI 0 (no comorbidity burden: 17.7%), CCI 1 (mild: 21.8%), CCI 2 (moderate: 18.7%), CCI ≥3 (severe: 41.8%). Patients with higher CCI class were more likely to undergo ICD and CRT-D implantation instead of a dual chamber PPM. (**Table 8.2**)

Table 8.2. Sociodemographic and patient characteristics of the study groups

Variable/CCI Class (% within cohort)	**0** (17.7%)	**1** (21.8%)	**2** (18.7%)	**≥3** (41.8%)
Number of weighted discharges	84205	103470	88545	198255
Type of CIED, %				
Single Chamber PPM	6.2	8.0	8.8	9.6
Dual Chamber PPM	84.6	67.9	60.4	55.2
CRT-P	1.2	3.2	3.9	4.7
CRT-D	0.6	6.2	8.1	11.0
ICD	7.2	14.3	18.4	18.9
Sociodemographic				
Age (years), median (IQR)	74 (64,82)	75 (65,83)	76 (66,83)	76 (67,83)
Males, %	49.9	52.1	55.4	59.6
Elective Admission, %	16.3	17.3	16.6	14.8
Weekend admission, %	19.2	19.1	19.8	20.0
Ethnicity, %				
White	82.2	78.7	78.2	73.5
Black	6.4	9.2	10.0	14.2
Hispanic	6.2	7.1	6.7	7.4
Asian/Pacific Islander	2.3	2.2	2.2	2.1
Native American	0.2	0.3	0.4	0.5
Other	2.7	2.5	2.4	2.4
Primary expected payer, %				
Medicare	68.2	71.2	75.0	80.8
Medicaid	5.7	6.5	6.2	5.5
Private Insurance	22.2	18.3	15.1	10.8
Self-pay	1.7	1.7	1.5	1.0
No charge	0.1	0.2	0.2	0.1
Other	2.0	2.1	2.0	1.7
Median Household Income (Percentile), %				
0-25th	23.3	25.7	27.4	29.4

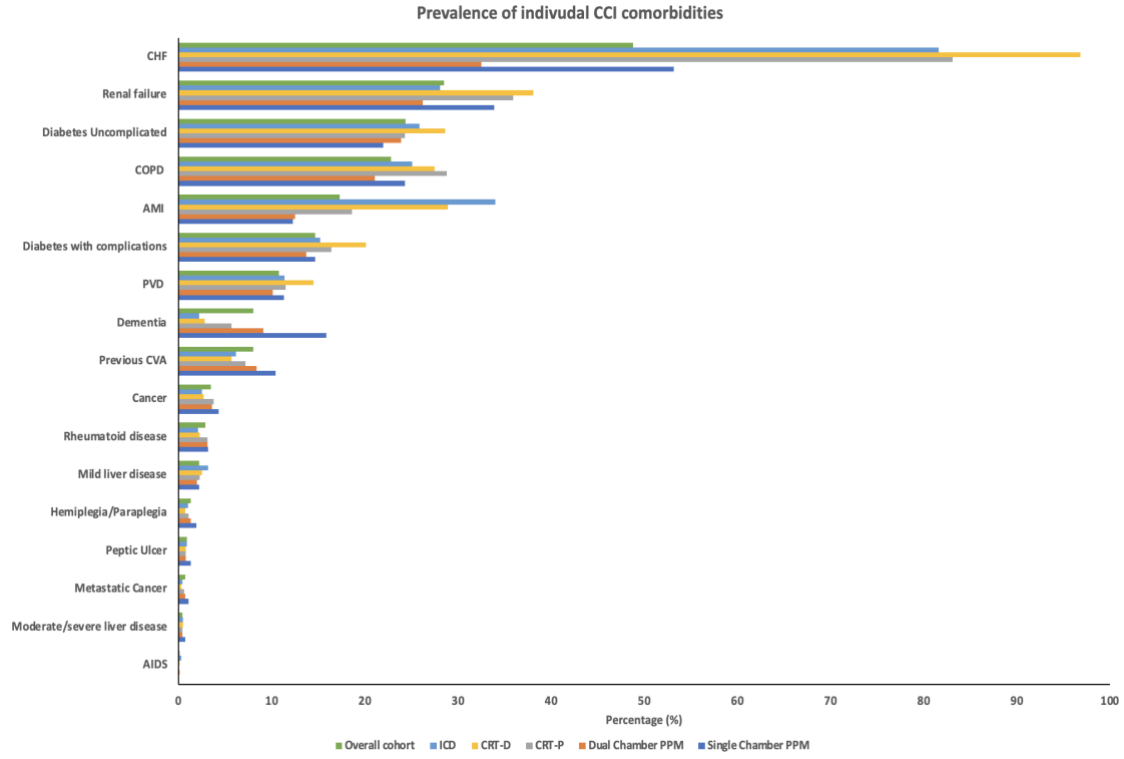
Variable/CCI Class (% within cohort)	0 (17.7%)	1 (21.8%)	2 (18.7%)	≥3 (41.8%)
26-50th	26.3	26.4	26.4	26.7
51-75th	26.2	25.2	24.7	24.0
76-100th	24.3	22.7	21.5	19.9
Hospital bed size, %				
Small	14.6	14.0	13.5	13.2
Medium	29.6	28.9	28.5	28.5
Large	55.8	57.1	58.0	58.3
Hospital Region, %				
Northeast	22.8	23.1	23.4	21.0
Midwest	23.5	23.6	23.9	26.6
South	39.0	39.1	39.0	38.7
West	14.8	14.2	13.6	13.7
Location/ Teaching status, %				
Rural	5.5	5.0	5.2	4.7
Urban non-teaching	23.6	22.9	21.7	20.6
Urban- teaching	70.9	72.1	73.0	74.8
Comorbidities, %				
Pre-procedure cardiogenic shock	0.9	2.4	3.1	4.2
IABP or LV assist device	0.0	0.1	0.2	0.2
Cardiac Arrest	5.3	5.9	6.0	5.8
Ventricular Tachycardia	6.6	12.0	14.4	15.7
Ventricular Fibrillation	3.1	4.6	4.7	3.9
Atrial Fibrillation	27.3	30.2	31.7	34.5
AIDS	0.0	0.0	0.0	0.2
Dyslipidaemia	44.8	52.8	58.6	63.4
Smoking	0.7	0.9	1.0	0.7
Thrombocytopenia	3.6	5.4	6.3	8.7
Previous AMI	0.0	6.6	19.4	29.4
Previous PCI	5.0	9.2	14.7	17.9
Previous CABG	8.6	14.9	22.3	29.3
Previous CVA	0.0	4.5	7.8	13.2
Anaemias	8.7	12.7	17.3	29.7
Congestive heart failure	0.0	37.3	55.2	72.6
Chronic obstructive pulmonary disease	0.0	13.5	26.5	35.6
Coagulopathy	4.7	6.8	7.9	10.7
Diabetes without complications	0.0	22.1	31.0	33.2
Diabetes with complications	0.0	0.0	2.7	33.8
Hypertension	65.3	60.1	45.8	18.0
Liver disease (mild)	0.0	1.0	2.1	3.9
Liver disease (moderate or severe)	0.0	0.0	0.0	1.1
Rheumatologic disease	0.0	2.1	3.2	4.5
Peptic Ulcer	0.0	0.4	0.8	1.5
Hemiplegia/hemiparesis	0.0	0.0	0.6	2.7
Any malignancy including leukaemia and lymphoma	0.0	0.0	2.2	7.2
Metastatic cancer	0.0	0.0	0.0	1.6
Peripheral vascular disease	0.0	5.0	10.3	18.7
Renal failure (chronic)	0.0	0.0	11.8	62.8

Variable/CCI Class (% within cohort)	0 (17.7%)	1 (21.8%)	2 (18.7%)	≥3 (41.8%)
Valvular heart disease	11.2	15.7	17.2	18.7
Dementia	0.0	7.5	9.2	11.2

AMI: acute myocardial infarction; **CABG:** coronary artery bypass graft surgery; **CCI:** Charlson Comorbidity Index; **CIED:** cardiac implantable electronic device; **CRT:** cardiac resynchronization therapy with defibrillator (CRT-D) or pacemaker (CRT-P), **CVA:** cerebrovascular accident (stroke or transient ischemic attack); **IABP:** intra-aortic balloon pump; **ICD:** implantable cardioverter defibrillator; **IQR:** interquartile range; **PCI:** percutaneous coronary intervention; **LV:** left ventricular; **PPM:** permanent pacemaker.

Overall, the most common CCI comorbidities in the total CIED cohort were congestive heart failure (48.8%), followed by renal failure (28.5%), diabetes without complications (24.4%) chronic obstructive pulmonary disease (22.8%) and previous myocardial infarction (17.3%). (**Table 8.1, Figure 8.2**) This pattern was observed across CIED types.

Figure 8.2. Prevalence of individual CCI comorbidities



Legend: AMI: acute myocardial infarction; **CHF: congestive heart failure, CRT:** cardiac resynchronization therapy with defibrillator (CRT-D) or pacemaker (CRT-P); **CVA:** cerebrovascular accident (stroke or transient ischemic attack); **ICD:** implantable cardioverter defibrillator; **PPM:** permanent pacemaker; PVD: peripheral vascular disease.

Patient characteristics

In the total cohort, patients with a higher CCI class were older, more likely to be male, Black, admitted urgently (vs. elective), and admitted to urban teaching hospitals. As CCI class increased, there was an increase in the prevalence of in-hospital cardiac arrest and pre-procedure cardiogenic shock; a greater prevalence of ventricular tachycardia, atrial fibrillation, dyslipidaemia, previous PCI, anaemias (deficiency and chronic disease), and valvular heart disease (**Table 8.2**).

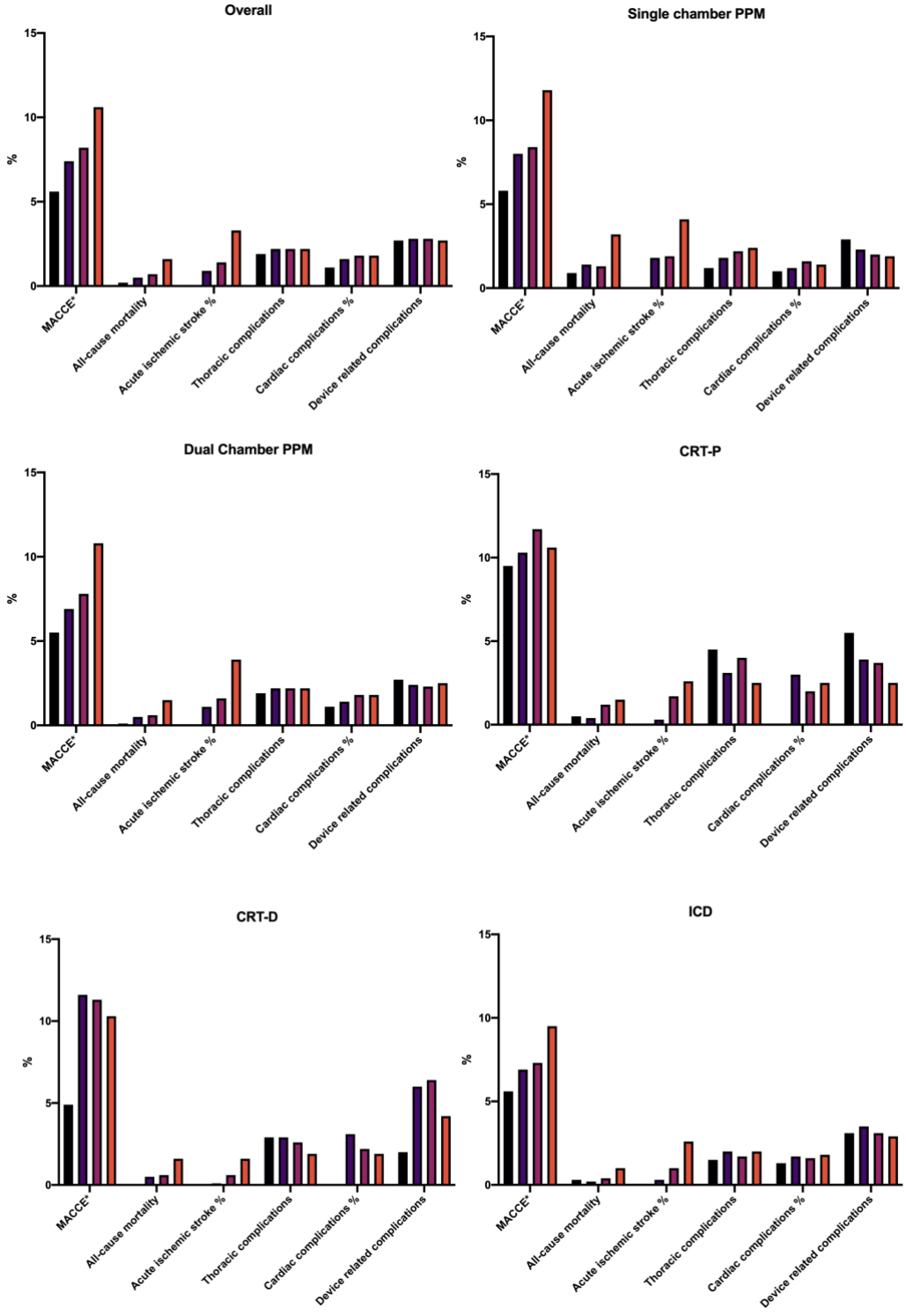
In-hospital outcomes

The crude rates of MACCE, primarily driven by all-cause mortality and acute ischemic stroke, as well as thoracic and cardiac complications, length of stay and total hospitalization costs in the total cohort increased in line with higher CCI class. (**Table 8.3**, **Figure 8.3**, p<0.001 for all) Whilst there was no difference in the total rate of device-related complications between CCI classes, the rates of device-related infection and wound disruption were marginally higher in those with CCI ≥3 (0.2% for both) compared with all other classes (0.1% for CCI 0, 1 and 2 of both outcomes).

