Device Therapy In Heart Failure Population In New Zealand

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ABSTRACT

Heart failure (HF) is a major burden in developed and developing countries. It is known that HF patients are at risk of sudden cardiac death (SCD). The research presented within this thesis aims to add to the current knowledge in understanding the use of implantable cardioverter-defibrillators (ICDs) and cardiac resynchronisation therapy (CRT) in HF patients in New Zealand and to improve the awareness of these evidence-based device-therapy in the contemporary management of HF patients.

Chapter 1 comprises a literature overview on providing background on SCD in HF patients and the role of ICDs in preventing SCD in HF management.

Chapter 2 contains a literature review on CRT use in the management of selected HF patients.

Chapter 3 describes a study that examines the use of cardiac resynchronisation therapy-pacemaker (CRT-P) versus cardiac resynchronisation therapy-defibrillator (CRT-D) in patients with impaired left ventricular ejection fraction (LVEF).

Chapter 4 describes a study that evaluates the role of a simple risk score to identify HF patients who should have CRT-D versus those who should be treated with a CRT-P even when fulfilling ICD implantation criteria.

Chapter 5 reports two observational studies describing the trends and utilisations as well as the outcomes of HF patients with ICD/CRT-D and CRT-P in the Northern Region of New Zealand. A third study reported the gender differences in the use of these devices in New Zealand.

An overview of quality of life (QoL) of HF patients has been presented in Chapter 6 followed by a study that describe the burden of hospitalisations, using the novel concept of "Days alive and out of hospital" (DAOH) in HF patients implanted with CRT devices in the Northern Region of New Zealand. The final study in Chapter 6 describes the outcomes of HF patients with primary prevention ICD/CRT-D who underwent unit generator replacement due to battery depletion.

Chapter 7 summarises the results of the studies and discusses the wider context and clinical relevance of the findings, as well as making some future research recommendations.

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LIST OF ABBREVIATIONS

AF	Atrial Fibrillation
AVN	Atrioventricular node
ATP	Anti-tachycardia pacing
CKD	Chronic kidney disease
CMR	Cardiac magnetic resonance
CRT	Cardiac resynchronisation therapy
CRT-D	Cardiac resynchronisation therapy with defibrillator
CRT-P	Cardiac resynchronisation therapy with pacemaker
HF	Heart failure
ICD	Implantable cardioverter-defibrillator
ICM	Ischaemic cardiomyopathy
IVCD	Intraventricular conduction delay
LBBB	Left bundle branch block
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
NICM	Non-ischaemic cardiomyopathy
NYHA	New York Heart Association
RBBB	Right bundle branch block
SCD	Sudden cardiac death
VF	Ventricular fibrillation
VT	Ventricular tachycardia

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1.1 INCIDENCE OF HEART FALURE

Heart failure (HF) is a complex clinical syndrome defined as an abnormality of the structure or function of the heart that leads to a failure of the heart to deliver sufficient oxygen to the metabolising tissues or when the heart can only do so with elevated diastolic filling pressures.[1] HF comprises a wide range of patients, from those with normal left ventricular ejection fraction (LVEF) [typically LVEF ⩾50%; so-called HF with preserved EF (HFpEF)] and those with reduced LVEF (typically LVEF <40). The LVEF measurement is usually obtained using echocardiography, a radionuclide technique or cardiac magnetic resonance (CMR). For those patients with an LVEF in the range of 40–49%, this represents the 'grey area', which is now define as HF with mid-range ejection fraction (HFmrEF).[1]

Differentiation of patients with HF based on LVEF is important due to different underlying aetiologies, demographics, co-morbidities and response to therapies. Most clinical trials published selected patients based on LVEF.[2] It is only in patients with reduced LVEF that therapies have been shown to reduce both morbidity and mortality.[2]

HF is common. It is estimated that about 26 million adults worldwide are living with HF currently.[3] In the United States, there were 5.8 million patients living with HF in 2012, and this is expected to rise to 8.5 million by 2030.[4] In developed countries, the prevalence of HF among adults is approximately 1–2% per years.[1]

HF becomes more common with increasing age. During the 30-years of follow-up in the Framingham study of 5209 patients, the incidence of HF doubled with each decade of age with a male predominance.[5] In North America and Europe, few patients with HF are 50 years of age or younger[6] and > 80% are ≥65 years of age.[3] The number of patients with HF is predicted to increase in countries with ageing populations.[7] In economically developing areas, such as Asia and Latin America, the numbers of patients with HF are also increasing.[8] This increase is due to the causes of mortality and morbidity having shifted from infectious diseases and/or