Table 8.3. In-hospital adverse outcomes and hospital charges according to CCI class

CCI class/Outcome	0	1	2	≥3	p-value
MACCE*, %	5.6	7.4	8.2	10.6	<0.001
All-cause mortality, %	0.2	0.5	0.7	1.6	<0.001
Acute ischemic stroke, %	0.0	0.9	1.4	3.3	<0.001
Thoracic complications, %	1.9	2.2	2.2	2.2	<0.001
Cardiac complications, %	1.1	1.6	1.8	1.8	<0.001
Device related complications, %	2.7	2.8	2.8	2.7	0.165
Device infection	0.1	0.1	0.1	0.2	<0.001
Lead revision	1.2	1.0	1.0	1.0	<0.001
Wound disruption	0.1	0.1	0.1	0.2	<0.001
Mechanical complications	2.2	2.3	2.3	2.1	<0.001
Length of stay (days), median (IQR)	3 (2,4)	4 (2,6)	4 (2,7)	5 (3,9)	<0.001
Total costs (US Dollars), median (IQR)	67084 (47044, 106677)	85572 (54556, 148949)	98761 (60200, 169803)	115156 (67918, 196113)	<0.001

Figure 8.3. Unadjusted rates of in-hospital adverse outcomes



The rates of MACCE, all-cause mortality and acute ischemic stroke were higher with more advanced CCI class in all CIED types, except for MACCE in the CRT-P group which was similar across CCI classes. (**Table 8.4, Figure 8.3**) Although the rates of other adverse

outcomes (thoracic, cardiac, and device-related complications) were generally higher in patients with CCI class>0 for most device types, there were differences between specific outcomes.

Table 8.4. In-hospital clinical outcomes according to CIED subtype and CCI class

CCI class/Outcome	0	1	2	≥3	p-value
MACCE					
Single Chamber PPM	5.8	8.0	8.4	11.8	<0.001
Dual Chamber PPM	5.5	6.9	7.8	10.8	<0.001
CRT-P	9.5	10.3	11.7	10.6	0.129
CRT-D	4.9	11.6	11.3	10.3	<0.001
ICD	5.6	6.9	7.3	9.5	<0.001
All-cause mortality					
Single Chamber PPM	0.9	1.4	1.3	3.2	<0.001
Dual Chamber PPM	0.1	0.5	0.6	1.5	<0.001
CRT-P	0.5	0.4	1.2	1.5	<0.001
CRT-D	0.0	0.5	0.6	1.6	<0.001
ICD	0.3	0.2	0.4	1.0	<0.001
Acute ischemic stroke					
Single Chamber PPM	0.0	1.8	1.9	4.1	<0.001
Dual Chamber PPM	0.0	1.1	1.6	3.9	<0.001
CRT-P	0.0	0.3	1.7	2.6	<0.001
CRT-D	0.0	0.1	0.6	1.6	<0.001
ICD	0.0	0.3	1.0	2.6	<0.001
Thoracic complications					
Single Chamber PPM	1.2	1.8	2.2	2.4	<0.001
Dual Chamber PPM	1.9	2.2	2.2	2.2	<0.001
CRT-P	4.5	3.1	4.0	2.5	<0.001
CRT-D	2.9	2.9	2.6	1.9	<0.001
ICD	1.5	2.0	1.7	2.0	<0.001
Cardiac complications					
Single Chamber PPM	2	1.2	1.6	1.4	0.008
Dual Chamber PPM	1.1	1.4	1.8	1.8	<0.001
CRT-P	0.0	3.0	2.0	2.5	<0.001
CRT-D	0.0	3.1	2.2	1.9	<0.001
ICD	1.3	1.7	1.6	1.8	0.043
Total device-related complications					
Single Chamber PPM	2.9	2.3	2.0	1.9	<0.001
Dual Chamber PPM	2.7	2.4	2.3	2.5	0.001
CRT-P	5.5	3.9	3.7	2.5	<0.001
CRT-D	2.0	6.0	6.4	4.2	<0.001
ICD	3.1	3.5	3.1	2.9	0.003
Device-related infection					
Single Chamber PPM	0.3	0.2	0.0	0.2	<0.001
Dual Chamber PPM	0.1	0.1	0.1	0.2	<0.001
CRT-P	0.0	0.1	0.4	0.1	<0.001
CRT-D	0.0	0.1	0.1	0.1	0.626
ICD	0.0	0.1	0.1	0.2	<0.001
Lead revision					

Single Chamber PPM	1.2	0.5	0.6	0.6	<0.001
Dual Chamber PPM	1.3	1.1	1.1	1.2	<0.001
CRT-P	0.5	1.0	0.7	0.9	0.305
CRT-D	0.0	2.0	1.9	1.0	<0.001
ICD	0.7	0.7	0.8	0.7	0.759
Wound disruption					
Single Chamber PPM	0.2	0.2	0.1	0.2	0.765
Dual Chamber PPM	0.1	0.1	0.1	0.2	<0.001
CRT-P	0.5	0.4	0.0	0.3	0.001
CRT-D	0.0	0.2	0.4	0.2	<0.001
ICD	0.1	0.2	0.2	0.2	0.313
Device mechanical complications					
Single Chamber PPM	2.1	1.7	1.7	1.3	<0.001
Dual Chamber PPM	2.2	1.9	1.8	1.8	0.001
CRT-P	5.0	3.0	3.0	1.9	<0.001
CRT-D	2.0	5.2	5.3	3.7	<0.001
ICD	2.6	3.0	2.6	2.3	0.003

After adjustment for all baseline differences, each unit CCI score was associated with an increase in odds of MACCE (OR 1.10; 95% CI 1.09, 1.11), all-cause mortality (OR 1.23; 95% CI 1.21, 1.25) and acute stroke (OR 1.45; 95% CI 1.44, 1.46). (**Table 8.5, Figure 8.4**, p<0.001 for all) These findings were consistent across CIED subtypes, although there was no difference in odds of mortality with increasing CCI score in the CRT-P and CRT-D groups. Increasing CCI score was associated with reduced odds of thoracic (OR 0.95 95% CI 0.94, 0.96), cardiac (OR 0.95 95% CI 0.94, 0.96) and device-related (OR 0.96 95% CI 0.95, 0.97) complications in the overall cohort, a pattern that was also observed in majority of individual device groups.

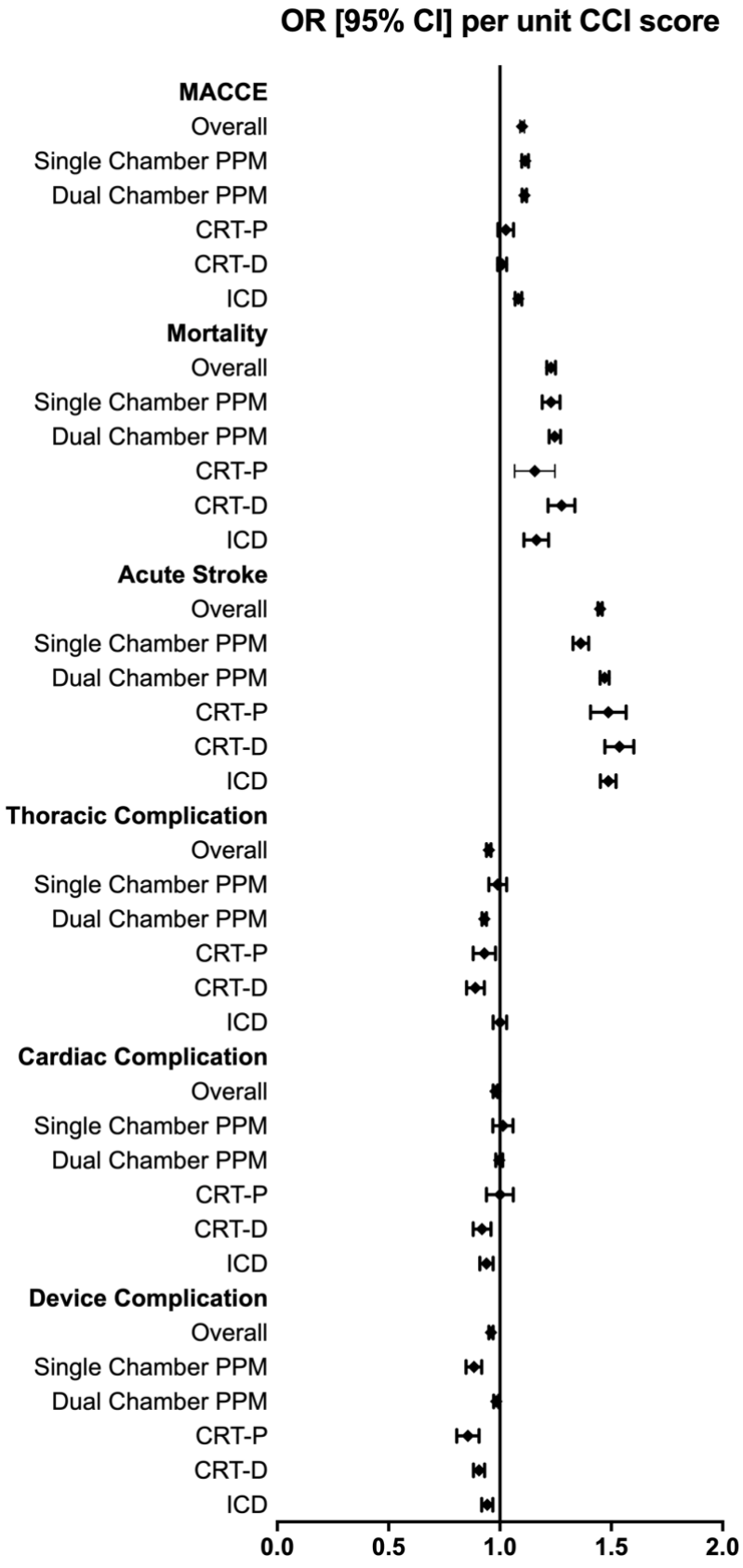
Table 8.5. Odds ratios (OR) of adverse outcomes per unit of CCI score

Outcome	OR (95% CI)	p-value
MACCE		
Total	1.10 [1.09, 1.11]	<0.001
Single Chamber PPM	1.11 [1.10, 1.13]	<0.001
Dual Chamber PPM	1.11 [1.10, 1.12]	<0.001
CRT-P	1.03 [0.99, 1.06]	0.064
CRT-D	1.01 [0.99, 1.03]	0.451
ICD	1.08 [1.07, 1.10]	<0.001
All-cause mortality		
Total	1.23 [1.21, 1.25]	<0.001
Single Chamber PPM	1.23 [1.19, 1.27]	<0.001
Dual Chamber PPM	1.24 [1.22, 1.26]	<0.001

CRT-P	1.15 [1.07, 1.25]	<0.001
CRT-D	1.27 [1.22, 1.34]	<0.001
ICD	1.16 [1.11, 1.22]	<0.001
Acute ischemic stroke		
Total	1.45 [1.44, 1.46]	<0.001
Single Chamber PPM	1.36 [1.33, 1.40]	<0.001
Dual Chamber PPM	1.47 [1.45, 1.49]	<0.001
CRT-P	1.48 [1.41, 1.57]	<0.001
CRT-D	1.54 [1.47, 1.60]	<0.001
ICD	1.49 [1.45, 1.52]	<0.001
Thoracic complications		
Total	0.95 [0.94, 0.96]	<0.001
Single Chamber PPM	0.99 [0.95, 1.03]	0.520
Dual Chamber PPM	0.93 [0.92, 0.94]	<0.001
CRT-P	0.93 [0.88, 0.98]	0.007
CRT-D	0.89 [0.85, 0.93]	<0.001
ICD	1.00 [0.97, 1.03]	0.804
Cardiac complications		
Total	0.95 [0.94, 0.96]	0.012
Single Chamber PPM	1.01 [0.97, 1.06]	0.580
Dual Chamber PPM	1.00 [0.98, 1.01]	0.540
CRT-P	1.00 [0.94, 1.06]	0.915
CRT-D	0.92 [0.88, 0.96]	<0.001
ICD	0.94 [0.91, 0.97]	<0.001
Device related complications		
Total	0.96 [0.95, 0.97]	<0.001
Single Chamber PPM	0.88 [0.85, 0.92]	<0.001
Dual Chamber PPM	0.99 [0.97, 0.998]	0.020
CRT-P	0.85 [0.81, 0.90]	<0.001
CRT-D	0.91 [0.88, 0.93]	<0.001
ICD	0.94 [0.92, 0.97]	<0.001

*Adjusted for the following: type of device, age, sex, elective admission, weekend admission, primary expected payer, median household income, hospital bed size, location and teaching status, pre-procedure cardiogenic shock, ventricular tachycardia and fibrillation, atrial fibrillation, dyslipidaemia, smoking status, thrombocytopenia, history of percutaneous coronary intervention and coronary artery bypass surgery, anaemias coagulopathies, hypertension and valvular heart disease.

Figure 8.4. Forest plot illustrating adjusted odds of adverse events per unit CCI score



5. Discussion

My analysis of more than 470,000 de novo CIED procedures is the largest to study the relationship between comorbidity burden and in-hospital procedural outcomes across all device types and concludes several significant findings. I show that patients undergoing CIED are often multi-morbid, with more than 4 out of every 10 patients classed as having a severe comorbidity burden (CCI score ≥3), especially in those undergoing CRT-D and ICD implantation. Furthermore, I find that patients with a high comorbidity burden are more critically unwell during their admission as evidenced by their higher rates of pre-procedure cardiogenic shock, cardiac arrest during admission, and ventricular tachycardia. However, despite adjustments for patient characteristics between comorbidity burden groups, CCI score correlated with worse MACCE, driven by higher all-cause mortality and acute stroke, while there was no positive relationship between CCI score and risk of thoracic, cardiac or device-related complications after implantation.

While individual patient comorbidities (e.g., diabetes, heart failure, chronic kidney disease, cancer) have been shown to impact CIED procedural outcomes, these often co-exist.[32, 55, 59, 128, 147, 170] Therefore, the overall burden of comorbidity is of equal importance when assessing the procedural risk of patients undergoing CIED implantation. Only few studies have examined the relationship between comorbidity burden and CIED procedural outcomes, although these were subject to certain limitations.[23, 61, 65, 72-75] For example, some studies have used the number of comorbidities as a surrogate of comorbidity burden instead of established comorbidity measures such as CCI that considers differences in the impact of each type of comorbidity.[23, 75] Certain studies focused on specific subtypes of cardiac devices (e.g. PPM or ICD only) or combined de novo and upgrade procedures, despite the differences in procedural complexity between device and procedure types, or examined composite outcomes (e.g. any in-hospital complication), leaving a gap in knowledge about

the impact of comorbidity burden, as measured by the CCI score, on a variety of postprocedural outcomes after CIED implantation.[61, 65, 72-74]

In my analysis, a significant number of patients undergoing CIED implantation were severely comorbid (CCI score ≥3), the least being those dual chamber PPM (36%) and the highest being those in receipt of CRT-D (60.8%). Although there was a positive relationship between comorbidity burden and the odds of all-cause mortality (16-27% increase per unit score of CCI) and acute stroke (36-54% per unit score), a higher comorbidity score was not associated with increased odds of procedure-related complications. These findings were generally consistent across device subtypes. My study is the first to assess the impact of comorbidity burden, measured objectively using the CCI score, on a range of in-hospital procedural outcomes after de novo CIED implantation. A previous study by Swindle et al., severe comorbidity (CCI≥3) was associated with a significant increase in odds of in-hospital mortality (OR ICD: 2.44 (1.47-4.05); CRT-P: 3.01 (1.17-7.77); CRT-D: 2.74 (1.62-4.65)) among heart failure patients (n=26,887) undergoing ICD and CRT implantation.[61] While this is consistent with my findings, their study included *de novo* and upgrade/revision procedures. Furthermore, all patients in that study had a minimum CCI of 1, which is the allocated score for congestive heart failure. Another study of 1,062 ICD and CRT-D procedures reported an increased hazard of 1-year mortality (HR 1.40 (1.20-1.60)) per additional CCI score. However, their cohort only included specific device subtypes, including upgrade and *de novo* CIED procedures.[65]

While no study has previously examined the impact of comorbidity burden on procedural outcomes, including cardiac, thoracic, and device-related complications, an analysis by Zhan et al. showed no increase in odds of 'any in-hospital complication' in patients with ≥3 comorbidities undergoing implantation of all CIED subtypes other than CRT-D. [23] However, their study does not provide insight into the relationship between

comorbidity burden and important procedural outcomes since their composite outcome was very broad (at least 7 individual outcomes), and they measured comorbidity burden subjectively, according to the number of comorbidities, ignoring the prognostic impact of each type of comorbidity.

Based on my study findings, a higher comorbidity burden does not pose a risk for complications after CIED implantation. However, it is possible that an element of selection bias exists, where healthier implanted are more likely to be selected for more complex devices such as CRT.

Limitations

The limitations of the present study pertain to the type and capture of the dataset (e.g., susceptibility to coding errors, limited information on pharmacotherapy and procedure indication) and are identical to those acknowledged in Chapters 4 to 7. However, these limitations are expected to be similar across different comorbidity groups and are not expected to influence the validity of these findings.

6. Summary

My analysis demonstrates a significant proportion of patients undergoing de novo CIED implantation are comorbid, with 4 out of 10 patients considered to have a severe comorbidity burden. Although increasing CCI score correlated with a higher risk of in-hospital all-cause mortality and acute ischemic stroke in my analysis, patients with a higher CCI score were at no increased risk of thoracic, cardiac, or device-related complications. These findings emphasise the need for assessing the overall comorbidity burden of patients undergoing CIED implantation based on objective scoring methods for reliable prognostication of mortality and stroke complications.

Chapter 9. Causes and predictors of 30-day hospital readmissions after de novo CIED implantation

Part of the work in this chapter is based on my study that was published in the International Journal of Cardiology (Appendix 5). [170]

1. Introduction

Permanent pacemakers (PPM) and implantable cardioverter-defibrillators (ICD) play a key role in the management of many serious cardiac rhythm disorders. Furthermore, cardiac resynchronisation therapy (CRT) has been shown to improve the quality of life and survival of patients with severe left ventricular failure who meet the eligibility criteria for these devices. Collectively, these are known as cardiac implantable electronic devices (CIED) and their utilisation has significantly increased in the last two decades.[44, 45] While the majority of complications after CIED implantation occur in the peri-procedural or post-procedural phase, a proportion of these can occur after the hospitalization episode.[55, 81]

Unplanned readmissions after a hospitalization episode are seen as a metric of the quality of care provided and represent a burden to patients as well as healthcare institutions from an economic and resource perspective. As such, many countries such as the United Kingdom (UK) and the United States (US) have introduced fines or penalties for institutions if patients are readmitted within 30 days.[82, 83] Only few studies have looked at the rates, causes and predictors of 30-day readmissions after CIED implantation and these were subject to several limitations, including the focus on all-cause readmissions only, without the analysis of cardiac-specific causes, or the lack of comparison between CIED types.[84-88] Consequently, there is limited data on the trend of 30-day readmissions after

CIED implantation over time, which is of great importance to cardiologists and other stakeholders when restructuring services and planning health policies. Furthermore, adequate knowledge on what proportion of these admissions is due to cardiac causes, and whether there are certain predictors of such events, is necessary to identify patients who require further optimisation or closer follow-up at discharge.

Sex has been shown to correlate with all-cause readmission, with females more likely to be readmitted within 30 days in two previous studies. [84, 87] However, it is unclear whether females are more likely to be readmitted due to cardiac and device-related causes than males and if any sex differences have persisted in recent years.

2. Objectives

The main objectives of this chapter included the following:

a) To examine the rates and causes of 30-day readmissions after CIED implantation from a national perspective.
b) Compare the rates and causes of 30-day readmissions between sexes as well as CIED types (PPM, CRT and ICD).
c) Study the trend of 30-day readmissions between 2010 and 2015 including differences in these trends between sexes.

3. Methods

A full description of the methodology relating to all chapters of my thesis is provided in Chapter 3.

a) Data Source

The data source for this study was the United States (US) Nationwide Readmissions Database (NRD). Further information on its structure and validation has been provided in Chapter 3.

b) Study Design and Population

My cohort included all 'index' hospitalisations during which adults (≥18 years) underwent *de novo* CIED implantation between January and November for the years 2010 to 2014, and January to August in 2015, as well as all readmissions within 30 days from the date of discharge from the index hospitalisation. The final month in each study year was excluded as no 30-day follow-up would have captured for these procedures given that patients' hospitalizations cannot be tracked over multiple calendar years. I extracted all patient and procedural characteristics using the International Classification of Diseases, ninth revision (ICD-9) diagnosis and procedural codes provided in the supplements (**Table 3.1**). I identified primary causes of readmission according to the Clinical Classification Software (CCS) codes provided in **Table 9.1**. Records with missing data as well as those where patients had a missing length of stay and death information were excluded (n=1170, 0.14% of the original dataset). (see **Figure 9.1** for flow diagram).

Figure 9.1. Flow chart of cohort selection

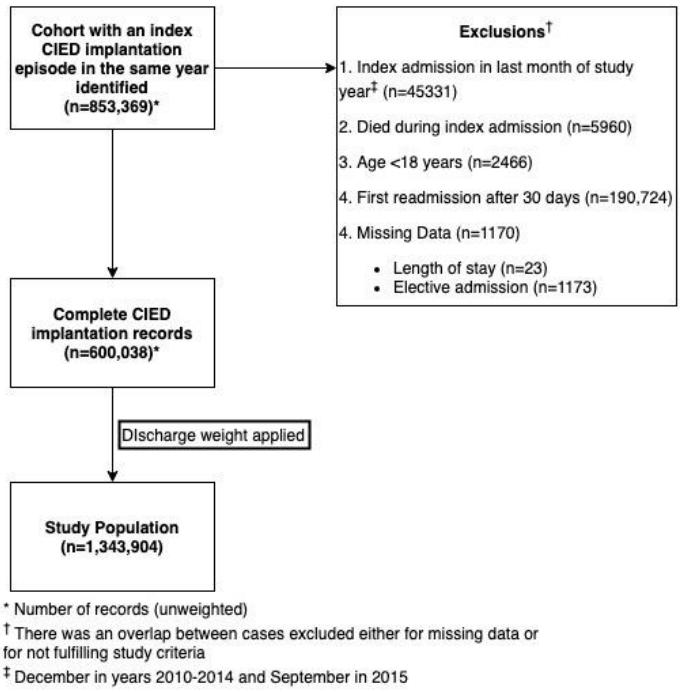


Table 9.1 Clinical Classification Software search codes

Category	Codes
Respiratory	127 128 130 131 132 133 134 221
Infection	1 2 3 4 5 6 7 8 9 76 77 78 90 122 123 124 125 126 129 135 197 201
Bleeding	60 153 182
Peripheral vascular disease	114 115 116 117 118 119
Genitourinary	159 160 161 162 163 164 165 166 170 175 215
Renal disease	156 157 158
Gastrointestinal	138-152, 154, 155, 214, 222, 250, 251
TIA/stroke	109-113
Trauma	207, 225-236, 239, 244, 260
Endocrine/metabolic	48-51, 53, 58, 186
Neuropsychiatric	650-663, 670, 79-85, 95, 216,
Haematological/neoplastic	11-47, 59, 61-64
Rheumatology	54
ENT	92-94
Non-specific chest pain	102
Oral health problem	136, 137
Obstetric	174, 176-181, 184, 185, 187-196, 218-220, 223, 224
Dermatology	198-200
Poisoning	241-243
Syncope	245
Other non-cardiac	10 45 52 55 56 57 120 121 167 168 169 172 173 202 203 204 205 206 208 209 210 211 212 217 237 238 240 246 247 248 252 253 254 255 256 257 258 259
Heart failure	108
Arrhythmia	106-107
Conduction disorder	105
Valve disorders	96
Pericarditis	97
Coronary artery disease including angina	101
Acute myocardial infarction	100
Hyper/hypotension	98, 99, 183, 249
Other cardiac	103, 104, 213

c) Outcomes

The primary outcome measures were 30-day all-cause and cardiac readmissions. Secondary outcomes included in-hospital mortality, acute stroke or transient ischemic attack (TIA), acute kidney injury (AKI), bleeding, device-related infection and device revision or removal during the readmission episode.

d) Statistical Analysis

Descriptive statistics were performed as previously explained in Chapter 3. I performed an exploratory analysis of 30-day all-cause and cardiac readmission rates, stratified by sex and further by CIED types. Sampling weights provided by the AHRQ were applied to all analyses. Trend analysis was performed by including time (years) as a covariate in linear regression models where the outcome was the variable of interest (e.g., 30-day all-cause readmission or 30-day device-related cause readmission).