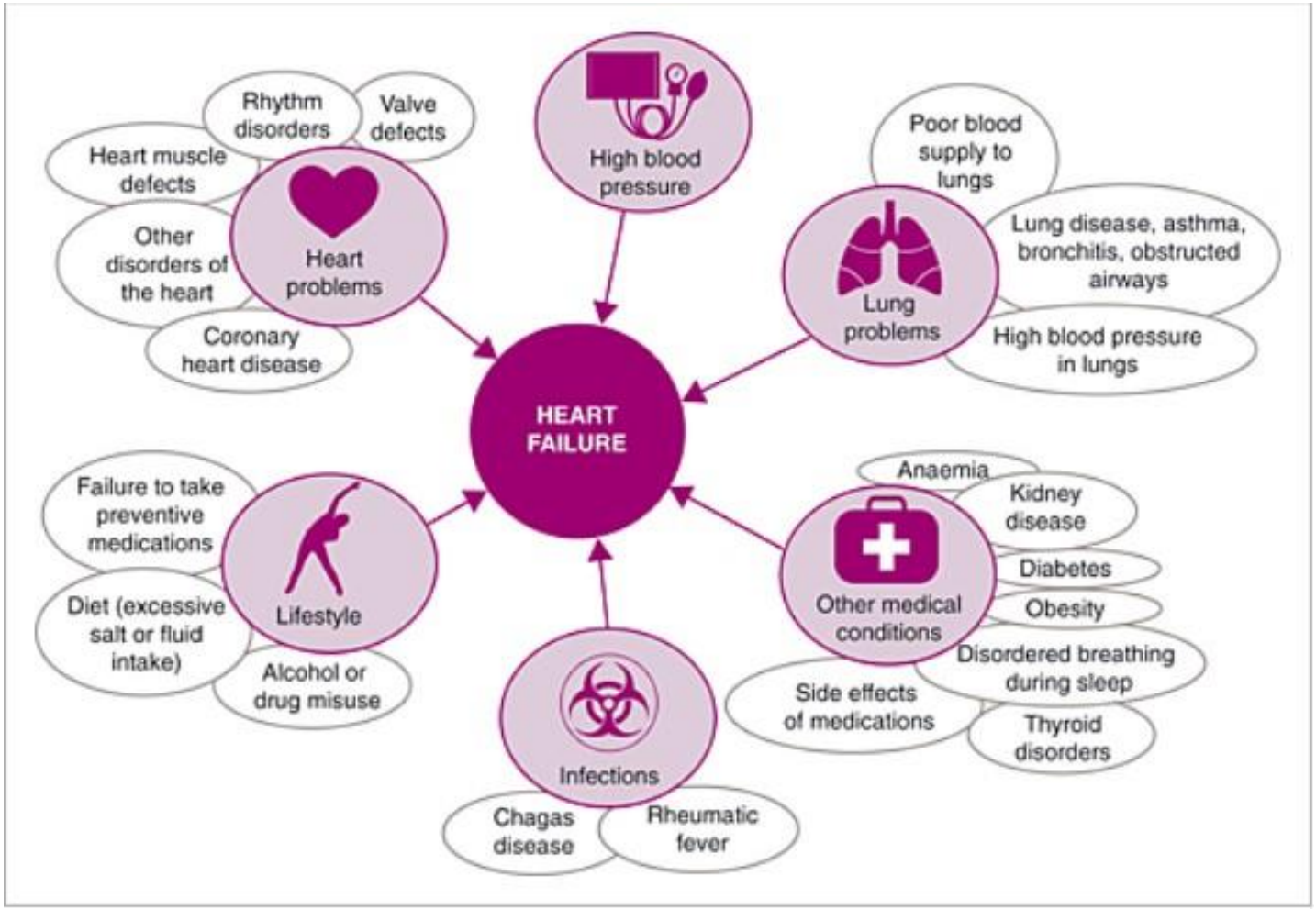
nutritional deficiencies to lifestyle-related diseases, such as cardiovascular disease and diabetes mellitus, together with the transition from developing to developed countries during the past decades, the so-called "the epidemiologic transition".[9] HF patients in the Asia Pacific region also tend to be younger than those in Western regions.[10]

The number of people with HF will inevitably increase in New Zealand in the future. This is attributed to people living longer, more effective treatments for coronary heart disease and a reduction in mortality from acute coronary events.[11,12] An increase in prevalence of cardiovascular risk factors such as diabetes and obesity in New Zealand is also contributing to the increasing prevalence of HF.[11] More patients with these conditions are surviving now than did in the past, and those who survive are at high risk of going on to develop HF.[13]

Reports from New Zealand, United States, Sweden, Scotland and the Netherlands documented the age-adjusted hospitalisation rates for HF increased considerably in the 1980s and early 1990s.[14] Recent data on temporal trends based on hospitalised patients suggested that the incidence of HF may be decreasing because of the improved diagnosis and advances in treatment. Data from Scotland (1986–2003) reported an initial rise and subsequent fall in the incidence of index HF hospitalisation and improvements in survival from 1986 to 2000, and data from Sweden (1987–2003) showed similar trends.[15-17] In Australia, progressive decreases in both the incidence of index HF hospitalisation (1989–2003) and in mortality (1980–2001) have been observed.[18] Similarly in New Zealand, there have been substantial changes in the epidemiology of HF. Wasywich et al. reported a rise and subsequent fall in the incidence of index hospitalisation for HF over a 20-year period and a progressive decline in mortality associated with HF from 1988 to 2000.[19]

The aetiology of HF is diverse (**Figure 1**). Whereas ischaemic cardiomyopathy (ICM) remains the most common aetiology, over one-third of HF patients have non-ischaemic cardiomyopathy (NICM).[20]

Figure 1: Common causes of heart failure



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1.2 INCIDENCE OF SUDDEN CARDIAC DEATH IN HEART FAILURE

Sudden cardiac death (SCD) is defined as a non-violent death due to cardiovascular causes in a patient with or without structural heart disease that cannot be explained; occurring in less than 24 hours from the onset of symptoms.[21] The incidence of SCD depends on the definition. Risk factors for SCD are multifactorial, and associated with a continuous risk function.[22]

SCD remains a major clinical and public health problem. The United States vital statistics mortality data reported 719456 cardiac deaths among adults aged ⩾35 years in 1998. Of these, 456076 (63%) were defined as SCD.[23] Among those aged 35 to 44 years, 74% of cardiac deaths were due to SCD. The death rates for SCD increased with age and were higher in men than women, although there was no difference at age ⩾85 years. From 1989 to 1998, the SCD rates increased 12.4% (56.3% to 63.9%).[23] During the same time, age-specific death rates for SCD increased 21% among women aged 35 to 44 years.[23]

Over the last 30 years, improvements in treatments have improved survival and reduced the hospitalisation rate in patients with HF. In the Framingham heart study, the 1- and 5-year mortality rates from HF in men have declined from 30% and 70% in the period 1950 to 1969 to 28% and 59% in the period 1990 to 1999.[24] In women, 1-year mortality rates decreased from 28% to 24% and the 5-year mortality rates decreased from 57% to 45% during the same period.[7,24]

The vast majority of HF patients die from cardiovascular causes. In the ATLAS (assessment of treatment with lisinopril and survival) trial, mode of death in 1381 NYHA functional class II–IV patients were as follows: 589 (43%) SCD, 443 (32%) progressive HF, and 349 (25%) due to other causes.[25] Despite improvements in medical treatment, symptomatic HF still confers a 20-25% risk of premature death in the first 2.5 years after diagnosis; and approximately 50% of these premature deaths are SCD.[26-29] In the Framingham study, the SCD

rate for patients with HF was 9x the general age-adjusted population rate.[30] The annual incidence of SCD is expected to increase coincident with the increasing incidence of HF.