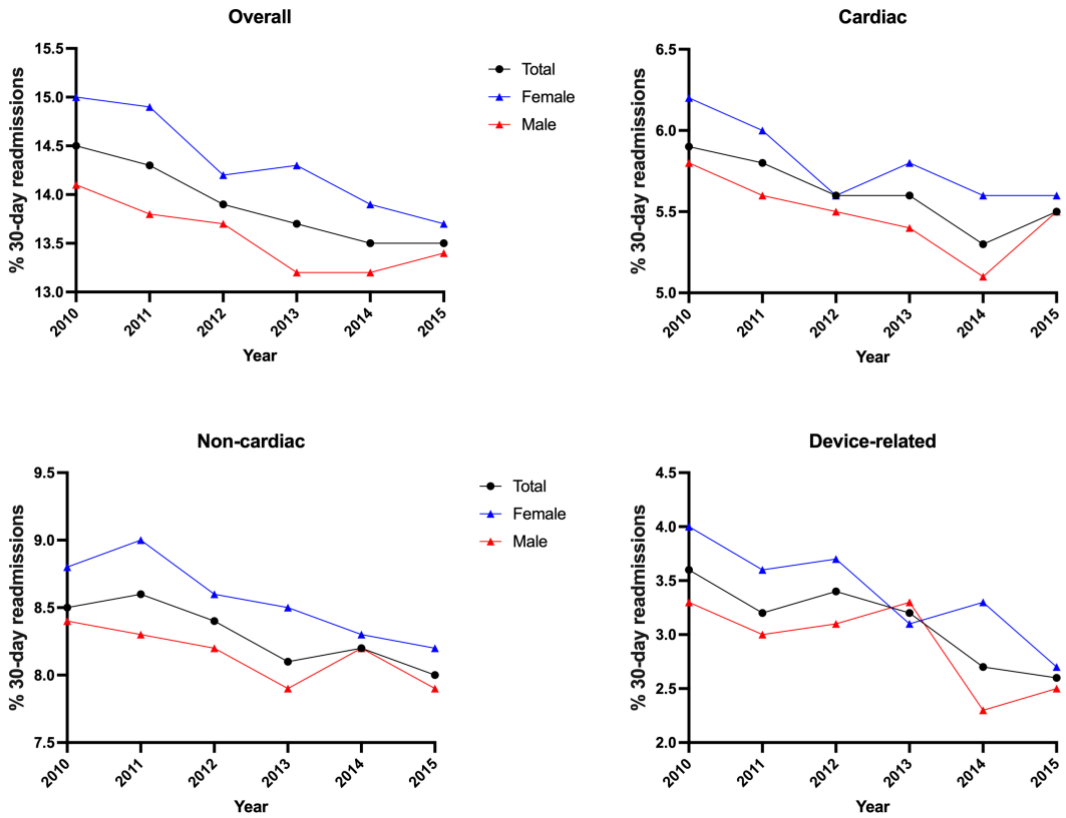
I performed multivariable logistic regression modelling to identify predictors of 30-day cardiac readmission as well as to examine the odds of 30-day cardiac and device-related readmissions in females, with male sex being the reference category. All associations are expressed as odds ratios (OR) along with 95% confidence interval (CI), adjusting for the following covariates in addition to sex, admission year and CIED type: age, weekend admission, primary expected payer, median household income, atrial fibrillation (AF), thrombocytopenia, ventricular tachycardia (VT) and fibrillation (VF), dyslipidaemia, smoking status, previous AMI, previous coronary artery bypass graft (CABG), previous PCI, previous cerebrovascular accidents (CVA) including stroke and TIA, family history of coronary artery disease (CAD), bed size of hospital, year of admission, Elixhauser comorbidities (acquired immune deficiency syndrome (AIDS), deficiency anaemias, chronic blood loss anaemia, rheumatoid arthritis/collagen vascular diseases, congestive heart failure, chronic pulmonary disease, coagulopathy, depression, diabetes (uncomplicated), diabetes with chronic complications, drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurological disorders, obesity, peripheral vascular disorders (PVD), psychoses, pulmonary circulation disorders, chronic renal failure, solid tumour without metastasis, peptic ulcer disease excluding bleeding, valvular heart disease, and weight loss),

and complications during index admission (acute stroke or TIA, AKI, procedure-related bleeding, thoracic and cardiac complications). Thoracic complications were defined as a composite of acute pneumothorax or haemothorax, with or without drainage, or thoracic vascular injury whereas cardiac complications were defined as a composite of cardiac tamponade, hemopericardium, pericardiocentesis.

4. Results

A total 1,155,992 index hospitalisations for de novo CIED implantation were recorded between January 2010 and August 2015. Overall, the rate of 30-day all-cause readmission was 14% (n=187,913) and this was higher in females (14.4%) than males (13.6%). The rate of 30-day all-cause readmission declined between 2010 and 2015 (14.5% to 13.5%, p<0.001), and this was evident in both sexes (males: 14.1% vs. 13.4%; females: 15% to 13.7%). (**Figure 9.2**)

Figure 9.2. Trends of all-cause, cardiac, non-cardiac and device-related 30-day readmissions



p<0.001 for trend; *2015: January to August only

Table 9.2. Patient characteristics of study groups

Variable/Group (%)	Not readmitted			Readmitted		
	Male (57.1)	**Female (42.9)**	**Total**	**Male (55.5)**	**Female (44.5)**	**Total**
Number of weighted discharges	660430	495562	1155992	104359	83554	187913
Type of CIED, %						
PPM	59.5	78.1	67.4	54.0	74.4	63.0
CRT-P	2.6	2.5	2.5	2.8	2.9	2.9
CRT-D	14.3	7.5	11.4	17.2	8.4	13.3
ICD	23.6	11.9	18.6	25.9	14.4	20.8
Age (years), median (IQR)	73 (64, 81)	77 (68,84)	75 (65,83)	74 (64,82)	78 (68,85)	76 (66,83)
Weekend admission, %	16.6	18.4	17.4	18.3	19.9	19.0
Primary expected payer, %						
Medicare	71.2	79.3	74.6	76.5	83.1	79.4
Medicaid	4.6	4.4	4.5	6.3	5.6	6.0
Private Insurance	19.4	13.7	17.0	13.4	9.3	11.6
Self-pay	1.9	1.2	1.6	1.5	1.0	1.2
No charge	0.2	0.2	0.2	0.2	0.1	0.2
Other	2.7	1.2	2.1	2.2	0.9	1.6
Median Household Income (Percentile), %						
0-25th	26.0	28.0	26.9	28.9	30.0	29.4
26-50th	25.7	26.1	25.9	25.4	26.0	25.7
51-75th	24.4	24.2	24.3	23.7	23.6	23.7
76-100th	23.8	21.7	22.9	21.9	20.3	21.2
Cardiac Arrest, %	4.4	4.0	4.2	4.2	4.3	4.3
Ventricular Tachycardia, %	9.2	5.2	7.5	11.7	6.4	9.3
Ventricular Fibrillation, %	4.4	2.9	3.7	4.1	2.8	3.5
Comorbidities, %						

Variable/Group (%)	Not readmitted			Readmitted		
	Male (57.1)	**Female (42.9)**	**Total**	**Male (55.5)**	**Female (44.5)**	**Total**
Dyslipidaemia	55.5	50.4	53.3	53.0	48.9	51.2
Smoking	29.9	17.8	24.8	28.8	17.8	24.0
Atrial Fibrillation	36.3	39.8	37.8	43.6	49.4	46.1
Thrombocytopenia	5.1	3.6	4.4	6.1	4.6	5.4
Previous AMI	15.2	7.5	12.0	16.4	9.5	13.3
History of IHD	54.9	34.4	46.2	61.5	43.5	53.6
Previous PCI	13.7	7.7	11.2	14.2	9.5	12.1
Previous CABG	16.9	6.4	12.5	18.0	8.3	13.7
Previous CVA	7.2	8.2	7.6	8.4	9.5	8.9
Family history of CAD	4.2	3.8	4.0	3.1	2.6	2.9
AIDS	0.1	0.0	0.0	0.1	0.0	0.1
Alcohol abuse	3.3	0.8	2.3	3.8	0.9	2.5
Deficiency anaemias	12.7	16.4	14.3	21.2	25.2	23.0
Chronic Blood loss anaemia	1.5	3.8	2.4	1.8	4.7	3.1
RA/collagen vascular diseases	0.4	0.6	0.5	0.8	1.1	0.9
Heart Failure	41.5	35.0	38.8	56.1	49.8	53.3
Chronic pulmonary disease	18.0	18.4	18.2	25.9	26.0	26.0
Coagulopathy	6.6	4.9	5.9	8.6	6.7	7.8
Depression	5.5	9.9	7.4	7.4	12.2	9.5
Diabetes	27.2	24.3	26.0	30.8	28.9	30.0
Diabetes with complications	5.3	4.6	5.0	8.7	7.7	8.2
Drug abuse	1.4	0.8	1.2	2.0	1.2	1.6
Hypertension	71.0	73.5	72.1	72.4	75.0	73.6
Hypothyroidism	9.2	23.3	15.1	10.7	24.1	16.6
Liver disease	1.4	1.1	1.3	2.3	1.6	2.0
Lymphomas	0.7	0.6	0.7	1.1	0.9	1.0

Variable/Group (%)	Not readmitted			Readmitted		
	Male (57.1)	**Female (42.9)**	**Total**	**Male (55.5)**	**Female (44.5)**	**Total**
Fluid and electrolyte disturbances	18.4	23.4	20.5	26.7	32.0	29.0
Metastatic cancer	0.4	0.4	0.4	0.8	0.7	0.7
Other neurological disorders	6.3	7.5	6.8	8.1	9.4	8.7
Obesity	12.1	12.9	12.4	12.7	14.7	13.6
Paralysis	1.6	1.7	1.6	2.5	2.6	2.6
Peripheral vascular disease	10.4	8.0	9.4	14.9	11.5	13.4
Psychoses	1.9	2.5	2.1	2.9	3.6	3.2
Pulmonary circulation disorder	0.6	0.9	0.8	1.2	1.9	1.5
Renal failure (chronic)	20.0	17.0	18.8	32.5	27.3	30.2
Solid tumour without metastases	1.5	0.9	1.2	2.2	1.3	1.8
Valvular heart disease	1.4	1.9	1.6	2.5	3.0	2.7
Weight loss	2.2	2.6	2.3	3.9	4.4	4.1
Dementia	1.6	2.2	1.9	2.1	2.7	2.4
Hospital bed size, %						
Small	8.2	9.0	8.5	7.3	8.1	7.6
Medium	20.9	22.0	21.4	20.4	21.7	21.0
Large	70.9	69.0	70.1	72.3	70.2	71.4

There were several differences in patient characteristics during the index admission between those who were subsequently readmitted within 30 days and those who were not. (**Table 9.2**) Overall, patients who were readmitted were older (median 76 vs. 75 years) and more likely to have been admitted over a weekend. Furthermore, patients who were later readmitted had a higher prevalence of VT, AF, chronic and deficiency anaemias, thrombocytopaenia, history of IHD (AMI, PCI, CABG) or CVA, heart failure, chronic pulmonary disease, PVD, renal failure and fluid and electrolyte disorders. Within the sex groups, women were older and had a higher prevalence of AF, anaemia (chronic and iron deficiency), previous CVA, hypertension, fluid and electrolyte disorders, and valvular heart disease. In contrast, men had a higher prevalence of heart failure, previous coronary-related disease and previous IHD (AMI, PCI and CABG), and diabetes.

Causes of readmission

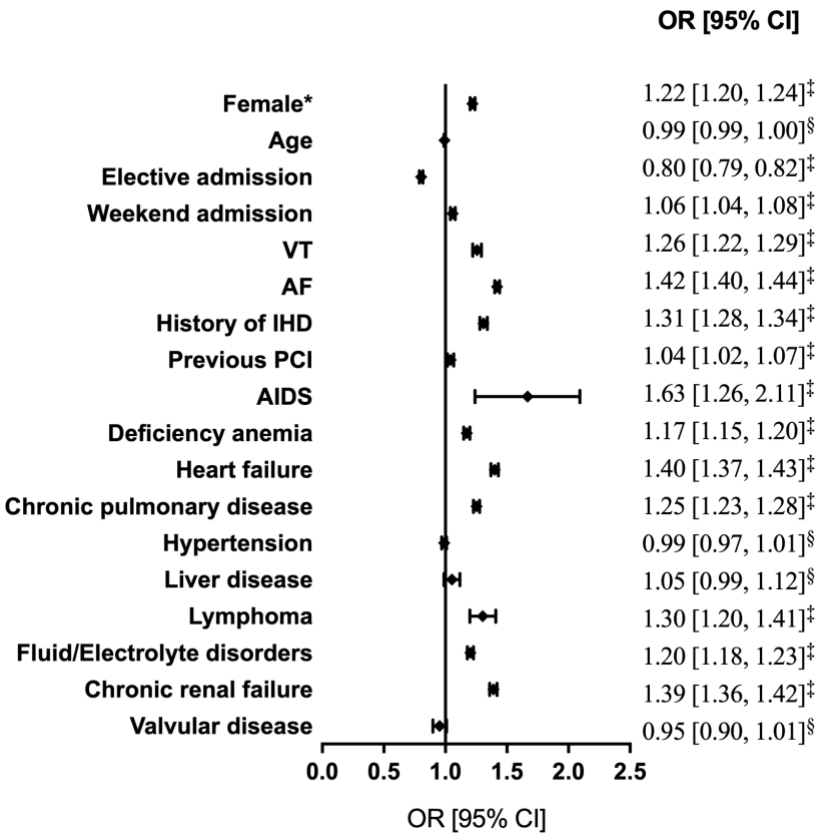
30-day readmissions were more commonly due to non-cardiac than cardiac causes (8.4% and 5.6%, respectively), and both were higher in females than males. The rate of 30-day readmissions due to cardiac and non-cardiac causes have declined over the study period in the overall cohort as well as in both sexes. (**Figure 9.2**) Despite adjustment for the aforementioned differences in patient characteristics, females were more likely to be readmitted for cardiac causes at 30 days (OR 1.22 95% CI 1.20, 1.24, **Figure 9.3**) and these odds were consistently higher in females compared with males throughout the study period. (**Figure 9.4**)

Although the majority of 30-day readmissions were due to non-cardiac causes, there were differences in the proportions of cardiac and non-cardiac readmissions between individual CIED groups. The PPM group had the lowest proportion of cardiac readmissions (35.7%) while the CRT-D and ICD groups had significantly higher proportions of cardiac readmission (49.1% and 48.7%, respectively). (**Figure 9.5**) Within the sex subgroups, the

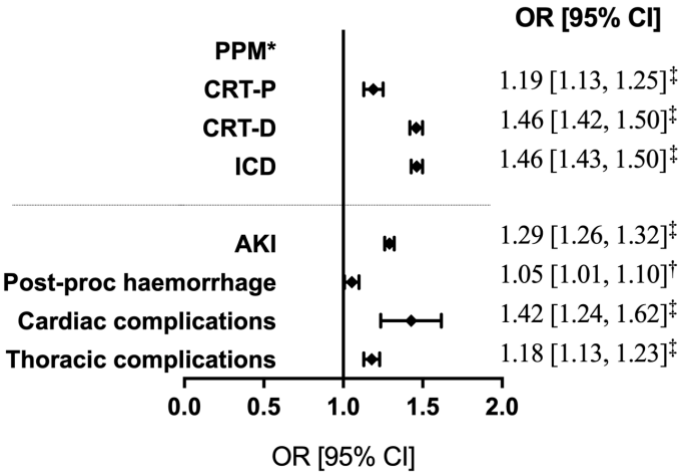
proportion of cardiac readmission was higher in females than males in the PPM and CRT-P groups but not the CRT-D groups where there were no differences in rates between sexes. In contrast, the proportion of cardiac readmission was lower in females than males who underwent ICD implantation.