The chronically failing heart is predisposed to ventricular arrhythmia. This is a result of a complex interplay between pathological substrate and a bewildering array of environmental triggers and facilitators evoked by left ventricular dysfunction and medical therapy.[31] For example, in patients with ischaemic heart disease these arrhythmias often have re-entrant mechanisms in scarred myocardial tissue. An episode of sustained ventricular tachycardia (VT) indicates a high risk for recurrent ventricular arrhythmias and SCD.[32] Electrolyte disturbances are common among patients with chronic HF and may be life-threatening. Patients with chronic HF are predisposed to hypokalaemia or hyperkalaemia caused by diuretic therapy, activation of the renin angiotensin-aldosterone system, and sympathetic activation as well as reduced renal clearance of potassium.[33,34] These electrolyte abnormalities predisposes to ventricular arrhythmia.

Some studies indicate that patients with relatively mild HF are more susceptible to arrhythmias and SCD, while patients with more advanced HF (NYHA class III and IV) often die from end stage ventricular pump failure.[7] Therefore SCD poses a major threats to HF patients. To date, there is no single clinical variable or diagnostic test that can accurately predict risk of SCD in patients with HF and reduced ventricular function. Buxton et al. studied 83 patients with documented episodes of non-sustained VT with electrophysiologic studies showed that a combination of inducible sustained VT and severe left ventricular dysfunction carries a high risk of SCD.[35] In the study, 36% of patients with these 2 factors had SCD. In the multivariate analysis, the most powerful predictor of risk for SCD is LVEF <40%.[35] Therefore, the severity of left ventricular dysfunction as reflected by the measurement of LVEF is the most potent predictor of mortality and SCD among patients with HF to-date.[28,36,37]

1.3 THE IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR (ICD) THERAPY

In view of the large proportion of HF patients suffering from major cardiac arrhythmias and SCD, a multifactorial approach to the prevention of SCD is clearly needed. These include modifying risk factors for coronary artery disease, identifying genetic predispositions to SCD, improving community-based cardiopulmonary resuscitation training, and using technological advances, such as the automatic external defibrillator.[38,39] Despite substantial efforts, the survival rates from cardiac arrest remain low.[21]

The inability to deal effectively with malignant ventricular arrhythmias outside the hospital setting has prompted the development of the automatic implantable cardioverter-defibrillator (ICD).[40] The main aim of ICD is to protect the patients who are at particularly high risk of SCD whenever and wherever they are stricken by these lethal ventricular arrhythmias. The ICD is programmed to monitor the cardiac rhythm continuously, to recognize ventricular fibrillation (VF) and VT, and to deliver corrective defibrillatory discharges when indicated.[40]

The first human ICD was implanted in 1980 via thoracotomy.[40] The early ICD system consists of a large pulse generator and patch electrodes for defibrillation placed directly on the heart or pericardium. Epicardial screw-in leads were also placed in the heart for rate-sensing. The implant procedure required general anaesthesia, and was associated with longer hospital stays, with perioperative mortality rate in the range of 4%.[41] The early ICD devices were limited by its size and few programming options.[42] It was also unable to discriminate rapid supraventricular arrhythmias from ventricular arrhythmias, leading to a high incidence of inappropriate shocks.[43,44]

With the advances in ICD lead systems and defibrillation waveforms, this has allowed for successful transvenous, pectoral ICD implantation in a manner similar to cardiac pacemakers without the need for general anaesthesia. Perioperative mortality is low < 1%.[45] Complications

such as infection, pneumothorax, pericardial tamponade, and pocket haematoma occur at similar rates to those seen with pacemaker implantation (< 3%).[46] The modern ICD can be programmed to detect several specified tachycardia zones, with antitachycardia pacing (ATP) therapy for slower, haemodynamically stable VT.[47] Furthermore, sophisticated algorithms now exist in modern ICDs to discern VT from rapid supraventricular arrhythmias. This has resulted in the decline of the inappropriate shock rate to < 5%.[48,49]

Two observational studies suggested that the ICD was effective in preventing recurrent cardiac arrest in survivors of sudden arrest.[50,51] Mirowski et al described that ICD substantially increases the prospects for survival of 52 consecutive patients who had had ICD implanted who have had ventricular tachyarrhythmias not responsive to treatment and had been resuscitated from at least 2 episodes of arrhythmic cardiac arrest not associated with acute myocardial infarction (MI).[50] In the hospital, the ICD treated 82 episodes of spontaneous and 81 of 99 episodes of induced malignant tachyarrhythmias. There were 62 automatic resuscitations from the ICD in 17 patients in the community. Twelve patients died; four of the deaths were not witnessed. The 1-year SCD mortality rate was 8.5%.[50] Winkle et al. subsequently reported the long-term outcome of 270 patients implanted with ICD because of life-threatening arrhythmias over a 7-year period.[51] The average LVEF was 34%, and 96% of these patients had had an average of 3.4 antiarrhythmic drug failures per patient before ICD implantation. ICD shocks were delivered to 58% of patients.[51] There were 7 SCD and 30 non-SCD, 18 of which were secondary to congestive HF.

In the late 1990s, 3 major randomised-controlled trials compared the best antiarrhythmic therapy with ICD therapy for the treatment of ventricular tachyarrhythmias in patients resuscitated from a cardiac arrest.[52-54] The Antiarrhythmics Versus Implantable Defibrillator (AVID) Trial demonstrated that ICD improved survival in patients who were resuscitated from VF or who had sustained VT causing haemodynamic compromise, compared with

antiarrhythmic-drug therapy.[52] At follow-up after 3 years, survival rates were 75% for the ICD group vs 61% for the antiarrhythmic group.[52] The Canadian Implantable Defibrillator Study (CIDS) reported a 20% relative risk reduction occurred in all-cause mortality and a 33% reduction in arrhythmic mortality with ICD therapy compared with amiodarone in a total of 659 patients with resuscitated VF or VT.[53] However this difference did not reach statistical significance. In the Cardiac Arrest Study Hamburg (CASH) study, 228 survivors of cardiac arrest were randomised to receive an ICD, amiodarone, propafenone or metoprolol.[54] The propafenone arm was withdrawn early due to an observed excess mortality rate. There was a 23% reduction in all-cause mortality rate found in patients receiving ICD therapy compared with amiodarone/metoprolol over a long-term follow-up although it was not statistically significant.[54] The reduction was much larger, 61%, for SCD. No differences were found in all-cause mortality and SCD rates between patients assigned to amiodarone and those assigned to metoprolol.[54]

Based on all these trials, the current international guidelines recommend a class I indication for ICD as secondary prevention in survivors of cardiac arrest not due to a reversible cause, for patients with syncope of unknown aetiology and inducible VT/VF, and in patients with spontaneous, sustained VT.[55]

1.4 PROPHYLACTIC IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR IN HEART FAILURE: THE GROWING EVIDENCE FOR ALL OR PRIMUM NON NOCERE FOR SOME?

Preface

HF is a growing problem in many developed and undeveloped countries. Despite the optimal medical treatment of HF, the risk of SCD in HF patients especially those with impaired left ventricular function remains significant.[37,56] The advent of the ICD has led to improved survival in defined subsets of HF patients. This has caused an increase in implants in these devices in recent years. However, these devices are not free of risks or short- or long-term complications. The research in the following section provides the review of current body of evidence on the pros and cons of the prophylactic ICD in HF patients.

The following manuscript was published in 2017 in the *Heart Failure Reviews* 2017; 22:305-16. Heart Failure Reviews is an international journal which develops links between basic scientists and clinical investigators, creating a unique, interdisciplinary dialogue focused on HF, its pathogenesis and treatment and its current impact factor is 3.481.

Contribution of Candidate

Khang-Li Looi was involved in conception of the review paper. She developed the structure and arguments for the paper and wrote the manuscript for publication. She also made critical revisions during the review stage of the manuscript prior to publication.

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Abstract

Heart failure (HF) is a common health problem and has reached epidemic in many western countries. Despite the current era of HF treatment, the risk of sudden cardiac death (SCD) in HF remains significant. Implantable cardioverter-defibrillator (ICD) support has been shown to reduce the risk of SCD in patients with HF and impaired left ventricular function. Prophylactic ICD implantation in HF patients seems a logical step to reduce mortality through a reduction in SCD. However, ICD implantation is an invasive procedure and both short and long-term complications can occur. This need to be carefully considered when evaluating the risk-benefit ratio of ICD implantation for individual patients. As the severity of HF increases, the proportion of SCD compared with HF-related deaths decreases. The challenge lies in identifying patients with HF who are at significant risk of SCD and who would most benefit from an ICD in addition to other antiarrhythmic strategies. This review offers insight on the applicability and practicability of ICD for this growing population.

Introduction

Heart failure (HF) is a major health burden in developed countries. The prevalence of HF is estimated at 1–2 % in the western world, and the incidence approaches 5–10 per 1,000 persons per year.[7] The number of people with HF is likely to increase within our ageing populations. Despite this, hospitalisation rates for HF are declining now and many HF patients are surviving longer.[15-19] HF is a chronic, long-term health condition but with the improved survival for HF patients, a substantial burden is imposed on patients and the healthcare system.

Despite the advances in the diagnosis and management of HF, sudden cardiac death (SCD) remains a significant threat to the long-term survival of patients with HF. The Framingham Heart Study showed that HF is associated with a 2.6- to 6.2-fold increased risk of SCD[37,56] However, the most common cause of death in New York Heart Association (NYHA) class IV HF patients remains pump failure. Ventricular arrhythmias (including non-sustained ventricular tachycardia [VT]) have been documented in up to 85% of patients with severe HF.[57] Currently, the most widely used risk stratification criterion for SCD is severe left ventricular impairment based on depressed left ventricular ejection fraction (LVEF). Most international guidelines use a cut-off inclusion criterion for eligibility of implantable-cardioverter-defibrillator (ICD) implantation with LVEF ≤35%.[22] However, patients with systolic dysfunction constitute less than half of the HF population.[58,59] It is recognized that HF can also occur in the presence of normal or near-normal EF: so-called 'heart failure with preserved EF (HFpEF). Currently there is no data to support the use of ICD for primary prevention of SCD in this sub-group of HF patients. The determination of LVEF lacks a "gold standard" and that there may be variation among the commonly used clinical techniques of LVEF determination and varies among laboratories and institutions. The LVEF used in clinical trials assessing the ICD for primary prevention of SCD ranged from <40% in MUSTT (Multicenter Unsustained Ventricular Tachycardia Trial) to <30% in MADIT II.(Multicenter Automatic Defibrillator

Implantation Trial II)[60-62] The MADIT I (Multicenter Automatic Defibrillator Implantation Trial I) and SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) used LVEF <35% as criteria.[61,63] The guidelines consensus was to offer ICD to patients with clinical profiles as similar to those included in the trials as possible to obtain the best benefits.[64]

Several studies have shown that ICDs decrease mortality relative to anti-arrhythmic medications in patients who have survived an episode of sustained VT or ventricular fibrillation (VF).[52,53] ICD therapy has been used for the primary prevention of SCD in patients deemed at high risk of cardiac arrest. However, these devices are not risk free and using them may worsen quality of life. A systematic review published in 2007 involved 12 randomised controlled trials with a total of 8516 patients with left ventricular systolic dysfunction showed that ICD were efficacious in reducing mortality.[65] Yet the peri-implant death rate was 1.2% (Confidence Interval [CI], 0.9% to 1.5%). The frequency of post-implantation complications per 100 patient-years included 1.4 (CI, 1.2 to 1.6) for device malfunctions, 1.5 (CI, 1.3 to 1.8) for lead problems, and 0.6 (CI, 0.5 to 0.8) for ICD site infections.[65] A more recent meta-analysis of 18 randomised controlled trials reported an overall complication rate of 9.6% over 16 months.[66]

With the current growing population of HF who potentially meet the eligibility criteria for ICD, improved risk stratification will be needed to best identity which patients benefit the most. We provide a review of the current literature regarding the clinical effectiveness and cost-effectiveness of ICD utilisation in selected HF populations.