Figure 9.3. A) Baseline and B) Index procedure-related predictors of 30-day cardiac readmissions*

A)

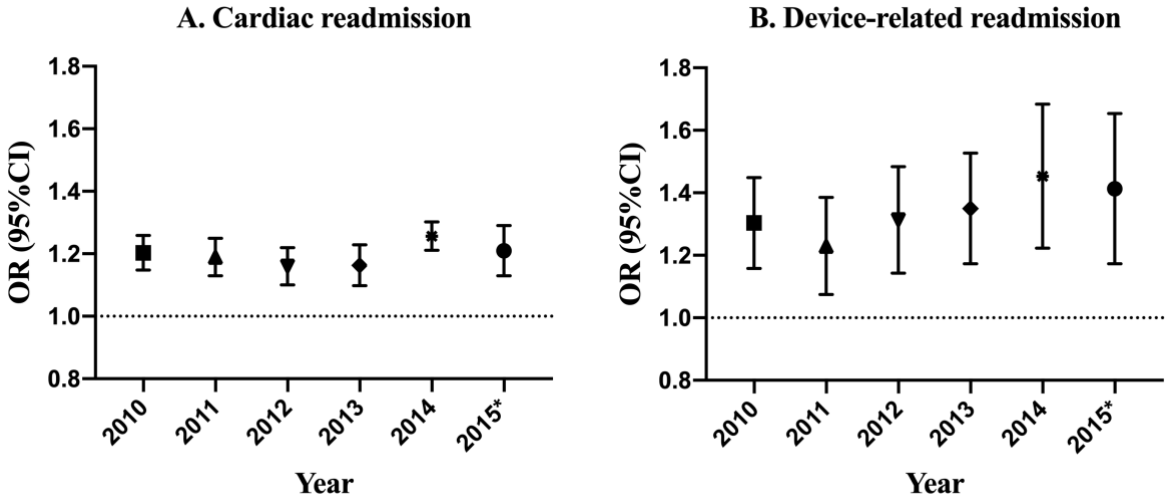


B)



* all predictors generated from a single multivariate regression model; § non-significant; † p<0.01; ‡ p<0.001

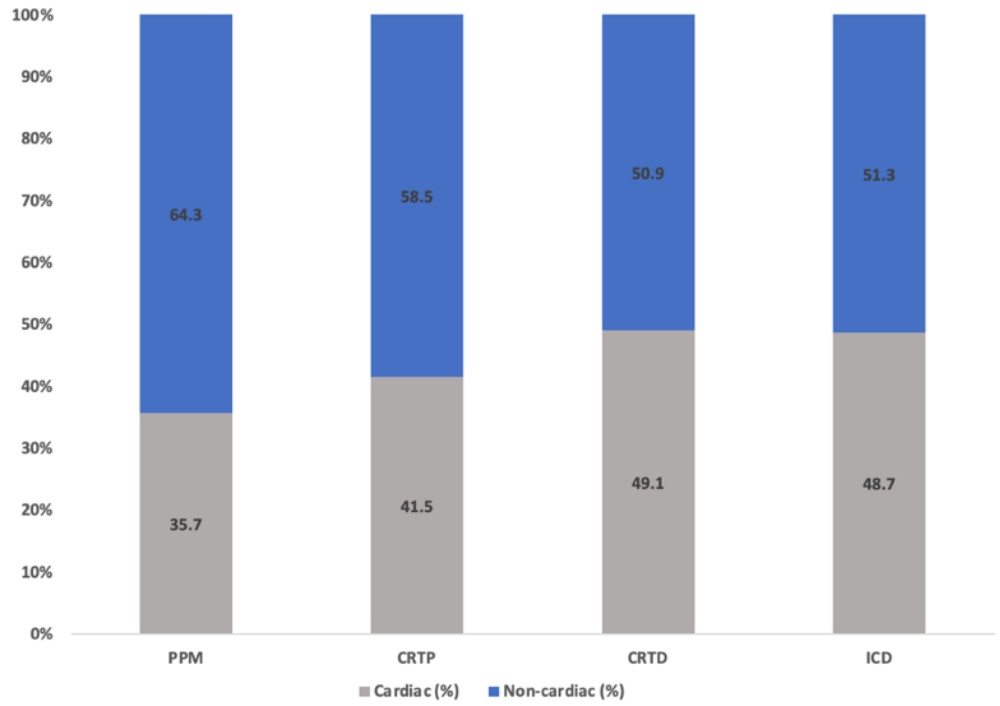
Figure 9.4. Temporal trend of odds ratio (OR) of 30-day readmissions due to A) cardiac causes and B) device-related complications in women compared to men



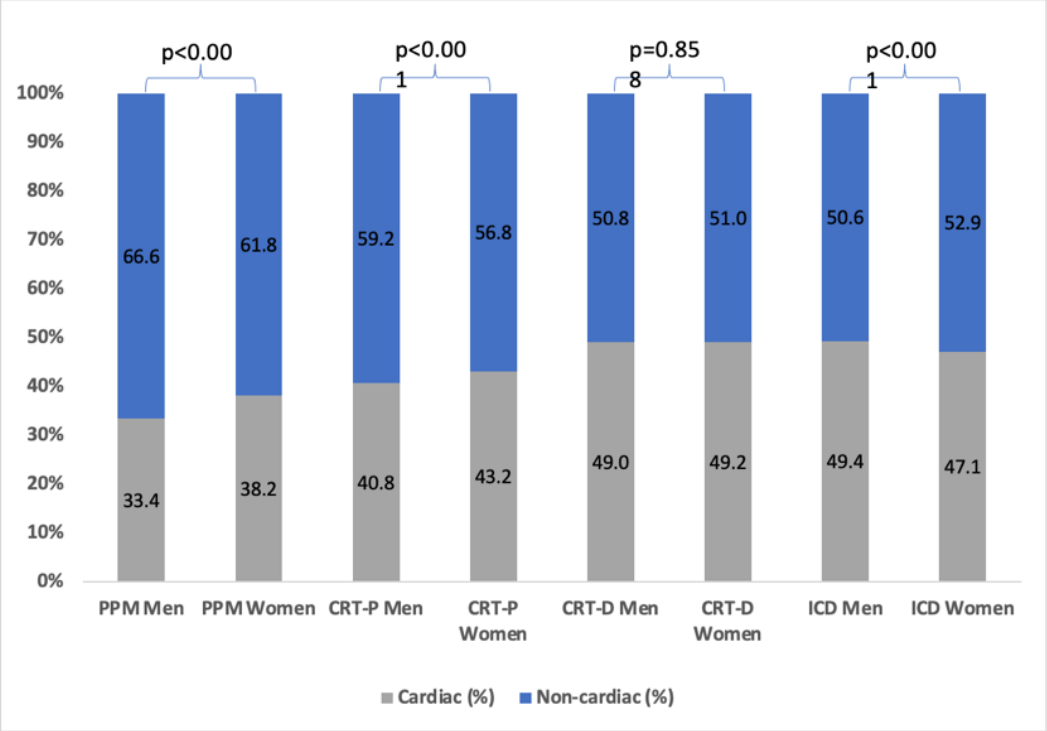
*2015: January to August only

Figure 9.5. Proportion of cardiac (vs. non-cardiac) readmissions according to device type in A) the overall cohort and B) individual sex groups

A)



B)



The top non-cardiac causes of readmission included infectious (10.7%), respiratory (5.6%), PVD (3.5%), renal (3.2%), gastrointestinal (4.8%) and stroke/TIA diagnoses (2.8%). (**Table 9.3**) Females had higher rates of readmission for respiratory and gastrointestinal causes but lower rates of renal and PVD-related readmissions. No difference in readmissions for infection and stroke/TIA were observed between sexes.

Table 9.3. Causes of 30-day readmission

Cause/% of readmissions	Male	Female	Total	p-value
Non-cardiac causes, %				
Infectious	10.7	10.8	10.7	0.538
Respiratory	5.1	6.2	5.6	<0.001
Bleeding	2.2	2.1	2.2	0.360
Peripheral Vascular Disease	3.8	3.3	3.5	<0.001
Renal	3.4	2.9	3.2	<0.001
Genitourinary	2.2	2.2	2.2	0.596
Gastrointestinal	4.6	5.0	4.8	<0.001
TIA/Stroke	2.7	2.8	2.8	0.137
Trauma	1.7	2.3	2.0	<0.001
Endocrine/Metabolic	1.5	1.7	1.6	0.002
Neuropsychiatric	2.9	2.6	2.7	<0.001
Haematology-Oncology	2.3	2.1	2.2	0.006
Rheumatology	0.2	0.1	0.1	<0.001

Cause/% of readmissions	Male	Female	Total	p-value
ENT	0.3	0.4	0.3	0.261
Dermatological	0.2	0.1	0.1	0.049
Poisoning	0.2	0.3	0.3	0.237
Syncope	1.5	1.4	1.5	0.121
Other non-cardiac	17.1	16.8	17.0	0.156
Cardiac Causes, %				
Device-related complications	3.0	3.5	3.2	<0.001
Arrhythmia	8.5	9.1	8.8	<0.001
Heart failure	17.8	17.6	17.7	0.242
Chest pain	2.2	2.3	2.3	0.161
Conduction disorders	0.3	0.3	0.3	0.873
Valve disorders	0.6	0.6	0.6	0.982
Circulatory disorder (hypo- or hypertension)	2.0	2.1	2.0	0.751
Pericarditis	1.3	1.5	1.4	<0.001
Coronary artery disease (including angina)	2.6	1.5	2.1	<0.001
Acute myocardial infarction	1.9	1.8	1.9	0.010

Heart failure was the most common cardiac cause of readmission (17.7%), and this was similar between sexes (p=0.242). (**Table 9.3, Figure 9.6**) Arrhythmias and device-related complications were the next most common cardiac causes of readmission and were both higher in females than males (9.1% vs. 8.5% and 3.5% vs. 3.0%, respectively, p<0.001 for both) in the total CIED cohort. In multivariable analysis, females were associated with increased odds of readmission for device-related complications (OR 1.26 95% CI 1.19, 1.33) compared with males. However, the rate of device-related complications declined over in the overall cohort as well as in both sexes throughout the pandemic. (**Figure 9.2**)

The causes of cardiac readmission are presented according to device group in **Table 9.4** and further stratified by sex in **Table 9.5**. Within the individual CIED groups, arrhythmias were more common in the ICD group while heart failure cause of admission was highest in the CRT-P and CRT-D groups. (**Table 9.4**) The highest rates of readmissions due to arrhythmias and device-related complications were in the CRT-D and ICD groups.

Figure 9.6. Top 10 causes of cardiac readmission stratified by sex in the overall CIED cohort

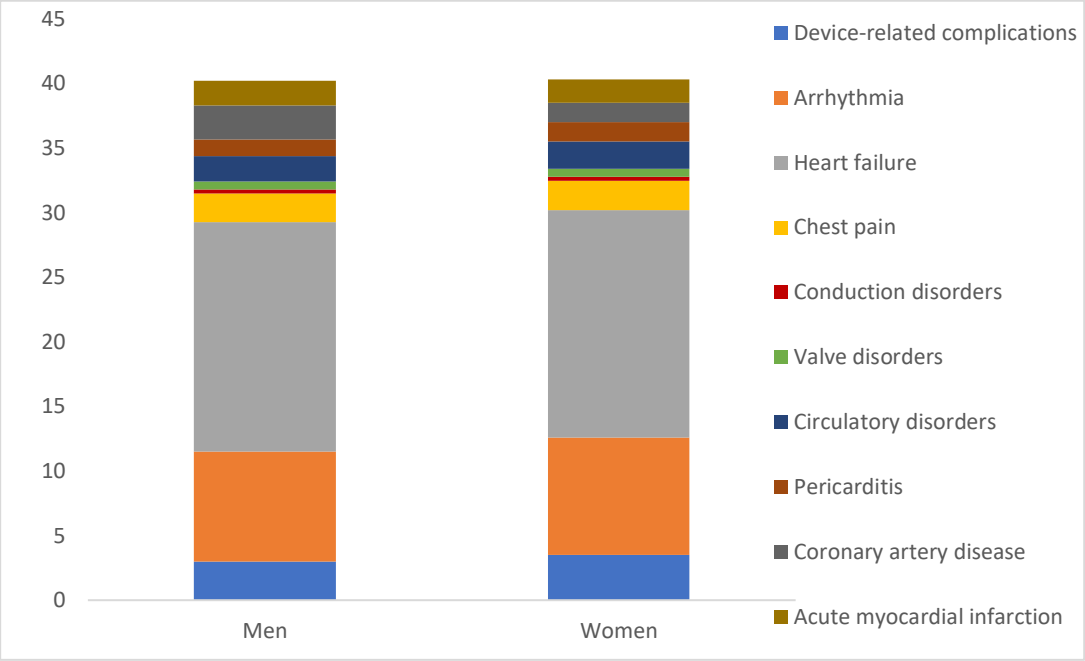


Table 9.4. Cardiac causes of readmission according to device type

Group (% within category)	PPM	CRT-P	CRT-D	ICD	p-value
Device-related complications	3.1	2.3	3.5	3.5	<0.001
Arrhythmia	8.0	6.1	9.1	11.4	<0.001
Heart failure	14.0	24.6	26.1	23.2	<0.001
Chest pain	2.3	1.6	2.0	2.5	<0.001
Conduction disorders	0.2	0.3	0.3	0.3	<0.001
Valve disorders	0.8	0.9	0.2	0.2	<0.001
Circulatory disorder (hypo- or hypertension)	1.9	2.0	2.7	2.2	0.071
Pericarditis	1.5	0.9	1.4	1.3	<0.001
Coronary artery disease (including angina)	2.1	1.3	2.0	2.4	<0.001
Acute myocardial infarction	1.9	1.5	1.7	1.7	0.013

When stratified by sex, the rates of device-related complications were higher in females off all CIED groups other than CRT-P where no difference was observed between sexes. (**Table 9.5**) The rates of heart failure admission were higher in females in the PPM group while no difference in between sexes was observed in all other device groups.