Primary prevention of sudden cardiac death in heart failure

The MADIT trial established for the first time that prophylactic ICD therapy used in conjunction with conventional medical therapy can improve survival in ischaemic cardiomyopathy patients in NYHA functional class I, II, or III with LVEF ≤35%; versus conventional medical therapy alone.[61] During an average follow-up of 27 months, there were 15 deaths in the ICD group (11 from cardiac causes) and 39 deaths in the conventional-therapy

group (27 from cardiac causes) (hazard ratio [HR] for overall mortality, 0.46; 95 % CI 0.26 to 0.82; p=0.009).[61] The subsequent MADIT-II study showed that there was a 31% reduction in the risk of death at any interval in patients with ischaemic cardiomyopathy who received prophylactic ICD therapy.[62]

In the MUSTT trial, antiarrhythmic therapy with ICD support led to an absolute reduction in the risk of cardiac arrest or death from arrhythmia of 7% after 5-years of follow-up.[60] The survival benefit was due solely to the use of ICD. Taken together with MADIT and MADIT-II, these trials indicate that ICD therapy is indicated in patients with coronary artery disease who meet eligibility criteria without significant non-cardiac comorbidity.

The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial found that in patients with non-ischaemic dilated cardiomyopathy (NICM) on standard medical therapy, the addition of ICD therapy significantly reduced SCD and was associated with a trend toward a reduction in all-cause mortality compared with standard medical therapy alone.[67] The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) showed that prophylactic ICD implantation in patients with ischaemic or NICM with LVEF ≤35% reduced mortality at 3 years. At 5 years, patients treated with an ICD continued to have lower mortality rates than patients treated with amiodarone or placebo (28.9% vs 34.1% vs 35.8%). Overall, ICD use was associated with a highly significant 23% reduction in all-cause mortality compared with placebo (p=.007).[63]

Taken together, these studies have formed the basis of the current clinical guidelines for primary prevention ICD implantation to prevent SCD in HF patients with impaired LVEF. According to current clinical guidelines, class I indications for ICD implantation for primary prevention of SCD in patients with HF include 1) Patients with LVEF ≤35% due to prior MI who are at least 40 days post-MI and are in NYHA Class II or III; 2) Patients with NICM who have an LVEF ≤35% and who are in NYHA Class II or III; 3) Patients with LV dysfunction

due to prior MI who are at least 40 days post-MI, have an LVEF ≤30%, and are in NYHA Class I.[64]

Table 1 summarised all the primary prevention trials of patients with left ventricular impairment for SCD or developing ventricular arrhythmias.

Table 1: Primary Prevention ICD trials in patients with impaired left ventricular function

Study	Number of Patients	Inclusion Criteria	ICD (n)	Mean Follow-Up	Main Findings
MADIT[61]	196	Previous MI, NYHA I–III, LVEF <35%, Asymptomatic NSVT with inducible sustained VT at EPS	95	27 months	54% relative risk reduction of SCD
CABG Patch[68]	900	CABG surgery, LVEF <36%, Abnormal SAECG	446	32+/-16 months	Non-significant
CAT[69]	104	NICM <9 months, NYHA II–III, LVEF <30%	50	22.8+/-4.3 months	Non-significant
MADIT-II[62]	1232	Prior MI, LVEF <30%	742	20 months	31% relative risk reduction of SCD
AMIOVIRT[70]	103	NICM, NYHA I–III, LVEF <35%, Asymptomatic NSVT	51	2.0 ± 1.3 years	Non-significant
DEFINITE[67]	458	NICM, LVEF <36%, PVC or NSVT	229	29.0+/-14.4 months	35% relative risk reduction of SCD
SCD-HeFT[63]	2521	IHD or NICM, NYHA II–III, LVEF <35%	829	45.5 months	23% relative risk reduction of SCD
MUSTT[60]	704	IHD, LVEF <40%, Asymptomatic NSVT with inducible sustained VT at EPS	161	39 months	27% relative risk reduction of SCD

Abbreviations:
CABG, coronary artery bypass graft; EPS, electrophysiological study; ICD, implantable cardioverter-defibrillator; IHD, ischaemic heart disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NICM, non-ischaemic cardiomyopathy; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; PVC, premature ventricular complex; SAECG, signal averaged ECG; SCD sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia

Given the vast pool of potential candidates for ICD, further studies were undertaken to evaluate whether specific populations of HF patients are more at risk of SCD and might benefit from ICD implantation. In the current American Heart Association guidelines, there is no differentiation between patients with ischaemic cardiomyopathy or NICM for prophylactic ICD implantation.[71] In contrast, the European guidelines distinguish between the groups; those with NICM have a Class IB recommendation as opposed to a Class IA recommendation for patients with ischaemic cardiomyopathy.[72] The randomised trials that showed a significant benefit of ICD in reducing all-cause mortality in NICM patients was SCD-HeFT and DEFINITE Trial.[63,67.] However, the positive effect of ICD was only confined to patients in NYHA class II. The recently published Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH) provided us another perspective when considering prophylactic ICD in patients with NICM.[73] After a median follow-up period of 67.6 months, the primary outcome of death from any cause had occurred in 120 patients (21.6%) in the ICD group and in 131 patients (23.4%) in the control group (HR, 0.87; 95% CI 0.68 to 1.12; p=0.28).[73]Whilst SCD occurred in 24 patients (4.3%) in the ICD group, there was no improved survival benefit overall for the ICD group (HR, 0.50; 95% CI, 0.31 to 0.82; p=0.005).[73]

To date, prophylactic ICDs have been shown to reduce the risk of SCD among patients with left ventricular systolic dysfunction after myocardial infarction (MI). However, the evidence of a benefit remains less robust for those with NICM and warrants ongoing assessment.

Implantable cardioverter-defibrillator with or without cardiac resynchronisation therapy

In the general population, QRS prolongation and/or left bundle branch block (LBBB) on the electrocardiogram (ECG) is present in <1% at middle age, increasing to 5–17% over age 80. LBBB occurs more commonly in males, those with HF, coronary artery disease, hypertension,

and left ventricular hypertrophy, and is associated with adverse outcomes.[74-77] In a Swedish Heart Failure Registry, QRS prolongation ≥120 ms was present in 31% of patients with HF.[78] The electrical-conduction disturbances play an important role in the progression of HF. In those with LBBB, the normal sequence of electrical activation is reversed leading to significant electromechanical coupling delay. A population-based study of HF patients showed that those with LBBB had features consistent with more severely decompensated HF.[79] Furthermore, even after accounting for these baseline differences in validated predictors of mortality, a LBBB pattern on the admission ECG conferred a 10 % increased risk of death and a 32 % increase in HF rehospitalisation in long-term follow-up.[79]

Cardiac resynchronisation therapy (CRT) can restore more-normal electro-mechanical coupling and, when combined with defibrillation (CRT-D), can have a major impact on the mortality and morbidity of HF.[80-84] The two landmark studies, Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) and Cardiac Resynchronization-Heart Failure (CARE-HF) established the clinical indications for CRT in HF patients on optimal medical treatment, which form the basis for consensus international guidelines.[83-85] These two trials showed that CRT reduced the risk of death from any cause and hospital admission for worsening HF.[83,84]

The ICD is an effective treatment for the prevention of SCD, and the addition of the ICD can potentially decrease the risk of SCD in CRT patients. The Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy (MADIT-CRT) and the Resynchronization/Defibrillator for Ambulatory Heart Failure Trial (RAFT) studies comparing CRT-D with ICD alone in HF patients, have shown survival benefit in patients with CRT-D as compared with those in the ICD only group.[86,87] A recent meta-analysis of five randomised trials demonstrated a significant decrease in mortality with CRT (odds ratio [OR] 0.78, p=0.024), the benefit being largely driven by the RAFT study.[88] CRT was shown to reduce HF

events (OR 0.63, p<0.001) and induced significant left ventricular (LV) reverse remodelling (p<0.001).[88] The meta-analysis also showed that CRT was associated with a delay progression of HF symptoms (OR 0.54, p=0.026) and a significant improvement in exercise tolerance (p<0.001). Given the overlapping indications for ICD and CRT, the 2013 European Society of Cardiology (ESC) Guidelines state that CRT (preferably a CRT-D) is a class IA indication for NYHA class II HF patients with LVEF ≤ 35 % and QRS duration ≥150ms.[85]

It remains to be determined which CRT patients get the highest benefit from ICD and whether some patients fulfilling implantation criteria do not get any benefit at all. The benefit of the CRT-D compared with CRT-pacemaker (CRT-P) has not been extensively evaluated.[84,87] Although the COMPANION trial suggested that the addition of ICD to CRT incrementally increased the survival benefit, a post hoc analysis of this trial has shown that CRT-P was not significantly different from CRT-D for either time to SCD or HF death in NYHA Class IV patients.[89] A recent observational study failed to show significant survival advantage for CRT-D compared with CRT-P at a relatively long-term follow-up.[90] In patients with HF who receive either ICD or CRT-D for primary or secondary prevention, the most common cause of death is progressive HF rather than SCD.[91,92] In a sub-analysis of MADIT-II, Goldenberg et al. have shown that a simple risk score constructed as a count of five risk factors (NYHA functional class > II, age ⩾70 years, blood urea nitrogen [BUN] > 26 mg/dl, QRS duration > 120ms, and atrial fibrillation) could differentiate between patients who would benefit from the ICD versus those who would not.[93] Recently, a single-centre, retrospective, observational, cohort study of patients with ischaemic or NICM utilised the Goldenberg score to predict all-cause mortality risk of patients receiving CRT. This study showed that patients with 0–2 risk factors had a significant mortality benefit in the first 4 years of follow-up if implanted with a CRT-D rather than CRT-P, while patients with ≥ 3 risk factors did not get any additional mortality benefit.[94] Likewise, the benefit of ICD in addition to CRT in patients with severe renal dysfunction

(creatinine ≥ 2.5 mg/dL and/or urea ≥ 50 mg/dL) was limited.[94] In the most recently published DANISH study, effect of ICD implantation was independent of CRT status.[73]

In the multicentre CeRtiTuDe cohort study that included 1705 consecutive patients implanted with CRT devices, the annual overall mortality rate was 83.8 (95% CI 73.41 - 94.19) per 1000 person-years.[95] The crude mortality rate among CRT-P patients was double compared with CRT-D but 95% of the excess mortality among CRT-P patients was related to an increase in non-SCD. Similarly, in a sub-analysis of the COMPANION trial examining the mode of death, pump failure (44.4%) remained the most common cause of death followed by SCD (26.5%) in patients with advanced HF even though both CRT-D and CRT-P modestly reduced mortality.[96] The CARE-HF trial, where only the impact of CRT-P was assessed on HF confirmed that pump failure deaths remain the leading cause of death in its HF population.[83] These studies serve to remind us of the need to better stratify patients most likely to benefit from certain interventions, and to avoid unnecessary or even inappropriate treatments.

In HF patients with CRT indication and no history of ventricular arrhythmias, the addition of the ICD conveys a significant survival benefit in well-selected patients with ischaemic cardiomyopathy. However, in patients with NICM the benefit of additional ICD to CRT remain less clear. NICM is a known predictor of better response to CRT compared to those with ischaemic cardiomyopathy.[97-99] Therefore, their subsequent risk of ventricular arrhythmias may be lower, which will reduce the beneficial impact of the ICD. This consideration is particularly relevant given the higher cost of the CRT-D and the higher risk of device-related complications, in particular infection and lead dysfunction.[100] The current transvenous ICD leads are relatively easy to implant, less costly and associated with decreased morbidity and mortality. However, the longevity of these leads varies in different trials from 91-99% at 2 years, 85-98% at 5 years, and 60-72% at 8 year.[101,102] Extraction of chronically implanted leads

remains a difficult procedure in particular the potential lead adhesions increase the risk during extraction procedures.[103]

The benefit of CRT depends upon achieving a near 100% biventricular pacing.[104,105] CRT-D battery longevity is shorter than ICD or CRT-P alone. The need for nearly 100% biventricular pacing results in a significant battery drain and is usually the major determinant of battery longevity and thus of the time from device implant to the elective replacement indicator (ERI). A recent head-to-head comparison of CRT-D battery performance across 3 major manufacturers demonstrate a large discrepancy in CRT-D battery longevity.[106] Battery longevity has significant implications on patient care and outcomes. Shorter battery life requires more frequent device replacement, which increases healthcare costs and complications. Device replacements are associated with a 1–2% rate of device infections, with a substantial cohort potentially requiring surgical or percutaneous procedures for device explantation and lead extractions, followed at a later stage by new device implantation.[107,108] In the REPLACE registry, 7% of patients undergoing CRT-D generator replacement without addition or replacement of leads had major complications in the 6 months following the procedure.[109] For all these reasons, it is desirable to select the most appropriate patients that would be best served with CRT-D or CRT-P to minimize the number of generator changes for battery depletion and the considerable risks of complications.