Table 9.5. Cardiac causes of readmission according to device type and sex

	PPM			CRT-P			CRT-D			ICD		
Group (% within category)	**Male (47.8)**	**Female (52.2)**	**p-value**	**Male (55.6)**	**Female (44.4)**	**p-value**	**Male (72.1)**	**Female (27.9)**	**p-value**	**Male (69.5)**	**Female (30.5)**	**p-value**
Device-related complications	2.7	3.4	<0.001	2.3	2.4	0.647	3.2	4.2	<0.001	3.3	3.8	0.028
Arrhythmia	6.6	9.2	<0.001	5.7	6.7	0.136	9.4	8.3	0.008	12.1	9.7	<0.001
Heart failure	12.4	15.4	<0.001	23.8	25.6	0.126	26.2	26.0	0.743	23.2	23.2	0.975
Chest pain	2.3	2.3	0.826	1.2	2.1	0.016	1.7	2.6	<0.001	2.6	2.4	0.456
Conduction disorders	0.2	0.2	0.899	0.3	0.1	0.135	0.3	0.5	0.001	0.3	0.4	0.119
Valve disorders	0.9	0.8	0.005	0.9	0.8	0.661	0.2	0.2	0.629	0.3	0.2	0.122
Circulatory disorder (hypo- or hypertension)	1.7	2.0	<0.001	2.2	1.8	0.320	2.8	2.5	0.262	2.3	1.9	0.004
Pericarditis	1.4	1.5	0.128	0.9	0.9	0.880	1.2	1.8	<0.001	1.1	1.6	<0.001
Coronary artery disease (including angina)	2.9	1.4	<0.001	1.6	1.0	0.056	2.3	1.2	<0.001	2.5	2.0	0.001
Acute myocardial infarction	2.1	1.8	<0.001	1.8	1.3	0.168	1.7	1.7	0.881	1.7	1.9	0.123

Predictors of 30-day cardiac readmission

Other than female sex, several other patient and device-related factors during the index admission were found to be associated with greater odds of 30-day cardiac readmission (**Table 9.6, Figure 9.3**) All complex types of CIED were associated with increased odds of cardiac readmission compared with PPM, with CRT-D and ICD groups being associated with the highest odds (OR CRT-P: 1.19 95% CI 1.13 - 1.25, CRT-D: 1.46 95% CI 1.42 - 1.50, ICD: 1.46 95% CI 1.43 - 1.50). In-hospital complications during the index admission (AKI, acute stroke, thoracic and cardiac complications and post-procedural haemorrhage) were all associated with increased odds of cardiac readmission, especially cardiac complications (OR 1.42 95% CI 1.24 - 1.62) and AKI (OR 1.29 95% CI 1.26 - 1.32). Other patient-related comorbidities associated with increased odds of cardiac readmission were history of HF, VT, AF, deficiency anaemias, chronic pulmonary disease, coagulopathies and lymphoma.

Table 9.6. Predictors of 30-day readmission due to cardiac causes*

Variable	**OR [95% CI]**	**p-value**
Female	1.22 [1.20, 1.24]	<0.001
Index admission related variables:		
PPM (reference)	-	-
CRT-P	1.19 [1.13, 1.25]	<0.001
CRT-D	1.46 [1.42, 1.50]	<0.001
ICD	1.46 [1.43, 1.50]	<0.001
Acute kidney injury	1.29 [1.26, 1.32]	<0.001
Post-procedural haemorrhage	1.05 [1.01, 1.10]	0.014
Cardiac complications	1.42 [1.24, 1.62]	<0.001
Thoracic complications	1.18 [1.13, 1.23]	<0.001
Baseline predictors:		
Age in years at admission	0.99 [0.99, 1.00]	0.173

Elective admission	0.80 [0.79, 0.82]	<0.001
Weekend admission	1.06 [1.04, 1.08]	<0.001
VT	1.26 [1.22, 1.29]	<0.001
Dyslipidaemia	0.93 [0.91, 0.95]	<0.001
Smoking	0.98 [0.97, 1.00]	<0.001
AF	1.42 [1.40, 1.44]	<0.001
History of ischemic heart disease	1.31 [1.28, 1.34]	<0.001
Previous percutaneous coronary intervention	1.04 [1.02, 1.07]	<0.001
Acquired immune deficiency syndrome	1.63 [1.26, 2.11]	<0.001
Deficiency anaemia	1.17 [1.15, 1.20]	<0.001
Chronic blood loss anaemia	1.01 [0.97, 1.06]	0.587
Rheumatoid arthritis/collagen vascular diseases	0.95 [0.86, 1.04]	0.244
Heart failure	0.96 [0.94, 1.00]	0.360
Chronic pulmonary disease	1.25 [1.23, 1.28]	<0.001
Coagulopathy	1.18 [1.12, 1.25]	<0.001
Depression	1.03 [1.00, 1.06]	0.080
Diabetes, uncomplicated	1.07 [1.05, 1.09]	0.000
Diabetes with chronic complications	1.09 [1.05, 1.12]	0.000
Hypertension	0.99 [0.97, 1.01]	0.136
Hypothyroidism	1.01 [0.99, 1.04]	0.223
Liver disease	1.05 [0.99, 1.12]	0.088
Lymphoma	1.30 [1.20, 1.41]	<0.001
Fluid and electrolyte disorders	1.20 [1.18, 1.23]	<0.001
Other neurological disorders	0.92 [0.89, 0.96]	<0.001
Obesity	1.02 [0.99, 1.04]	0.15
Peripheral vascular disorders	1.07 [1.04, 1.09]	<0.001
Psychoses	1.02 [0.97, 1.07]	0.457
Pulmonary circulation disorders	1.02 [0.95, 1.10]	0.607
Chronic renal failure	1.39 [1.36, 1.42]	<0.001
Solid tumour without metastasis	1.00 [0.93, 1.07]	0.922

Peptic ulcer disease excluding bleeding	1.00 [0.62, 1.59]	0.984
Valvular disease	0.95 [0.90, 1.01]	0.072

*All predictors are derived from index admission records.

5. Discussion

My study is the first to systematically examine the rates, causes and predictors of cardiac readmission after de novo CIED implantation across all types of cardiac devices with a comparison between sexes in a national procedural cohort from the US. My findings show a decline in all-cause and 30-day readmissions over a six-year period, a finding that was observed in both females and males. I also find that, throughout the study period, females were more likely than males to be readmitted within 30 days for cardiac, non-cardiac as well as and device-related causes. I also highlight differences in the cause of admission between CIED types and identify important patient and device-related factors in the index hospitalisation that are predictive of 30-day readmission.

Hospital readmissions have significant implications to patients and healthcare institutions and, therefore, as are viewed as a surrogate of the care provided for patients. [174, 175] Some previous studies have looked at the rates and causes of 30-day readmissions after CIED implantation, however, these were limited by several factors such as the focus on overall readmissions without the analysis of specific cardiac causes, especially in their analysis of predictors, and the lack of stratification by type of CIED. [84-88] The focus on cardiac causes of readmission and their predictors is of vast importance as these could be potentially avoidable in this population, unlike non-cardiac causes. Moreover, no study has examined de novo procedures exclusively, which carry a different risk of complications compared with upgrade/replacement procedures. It is also unclear whether sex differences exist in the rates and causes of 30-day cardiac readmission after CIED implantation. Furthermore, there have been significant limitations in the analytical approach of the

studies that have examined all-cause 30-day readmissions from the NRD database, which are likely due to the means they have coded and identified readmissions. For example, a study Ahmad et al. from the NRD database looking at 30-day readmissions after CIED implantation in 2013 identified 290,420 index procedures at a national level. [84] However, another study by Patel et al. for the year 2014 from the same database only identified 70,223 index procedures in the US, which is significantly lower and almost definitely explained by an issue with their analysis.[87]

My analysis shows that 14% of all patients undergoing de novo CIED implantation are readmitted within 30 days for any cause, but this has declined over the study period. This is in keeping with findings from previous reports. [84-88] While 30-day readmissions were mainly due to non-cardiac causes, which represented 60% of all readmissions, the rate of cardiac readmissions was significant and ranged between 35-49% depending on the type of CIED, the highest being in the CRT-D and ICD groups. Heart failure was the most common cause of cardiac readmission across all device groups, albeit more common in the CRT and ICD groups as expected, followed by arrhythmias and device-related complications, which were higher in the ICD and CRT-D groups. However, these differences are likely related to the complexity of these devices, which are more likely to result in complications, as well as patients' underlying conditions for which they received these devices in the first place. For example, patients with severe left ventricular dysfunction as those who qualify for CRT and ICD devices and, therefore, are the ones more likely to readmitted with heart failure exacerbation.

A positive finding in my study is the decline in 30-day readmissions for cardiac and device-related complications over the study period, which was observed in both females and males. This is likely due to advances in implantation techniques, the overall quality of care provided for patients, the awareness of risk factors for complications and better follow-

up on discharge. [42, 53, 81, 118, 119, 176] However, a finding of concern was the persistently higher cardiac readmission rates of females throughout the study period, including for device-related complications. While the rates of readmission for heart failure, the most common cardiac cause, were similar between sexes, other common cardiac causes such as arrhythmias and device-related complications were more common in females. Despite adjustment for baseline differences in patient characteristics and type of device received between sexes, females were 22% more likely to be readmitted for cardiac causes and 26% more likely to be readmitted for device-related complications compared with males. This is likely due to the higher rate of complications in females during the index admission as demonstrated in my previous work as well as other studies. [91, 112] While some previous studies have shown that females are more likely to be readmitted within 30 days after implantation, they only looked at all all-cause readmission. For example, Patel et al. showed a 9% increase in odds of 30-day readmission in females (OR 1.09 95% CI 1.04, 1.14, p=0.001) in their analysis of 70,223 CIED procedures in the US. [87] However, these findings do not provide insight with regards to cardiac-specific readmissions that may be more avoidable in those undergoing CIED.

My findings regarding the higher rate of readmissions for device-related complications in females differ from those in a study by Moore et al., which analysed ~80,000 CIED implantations in Australia and New Zealand and reported no difference between sexes in hospitalizations for device-related complications as part of their secondary outcomes (women: 3.4% vs. men: 3.5%, OR 1.05 [0.97, 1.13]).[91] However, their cohort was much smaller and included a lower proportion of women (37.9% vs. 43.1%) and those undergoing complex device implantation (CRT and ICD: 24.2% vs. 36.6%). Therefore, their study may have been underpowered to detect differences between sexes. Several factors place females at a higher risk of procedure-related complications after CIED

implantation including their smaller thoracic cavity and smaller vessel diameters, making them more likely to experience thoracic and vascular complications during implantation, as well as their thinner right ventricular walls that may be more prone perforation.[53, 118-120]

I identify several important predictors of 30-day cardiac readmission from the index admission in my analysis, including certain patient and admission-related variables other than sex. Device complexity was an important predictor of cardiac readmission, with the odds increasing as high as 46% with CRT-D and ICD devices, compared with PPM. Similarly, complications experienced during the index admission (e.g., cardiac and thoracic, as well as AKI) were associated with increased odds of 30-day cardiac readmission. Certain strategies could be employed to minimise the risk of complications in those undergoing CIED implantation and, in turn, reduce their rates of readmission for device-related complications. The use of ultrasound guidance for vascular access, routine cephalic vein cut down, as well as true septal (vs. apical) implantation of RV leads could all minimise procedure-related complications, especially in females. Other comorbidities such as heart failure, arrhythmias (VT and AF), and chronic pulmonary disease were also associated with increased likelihood of cardiac readmission. Knowledge on the role of these patient-related predictors as important predictors of cardiac readmission could help physicians identify high-risk groups who may benefit from further optimisation during their index admission as well as closer follow-up after discharge, which may have an impact on their readmission rates.

Limitations

Several limitations of my study related to the nature of the dataset from which it was conducted. Diagnoses and procedures in the NRD are coded according to the ICD-9 coding system by administrators and healthcare professionals. Therefore, coding inaccuracies are possible. However, the use of ICD codes has been previously shown to

reliably capture complications in CIED studies upon comparison with patients' chart and medical notes. [110] Furthermore, information on the indication for CIED, operator experience, as well as pharmacological information (e.g., heart failure secondary preventative therapy) is not captured in NRD and so these variables were not adjusted for between the study groups. However, the implantation of complex devices such as CRT, which was the group with the highest rate of heart failure readmissions in my analysis, is usually contingent on the trial of optimal pharmacological therapy first for at least 3 months. [8] Therefore, it is unlikely that significant differences were observed between patients who received these devices. Finally, my dataset did not include post-discharge mortality which is a competing risk for readmission.