At present, the best we can do in assisting our patients to make decisions about CRT-D versus CRT-P is to have a balanced conversation regarding the individual risks and benefits.

Implantable cardioverter-defibrillator and women with heart failure

Epidemiological and clinical registry data suggest that women account for approximately one half of the patients hospitalised for HF.[110-112] Previous studies have shown that women treated for HF are more likely than men to have preserved systolic function and significantly less likely to be prescribed guideline-recommended evidence-based medications, and when these are

prescribed for women, they tend to be prescribed at suboptimal doses.[111,113,114] The reasons behind the discrepancy in management of HF in men and women remain unclear.

Clinical trials of ICDs have demonstrated the overall survival benefits of primary prevention ICDs.[60-63,67] The recommendations of ICDs have not differed for men and women according to current guidelines.[64] However, many of the clinical trials of ICDs were underpowered to assess the impact of ICDs for women. Only small numbers of women were enrolled into and received ICDs in these trials: <20 each in MUSTT and MADIT trials and only 185 in SCD-HeFT.[61,63,115]

Despite multiple studies demonstrating a significant mortality benefit with CRT in eligible HF patients, women remain significantly under-represented in CRT trials.[83,84,86,87] Various studies have examined the relationship of gender and response to CRT. Xu et al. retrospectively evaluated sex differences in CRT effectiveness. In this cohort study that included 728 patients, women seemed to achieve greater survival benefit than men and its benefit was majorly driven by NICM.[116] Another prospective study showed that women experienced better survival, longer event-free survival from death/HF hospitalisation and significant improvements in NYHA functional class, LVEF and LV reverse remodelling with CRT compared with men.[117] In multivariable Cox proportional hazards analyses, the association between female gender and cardiovascular survival was independent of age, LVEF, atrial rhythm, QRS duration, CRT device type, NYHA class, and LV reverse remodelling (adjusted HR: 0.48, p= 0.0086).[117]

The presence of LBBB is predictive of a positive response to CRT.[118,119] Because women have smaller ventricles and shorter baseline QRS duration than men, they are more likely to have a true LBBB compared with men. In a study from National Cardiovascular Data Registry (NCDR) ICD Registry, women with LBBB who received CRT-D have a lower mortality risk than men with LBBB.[120] Among all patients with LBBB, longer QRS duration at inclusion was associated with better survival, although this lower mortality risk plateaued at a QRS duration > 140ms in women and > 150 ms in men. In contrast, in the non-LBBB patients, no gender

differences in mortality were found and mortality risk was similar regardless of QRS duration.[120]

Another meta-analysis of patient data pooled from 3 CRT-D vs ICD trials with 4076 patients (22% were women) showed that women with LBBB benefited from CRT-D at a shorter QRS duration than men with LBBB.[121] In women with LBBB and a QRS duration of 130 to 149ms there was a 76% reduction in HF or death (absolute CRT-D to ICD difference, 23%; HR, 0.24, [95% CI, 0.11-0.53]; $p < .001$) and a 76% reduction in death alone (absolute difference 9%; HR, 0.24, [95% CI, 0.06-0.89]; $p=0.03$).[121] Neither women nor men with LBBB benefited from CRT-D at QRS duration < 130 ms, while both gender with LBBB benefited at QRS duration ≥of 150 ms. This is important because the current guidelines limit the class I indication for CRT-D to patients with LBBB and QRS duration ≥ 150 ms. The extent to which the benefit from CRT-D differs according to gender is of particular interest. A recent large observational multicentre study compared CRT-D vs. CRT-P in 5307 patients to determine whether the addition of the ICD to CRT devices would offer a more pronounced survival benefit in men compared to women.[122] In this study, only 9.1% of deaths were SCD. In both device groups, SCD was more frequent in men than in women and the proportion of deaths due to SCD was also higher in male vs. female patients (10.1% vs. 7.4% in CRT-D patients, and 8.3% vs. 5.5% in CRT-P patients).[122] SCD rates were very low amongst female patients with NICM regardless of device they received (2.4 vs. 1.8 per 1000 patient-years in CRT-D and CRT-P patients, respectively). In women with ischaemic cardiomyopathy, the number needed to treat (NNT) to prevent one SCD was 148 in this study.[122]

Some studies suggest that women are at particularly high risk for procedural complications compared with men.[123,124] In the analysis of over 30,000 Medicare beneficiaries undergoing new ICD implantation, women were more likely to experience a procedural-related complication.[125] Data from the NCDR ICD Registry showed that women are more likely than

men to have in-hospital adverse events related to ICD implantation.[126] Recently, Russo et al. reported that on the adjusted OR for all complications (OR 1.39; 95% CI 1.26-1.53; p<0.001), all cause 6-month readmission (OR 1.22; 95% CI 1.16-1.28; p<0.001), and 6-month HF hospitalisation (OR 1.32; 95% CI 1.23-1.42; p<0.001) were statistically significantly higher in women who received primary prevention ICD even after adjusting for patient and procedural characteristics.[127]Similarly, Ranasinghe et al. showed in the observational study that compared with simpler devices, CRT-D devices have a 38% higher rate of complications.[128] Women and black patients had a somewhat higher risk of complications compared to men and white patients.[128]

The mechanisms for higher complication rates in women are unclear; however, amongst the proposed mechanisms are smaller vasculature and smaller body habitus. Gender differences in mortality might be explained by the differences in the mode of death between men and women. It is possible that women who receive ICD may be more likely to die of non-cardiac or non-arrhythmic causes compared with men who received ICD.[30,127,129,130]

There appears to be a number of potential barriers to women gaining access to ICD/CRT-Ds, since the original trials focussed heavily on ventricular arrhythmias and ischaemic cardiomyopathy, which was more common in men. In addition, the differences in disease pattern and LV impairment between the genders may have contributed to under-representation of women in more recent trials. Although these results should not preclude women from receiving ICDs, a broader perspective of the consequences of adverse events on outcomes such as cost and quality of life is needed to inform decisions around primary ICD implantation in women with HF.