6. Summary

My study of a national cohort of CIED implantations over a six-year period shows that 30-day readmissions are common, with a significant proportion being for cardiac causes, including device-related complications, in both sexes. While the rate of readmissions has declined over the study period, there is potential for further work to reduce the rate of cardiac readmissions especially in females are at a higher risk of readmission due to cardiac and device-related causes compared with males. My analysis identifies important patient and procedure-related predictors of cardiac readmission that should be considered in the risk-assessment of patients prior to discharge and when planning follow-up to improve readmission rates. Furthermore, my work emphasises the need for further strategies to minimise complications during the index admission given their correlation with higher rates of 30-day cardiac readmission.

Chapter 10. Discussion

While there is ample evidence on the impact of several patient-related factors on procedural outcomes of CIED implantation, this is often based on findings from randomised controlled trials (RCT's) that recruit highly selected and often healthier patient groups. [34-37] As such, there is limited data on procedural outcomes of high-risk patients who are often under-represented or excluded from clinical trials such as females, patients with significant comorbidities, frailty or limited life expectancy, as well as those with cancers. Furthermore, patients enrolled into trials often receive more optimised management which is frequently associated with better outcomes.

This drives the need for 'real-world' studies that would focus on patients who are less likely to be represented in RCT's, particularly from large national datasets that are representative of the wider target population as opposed to single-centre studies or individual registries from large tertiary centres where there are more experienced operators with higher procedural volumes.

The present thesis utilised two large datasets from the United States to study the association between patient-related characteristics and the management as well as outcomes of patients undergoing de novo CIED implantation, including hospital readmissions that are classed as a measure of the quality of care provided to patients undergoing CIED implantation.

1. Key Messages

Several key messages can be concluded from my thesis regarding its three main objectives. First, patient factors such as age, sex and history of ischaemic heart disease influence the choice of cardiac resynchronisation therapy (CRT) type offered to patients who are eligible for this intervention.

Second, I demonstrate the impact of several patient-related factors on in-hospital procedure-related outcomes after *de novo* CIED implantation: **i)** in my study on sex differences in procedural outcomes, I showed that female sex was an independent predictor of mortality and procedure-related complications and that this higher risk in females persisted for more than a decade of procedures; **ii)** my study on frailty and CIED procedural outcomes showed an incremental rise in the risk of in-hospital adverse outcomes including mortality and procedure-related complications with increasing frailty risk, a finding that was consistent across all CIED types; **iii)** in my study of cancer patients undergoing CIED implantation I reported no increased risk of post-procedure adverse outcomes in those with previous cancer while patients with active cancer were associated with significantly higher rates of mortality and adverse outcomes after CIED implantation. My work has also shown that the risk of adverse outcomes differed according to the type of cancer and highlighted further differences according to the type of CIED implanted; **iv)** my study focusing on the influence of comorbidity burden on procedural outcomes showed that severe comorbidity burden was associated with increased likelihood of in-hospital mortality and stroke, irrespective of the type of comorbidity. However, I found that comorbidity burden was not associated with an increased risk of procedure-related complications (thoracic, cardiac and bleeding).

Finally, my work demonstrates that hospital readmissions with 30 days after CIED implantation are common, with up to 1 in 7 patients readmitted for any cause. While the majority of 30-day readmissions were due to non-cardiac causes, the rate of cardiac readmission was significant, including that for device-related complications. My study highlighted important differences in causes of readmissions between sexes and CIED types and identified important predictors of 30-day cardiac readmission.

2. Interpretation of findings and clinical implications

a) What patient-related factors influence the choice of CRT device?

In view of the limited recommendations on which patient groups should receive CRT with pacemaker (CRT-P) or CRT with defibrillator (CRT-D) devices in those eligible for this intervention, Chapter 4 of my thesis investigated patient-related factors favouring the receipt of CRT-P in a national procedural cohort in the United States (US). My study concluded that females, elderly patients (>60 years) and those with malignancies and chronic renal failure were more likely to receive CRT-P than CRT-D while males, previous ischaemic heart disease and a history of ventricular arrhythmias favoured the received of CRT-D. Sex, in particular, was a strong predictor of CRT type, with female patients much less likely to receive CRT-D than over CRT-P an 11-year period. This disparity between sexes could be explained by several factors as discussed in the relevant chapter. However, it is unclear whether this has an impact on the long-term outcomes of females. Another important factor favouring CRT-P is age, which is often synonymous with patients' overall health condition and the burden of their comorbidities, and this could explain the reluctance of some cardiologists to implant CRT-D devices in elderly individuals given their higher cost and also the requirement of their deactivation towards the end of life. Perversely, the risk of fatal arrhythmias also increases in with age, increasing the need for defibrillator use in these patients. These findings warrant an individualised assessment of the benefits and risks of each type of device when counselling patients prior to device implantation.

b) Identifying patient groups at risk of adverse outcomes after CIED implantation

In Chapters 5 to 8 of my thesis I studied the association between several patient characteristics and in-hospital outcomes of *de novo* CIED implantation, with comparisons between different CIED types. In Chapter 5 I reported an increased risk of in-hospital procedure-related complications (thoracic, cardiac and cardiac) but not mortality in females

irrespective of the type of CIED implanted. Furthermore, this risk persisted over the whole 11-year study period.

Similarly, my study on CIED outcomes in cancer patients (Chapter 6) showed that patients with an active (current) cancer malignancy were at an increased risk of in-hospital mortality and procedure-related complications, whose prevalence increased amongst all CIED implantations over 11 years, while those with a history of cancer were not associated with an increased risk of either event. Further differences were observed when I stratified my analysis by cancer type with lung malignancies being associated with the highest risk of mortality and thoracic complications, and prostate and colon cancers with the highest odds of procedure-related bleeding.

In Chapter 7, I objectively measured frailty-risk amongst those undergoing *de novo* CIED implantation using a validated score (the Hospital Frailty Risk Score) and found the prevalence of CIED procedures performed on frail individuals has significantly risen over a decade with up to one in three patients classed as intermediate or high-risk frail in 2015. My work demonstrates a correlation between frailty risk and procedure-related outcomes as well as mortality. Specifically, high-risk frailty was associated with almost a two-fold increase in procedure-related complications and as high as 9-fold increase in mortality compared with low-risk frailty.

Chapter 8 of my thesis focused on the impact of comorbidity burden, as measured by the CCI score, on procedural outcomes after *de novo* CIED implantation. Patients classed as having severe comorbidity burden represented at least 40% of those undergoing CIED implantation. While comorbidity burden was shown to correlate with in-hospital mortality and the risk of post-procedural stroke, it was not associated with a higher risk of procedure-related complications.

Together, these findings provide cardiologists with insights about important patient-related factors that require assessment prior to CIED implantation to identify high-risk patients who may benefit from certain strategies to reduce their risk of procedure-related complications or even a different type of CIED. For example, patients found to be at high risk of frailty could be offered a simple PPM or subcutaneous ICD in order to reduce their risk of thoracic complications. Similarly, routine use of ultrasound-guided venous access in females could lead to lower rates of thoracic complications and vascular injury.

c) Hospital readmissions after CIED implantation

My work in Chapter 9 shows that 30-day readmissions after CIED implantation are common, with a significant proportion being for cardiac causes (up to 40%) including device-related complications. Heart failure was the most common cause of cardiac readmission irrespective of patient sex and the type of device implanted. Over a period of six years females were more likely to be readmitted for cardiac and device-related causes than males, but cardiac readmissions declined overall in both sexes over that time. Other than females, patients with a greater propensity for cardiac readmissions within 30 days were those with HF, VT, AF, anaemia, chronic pulmonary disease, coagulopathies and lymphoma. Information on the rates of 30-day cardiac readmission from a national perspective provides a benchmark for individual hospitals to compare with their local practice and identify room for improvement. Furthermore, an insight into the common causes as well as predictors of cardiac readmission after CIED implantation could help cardiologists and other stakeholders identify patients with a high likelihood for readmission for whom interventions could be devised to reduce their rates of readmission. These could include a more rigorous assessment prior to discharge, more intensified education on warning signs and symptoms that should prompt them to seek medical attention and closer follow-up on discharge (e.g., earlier outpatient appointments, telephone consultations).

3. Limitations

a) Quality of data

The two datasets used in my thesis, the National Inpatient Sample (NIS) and Nationwide Readmissions Database (NRD), are administrative datasets coded using the International Classification of Diseases (ICD) manual. These are based on discharge summaries from the hospitalisation episodes prepared by clinicians and may have not undergone a full review by clinical coders. Furthermore, many discharge summaries are completed by junior clinicians who may have not had sufficient contact with the patient, if at all, and are tasked with their completion under time pressures, making the omission of certain comorbidities a possibility. While major conditions and procedures are likely to have been coded appropriately, it is possible that less important conditions or procedures were not included if they did not have a major role in the financial claims process through insurance companies.

b) Variables studied

All acute diagnoses and procedures as well as patient comorbidities in the NIS and NRD datasets are coded according to the ICD system. While ICD-9 and ICD-10 coding systems have been previously validated in multiple cardiovascular cohorts in studies comparing ICD codes with patients' medical records and inpatient charts, coding inaccuracies are possible due to human error. Furthermore, many variables identified through the ICD coding system do not reflect severity of a patients' given condition. For example, heart failure is a spectrum that ranges from mild to severe, each of these stages conferring different prognoses. The severity of certain conditions such as anaemia or thrombocytopaenia is measured based on laboratory values, which were not captured in my datasets. Similarly, pharmacological information including anti-arrhythmic and anti-

thrombotic medications are not captured in both NIS and NRD and, therefore, were not adjusted for in my analyses. Although these are unlikely to have significantly influenced in-hospital outcomes of CIED implantation, differences in the use of anti-thrombotic medications may have explained the higher bleeding rates in certain groups.

c) Indication for CIED implantation

One of the limitations in my studies is the lack of capture of indication for CIED implantation. While the indications for CRT therapy are clear due to the presence of well-recognised eligibility criteria, there are many indications for PPM and ICD devices. Knowledge of the indication for implantation is of particular importance in patients offered ICD devices, who may be receiving this device to prevent fatal arrhythmias from happening from for the first time (primary prevention) or after a cardiac arrest (secondary prevention), with the latter conferring a higher overall patient risk profile and, in turn, worse in-hospital mortality and adverse outcomes.

4. Future Work

a) Sex disparities in the choice of CRT device

My study on the choice of CRT device, as well as previous studies, showed lower utilisation of CRT-D (vs. CRT-P) in females, elderly patients, and those with malignancies. However, further prospective work is warranted to study factors that contribute to such decisions by clinicians. It is possible that physician behaviour is influenced by confounders that were not captured in my study such as patient comorbidities affecting their survival as well as patients' own wishes or their body habitus, and thereby favouring CRT-P. Furthermore, there may be other clinical criteria that led physicians to believe that females will be more superior responders to CRT therapy in terms of improvement of their left ventricular function and, therefore, less likely to experience ventricular arrhythmias that

will require defibrillation. Another important area of future work is the long-term follow up of patients in receipt of either device type to assess the appropriateness of therapy. For example, if females are less likely to receive CRT-D than males but have a similar survival at one or three years this would demonstrate that an appropriate choice of device was used at the time of implantation.

b) Risk scores

While there are established risk scoring systems for adverse outcomes and readmissions for cardiovascular procedures such as percutaneous coronary intervention and coronary artery bypass grafting, there are limited risk stratification tools for patients undergoing CIED implantation. [66-70] For example, the PADIT risk score has been recently described for the prediction of device-related infection after CIED implantation and was further validated in a US insurance claims database. [177, 178] While my thesis has described several patient-related factors that are associated with higher risk of procedure-related complications and hospital readmissions due to cardiac causes, further work is required from dedicated cardiac device registries that contain more granular procedural information (e.g. site of lead placement, procedure time, use of ultrasound guidance, etc) to establish and validate a scoring system that predicts these events, which have been shown to be quite common in my studies. A scoring system would help clinicians risk stratify patients at risk of adverse outcomes that are amenable to interventions to further reduce the incidence of such events. Furthermore, risk scoring systems help predict procedure risk and, in turn, procedural outcomes which are considered performance indicators for operators, institutions and the wider healthcare system. This is particularly relevant in the current era where there is a trend towards national reporting of outcomes, and such outcomes need to be weighed according to the individual procedural risk. For example, higher volume centres are more likely to perform more complex cases for higher-risk patients and without

objective measurement of the procedural risk they will appear to have worse overall outcomes compared with smaller centres.

c) Alternative devices for high-risk patients

The role of newer CIED technologies such as intracardiac (leadless) pacemakers and subcutaneous ICD devices should be prospectively studies in patient groups identified as high-risk for procedure-related complications of traditional (transvenous) CIED implantation. While these devices have gained popularity in recent years, they are more expensive and are not routinely offered in all cardiac centres. Furthermore, there have been limited studies comparing their long-term outcomes to traditional PPM and ICD devices in high-risk patient groups. [179-183] Exploring real-world outcomes of these devices in high-risk patients such as those with significant frailty or active malignancy would provide CIED implanters with important insights about their utility as reliable alternatives to those at high-risk of procedure-related complications after traditional CIED implantation.

5. Conclusions

In conclusion, my thesis investigated the role of several patient-related characteristics in the management and in-hospital outcomes of de novo CIED implantation. Differences in the choice of CRT device type were observed in females, elderly patients, and those with certain comorbidities. Several patient-related factors conferred worse procedural outcomes after CIED implantation, including mortality, in-hospital procedure-related complications and post-discharge cardiac readmissions (including for device-related complications). Factors such as sex, active malignancy, high-frailty risk, severe overall comorbidity burden are all predictors of these adverse outcomes. These findings emphasise the need for an individualised approach to the risk stratification of patients taking these factors in to consideration in order to identify patients who require further

optimisation prior to their procedure and post-procedure and those who would benefit from technical strategies to reduce their procedure-related complications.

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Appendix: Thesis related publications

Appendix 1

ELSEVIER

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Clinical Research

Sex Disparities in the Choice of Cardiac Resynchronization Therapy Device: An Analysis of Trends, Predictors, and Outcomes

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ABSTRACT

Background: There is limited evidence on the influence of sex on the decision to implant a cardiac resynchronization therapy device with pacemaker (CRT-P) or defibrillator (CRT-D) and the existence of sex-dependent differences in complications that may affect this decision.
Methods: All patients undergoing *de novo* CRT implantation (2004-2014) in the United States National Inpatient Sample were included and stratified by device type (CRT-P and CRT-D). Multivariable logistic regression models were conducted to assess the association of female sex with receipt of CRT-D and periprocedural complications.

RÉSUMÉ

Contexte : On dispose de peu de données sur l'influence du sexe du patient dans la décision d'implanter ou non un dispositif de thérapie de resynchronisation cardiaque (TRC) avec stimulateur cardiaque (TRC-P) ou avec défibrillateur (TRC-D) et sur l'existence de différences entre les sexes sur le plan des complications susceptibles d'influer sur cette décision.
Méthodologie : Tous les patients de l'échantillon national des patients hospitalisés (NIS, *National Inpatient Sample*) des États-Unis ayant reçu pour la première fois un dispositif de TRC entre 2004 et 2014 ont été

Cardiac resynchronization therapy (CRT) is a class 1 recommendation for the management of patients with symptomatic heart failure with reduced ejection fraction on guideline directed medical therapy and left bundle branch block (with a QRS duration > 150 ms).[1-5] Decision making can be difficult in patients with class 2a and 2b recommendations, such as those with atrial fibrillation, right bundle branch block, or QRS duration < 150 ms. In these situations, device type is often based on the implanter's choice.[6]

There are limited data on differences in the rate of utilisation of both CRT device types between sexes, and whether sex is independently associated with the choice of device therapy. Findings from the recently published European Society of Cardiology (ESC) CRT Survey II concluded that women are more likely to receive a CRT device with a pacemaker (CRT-P) than with a defibrillator (CRT-D).[7] In the absence of any randomized control trials, that survey was the first to examine predictors of receipt of CRT-P in a European cohort of more than 10,000 patients undergoing CRT implantation from October 2015 to January 2017. However, only an estimated 11% of patients undergoing CRT were thought to have been enrolled in the survey, making the findings less generalizable to the wider European population and other health care systems. Furthermore, it is unclear whether sex disparities in choice of CRT device type have changed from a national perspective over the years. The

Received for publication October 18, 2019. Accepted February 9, 2020.

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See page 7 for disclosure information.

https://doi.org/10.1016/j.cjca.2020.02.073

Appendix 2

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Clinical Research

Trends of Sex Differences in Outcomes of Cardiac Electronic Device Implantations in the United States

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See editorial by Humphries and Hawkins, pages 16–18 of this issue.

ABSTRACT

Background: The disparity in outcomes of cardiac electronic device implantations between sexes has been previously demonstrated in device-specific cohorts (eg, implantable cardioverter-defibrillators [ICDs]). However, it is unclear whether sex differences are present with all types of cardiac implantable electronic devices (CIEDs) and, if so, what the trends of such differences have been in recent years.

Methods: With the use of the National Inpatient Sample, all hospitalizations from 2004 to 2014 for *de novo* implantation of permanent pacemakers, cardiac resynchronization therapy with or without a defibrillator, and ICDs were analyzed to examine the association between sex and in-hospital acute complications of CIED implantation.

Results: Out of 2,815,613 hospitalizations for *de novo* CIED implantation, 41.9% were performed on women. Women were associated with increased adjusted odds (95% confidence interval) of adverse

RÉSUMÉ

Contexte : La disparité des résultats de l'implantation d'un dispositif cardiaque électronique chez les hommes et chez les femmes a déjà été démontrée dans des cohortes de sujets ayant reçu un dispositif particulier (p. ex. un défibrillateur cardioverteur implantable [DCI]). On ne sait toutefois pas s'il existe une telle différence entre les hommes et les femmes pour tous les types de dispositifs cardiaques électroniques implantables (DCEI) et, s'il y en a une, quelles ont été les tendances à cet égard au cours des dernières années.

Méthodologie : À l'aide de la base de données NIS (*National Inpatient Sample*) des États-Unis, nous avons analysé toutes les hospitalisations qui ont eu lieu de 2004 à 2014 pour l'implantation *de novo* d'un stimulateur cardiaque permanent, un traitement de resynchronisation cardiaque avec ou sans défibrillateur ou la pose d'un DCI afin de déterminer s'il existe une association entre le sexe du patient et les

The rates of utilization of cardiac implantable electronic devices (CIEDs), including permanent pacemakers (PPMs), cardiac resynchronization therapy with pacemakers (CRT-P) or defibrillators (CRT-D), and implantable cardioverter-defibrillators (ICDs) continue to grow.[1] Despite advances in implantation techniques, CIED systems (leads and devices), and proficiency of operators, the rate of major complications remains significant.[2,3]

Previous studies have examined either the overall trends of CIED implant-related complications without differentiation between sexes, or the overall effect of sex on outcomes without analysis of historical trends.[2,4-7] To the best of our knowledge, no study has compared the trends in outcomes of CIEDs between sexes. Women are more prone to major complications after CIED implantation owing to anatomic differences such as smaller and thinner vessels, smaller chest cavities, and lower body weight.[8,9] Although these factors are less likely to change over the years, increasing awareness of complications risk and advancements in procedural techniques and skills to

Received for publication May 21, 2019. Accepted August 5, 2019.

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See page 77 for disclosure information.

https://doi.org/10.1016/j.cjca.2019.08.012

Appendix 3

ESC European Society of Cardiology

Europace (2020) **0**, 1–14
doi:10.1093/europace/euaa087

CLINICAL RESEARCH

Prevalence and in-hospital outcomes of patients with malignancies undergoing *de novo* cardiac electronic device implantation in the USA

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Received 14 February 2020; editorial decision 26 March 2020; accepted after revision 27 March 2020

Aims To study the outcomes of cancer patients undergoing cardiac implantable electronic device (CIED) implantation.

Methods *De novo* CIED implantations (2004–15; $n = 2\,670\,590$) from the National Inpatient Sample were analysed for characteristics and in-hospital outcomes, stratified by presence of cancer (no cancer, historical and current cancers) and further by current cancer type (haematological, lung, breast, colon, and prostate).

Results Current and historical cancer prevalence has increased from 3.3% to 7.8%, and 5.8% to 7.8%, respectively, between 2004 and 2015. Current cancer was associated with increased adjusted odds ratio (OR) of major adverse cardiovascular events (MACE) [composite of all-cause mortality, thoracic and cardiac complications, and device-related infection; OR 1.26, 95% confidence interval (CI) 1.23–1.30], all-cause mortality (OR 1.43, 95% CI 1.35–1.50), major bleeding (OR 1.38, 95% CI 1.32–1.44), and thoracic complications (OR 1.39, 95% CI 1.35–1.43). Differences in outcomes were observed according to cancer type, with significantly worse MACE, mortality and thoracic complications with lung and haematological malignancies, and increased major bleeding in colon and prostate malignancies. The risk of complications was also different according to CIED subtype.

Conclusion The prevalence of cancer patients amongst those undergoing CIED implantation has significantly increased over 12 years. Overall, current cancers are associated with increased mortality and worse outcomes, especially in patients with lung, haematological, and colon malignancies whereas there was no evidence that historical cancer had a negative impact on outcomes.

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Appendix 4

Canadian Journal of Cardiology 35 (2019) 1465–1474

Clinical Research

Prevalence, Outcomes, and Costs According to Patient Frailty Status for 2.9 Million Cardiac Electronic Device Implantations in the United States

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ABSTRACT

Background: Little is known about the impact of frailty on length of stay (LOS), cost, and in-hospital procedural outcomes of cardiac implantable electronic device (CIED) implantation procedures.

Methods: All *de novo* CIED implantations recorded in the United States (2004-2014) from a national database were stratified according to the Hospital Frailty Risk Score into low-risk (LRF; <5), intermediate-risk (IRF; 5-15), and high-risk (HRF; > 15) frailty groups. Regression analyses were performed to assess the association between frailty and procedural outcomes.

Results: Of 2,902,721 implantations, LRF, IRF, and HRF were 77.6%, 21.2%, and 1.2%, respectively. Frailty increased from 2004 to 2014 (IRF: 14.3% to 32.5%, HRF: 0.2% to 3.3%). Complications were 2- to 3-fold higher in the IRF and HRF groups, whereas all-cause mortality was 4- to 9-fold higher in the IRF (2.9%) and HRF (5.3%) groups, depending on the type of CIED ($P < 0.001$ for all). Rates of complications

RÉSUMÉ

Contexte : On en sait très peu au sujet de l'incidence de la fragilité du patient sur la durée de l'hospitalisation, le coût et les résultats de l'intervention en milieu hospitalier associés à la pose d'un dispositif cardiaque électronique implantable (DCEI).

Méthodologie : Toutes les implantations *de novo* d'un DCEI consignées entre 2004 et 2014 dans une base de données nationale aux États-Unis ont été stratifiées en trois groupes en fonction du score HFRS (*Hospital Frailty Risk Score*, score du risque de fragilité associé à l'hospitalisation) comme suit : risque de fragilité faible (RFF; < 5), intermédiaire (RFI; 5-15) ou élevé (RFE; < 15). L'association entre la fragilité et les résultats des interventions a été évaluée au moyen d'analyses de régression.

Résultats : Pour l'ensemble des 2 902 721 implantations réalisées, le RFF, le RFI et le RFE s'établissaient respectivement à 77,6 %, 21,2 % et 1,2 %. La fragilité des patients a augmenté entre 2004 et 2014; le

The association between frailty and cardiovascular outcomes has become increasingly recognized in recent years.[1-3] Frailty is defined as "a clinically recognizable state of increased vulnerability resulting from aging-associated decline in reserve and function across multiple physiologic systems such that the ability to cope with everyday or acute stressors is compromised."[4] Although frailty is synonymously used with ageing and multimorbidity in clinical practice, not all frail individuals suffer from chronic conditions or advanced age.[5,6] Several studies have demonstrated that young patients with chronic illnesses and multimorbidity are also considered "biologically frail,"[7] and up to 7% of frail individuals have no common chronic conditions, whereas 25% of frail individuals have only 1 chronic condition.[5]

Cardiac implantable electronic devices (CIEDs), including permanent pacemakers (PPM) and implantable cardioverter-

Received for publication June 6, 2019. Accepted July 30, 2019.

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See page 1474 for disclosure information.

https://doi.org/10.1016/j.cjca.2019.07.632

Appendix 5

International Journal of Cardiology xxx (xxxx) xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Sex differences in rates and causes of 30-day readmissions after cardiac electronic device implantations: insights from the Nationwide Readmissions Database

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ARTICLE INFO

Article history:
Received 31 October 2019
Received in revised form 29 November 2019
Accepted 9 December 2019
Available online xxxx

Keywords:
Cardiac devices
CIED
Pacemakers
Defibrillators
Cardiac resynchronization
Sex
Readmissions
Outcomes

ABSTRACT

Background: Women undergoing cardiac implantable electronic device (CIED) implantation are at a higher risk of procedure-related complications. The present study examined sex differences in rates and causes of 30-day readmissions following CIED implantation.
Methods: Using the United States Nationwide Readmissions Database (NRD), all adults who had undergone CIED implantation (cardiac resynchronization therapy (CRT), permanent pacemakers (PPM) and implantable cardioverter defibrillators (ICD)) between January 2010 and September 2015 were included. We compared rates, trends and causes of 30-day readmissions between sexes, and examined associations between sex and outcomes (adjusted odds ratios (aOR) and 95% confidence intervals (CI)).
Results: Out of 1,155,992 index hospitalizations for CIED implantation, 43.1% of the patients were women. All-cause 30-day readmissions were persistently higher in women than men but declined in both sexes over the study period, more so in women (women vs. men; 2010: 15.0% vs. 14.1%; 2015: 13.7% vs.13.4%). Women were at higher odds of readmission due to cardiac (aOR 1.22, 95%CI 1.20–1.24) and device-related complications (aOR 1.18, 95%CI 1.15–1.20) compared to men, but no difference odds of all-cause readmission were found between sexes (women: aOR 0.998, 95%CI 0.997–1.008). The most common cardiac and non-cardiac causes of readmission were heart failure and infection, respectively, and these were similar in both sexes (men vs. women: 17.8% vs. 17.6% and 10.7% vs. 10.8%, respectively).
Conclusion: Women are persistently at higher risk of readmission due to cardiac causes and device-related complications compared to men over a six-year period, but no difference in all-cause readmissions was found between sexes.

1. Introduction

The rate of cardiac implantable electronic device (CIED) implantations, including permanent pacemakers (PPM), cardiac resynchronization therapy with pacemakers (CRT-P) or defibrillators (CRT-D) and implantable cardioverter defibrillators (ICD), has grown considerably over the past decade, as has the rate of complications resulting from these procedures. [1–4]

Unplanned hospital readmissions may occur as a consequence of such complications following CIED implantation, or may result in the sub-optimal provision of care during the index hospitalization [5,6]. Hospital readmissions represent a significant burden for patients and healthcare systems, which may incur financial penalties as a result of high readmission rates, as they are frequently perceived as a measure of efficiency and quality of healthcare delivery [7]. Women have been shown to carry a higher risk of procedure-related complications following CIED implantation, partly due to their older age at the time of

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https://doi.org/10.1016/j.ijcard.2019.12.012
0167-5273/