Implantable cardioverter-defibrillator and elderly populations with heart failure

The elderly population is steadily increasing in size both in developed countries and the rest of the world. In the United States 44.7 million people are aged 65 years or older.[131] They currently

represent 14.1% of the U.S. population, about one in every seven Americans. By 2060, there will be about 98 million older persons, more than twice their number in 2013.[131] The proportion of people ≥ 65 years of age are expected to grow to 21.7% of the population by 2040.

The implementation of primary prevention ICD treatment in the current clinical guidelines will lead to a significant increase in patients who may benefit from an ICD. However, there is a lack of evidence regarding utility and outcomes associated with ICD in elderly patients. This may be because patients enrolled in the large trials were relatively young and had little co-morbidities. Elderly patients were also largely excluded and underrepresented in the pivotal ICD trials making the generalisability of this treatment to this group unclear.

Elderly patients were best represented in MADIT-II which included 204 (17%) patients were aged ≥75 years. The sub-study of MADIT-II showed that ICD treatment in patients aged ≥75 years was associated with a 44% relative reduction of all-cause mortality, which was comparable to their younger peers.[132] However, in a meta-analysis by Santangeli et al., which included five primary prevention trials (5783 patients of which 44% were ≥ 65 years), only a smaller survival benefit was observed in patients ≥ 65 years (HR: 0.75; 95% CI: 0.61–0.91; p = 0.004).[133]

One of the major differences between the elderly enrolled in the primary prevention trials and the elderly receiving ICD treatment in routine clinical practice is the burden of co- morbidities. In a large cohort (n = 2467; n ≥75 years = 425) of primary and secondary prevention patients, the presence of non-cardiac co-morbidities was associated with an increased risk of mortality in ICD patients.[134] Another real world retrospective multicentre study performed in 15 Spanish hospitals showed that the benefit of ICD is attenuated among those patients ≥ 75 years at the moment of device implantation.[135] This study comprised ∼15% of elderly patients≥ 75 years of age with more co-morbidities, including hypertension, chronic obstructive pulmonary disease, and renal failure, and more previous hospitalisations due to HF.[135]

When referring an elderly patient for ICD implantation, one needs to assess their risk of procedural and post-procedural complications. Tsai et al. evaluated the influence of age on perioperative complications among 150264 primary prevention ICD patients. The occurrence of any adverse event or in-hospital death increased from 2.8% in the youngest age group (<65 years of age) to 4.5% in the oldest age groups (≥80 years).[136] Multivariate analysis also found increased odds of any adverse event or death among 75–79-year olds (1.14 [95% CI, 1.03–1.25], 80-to 84-year-olds (1.22 [95% CI, 1.10–1.36], and patients ≥85 years (1.15 [95% CI, 1.01–1.32], compared to those under 65 years old.[136] Once patients reached 80 years of age, the rate of any events, including mortality, reached a plateau (4.5% in 80–84-year-old patients and 4.5% in those ≥85 years old).[136]

Chronological age per se should not be the decisive factor in the decision-making for ICD/CRT-D implantation in the elderly with HF. Although age is a predictor of mortality, it does not accurately identify patients who would benefit from the ICD when used in isolation. Some patients may be more youthful and healthier than their chronological age, whilst others have significant co-morbidities and appear much older and frailer than expected. Patient and physician expectations play an important role when contemplating ICDs, particularly in the elderly and other higher risk groups. Such decision making requires evidence to inform the discussions, which for the elderly is relatively sparse. Additional factors must therefore be taken into account when considering the role of ICD support for particular patients. There are several risk stratification scores that have been developed for the prediction of mortality in potential ICD patients. Goldenberg et al. constructed a simple risk score comprised of five risk factors (NYHA functional class > II, age ⩾70 years, blood urea nitrogen [BUN] > 26 mg/dl, QRS duration > 120ms, and atrial fibrillation) and showed no benefit in patients with zero risk factors (HR 0.96) and in very-high risk individuals (HR 1.0).[93] Among patients with ≥3 risk factors, mortality was only slightly lower in the ICD group than in the conventional therapy

group (29% vs. 32%).[93] Parkash et al. used a risk score that included age > 80 years, history of atrial fibrillation, creatinine > 1.8 mg/dL and NYHA class III or IV demonstrated that a risk score ≥2 predicted a 1-year mortality rate of 21%, whereas a risk score of <2 predicted a mortality rate of 4% at 1 year.[137] Another study involving approximately 45000 Medicare beneficiaries receiving primary prevention ICDs used 7 clinically relevant predictors of mortality and developed the "SHOCKED" predictors[138]. Age ≥75 years(HR): 1.70; 95% CI: 1.62 to 1.79), NYHA class III HF (HR: 1.35; 95% CI: 1.29 to 1.42), atrial fibrillation (HR: 1.26; 95% CI: 1.19 to 1.33), chronic obstructive pulmonary disease (HR: 1.70; 95% CI: 1.61 to 1.80), chronic kidney disease (HR: 2.33; 95% CI: 2.20 to 2.47), LVEF≤ 20% (HR: 1.26; 95% CI: 1.20 to 1.33), and diabetes mellitus (HR: 1.43; 95% CI: 1.36 to 1.50) accurately identifies patients at highest risk for death after device implantation.[138]

Currently the data on the beneficial effect of ICD in the elderly, especially with co-morbidities, are scarce. This population has less or even no benefit from ICD treatment as compared to their younger peers. Age itself should not be the sole criterion for withholding ICD implantation but one should accept that in an older population with concomitant co-morbidities, the small potential benefits of ICD treatment might not outweigh the costs and burden of device-related complications. A great proportion of death in elderly patients, even those at risk for ventricular arrhythmias, are attributable to medical conditions that cannot be addressed by an ICD alone.

Implantable cardioverter-defibrillator and patients with chronic kidney disease and heart failure

Chronic kidney disease (CKD) is a worldwide health problem affecting approximately 13.1% of the American population.[139] From the early stages of CKD to end-stage renal disease (ESRD), cardiovascular involvement is present, in part due to the aging population and in part due to higher rates of diabetes mellitus, dyslipidaemia and hypertension among the CKD

population.[140] Cardiovascular diseases represent the main causes of morbidity and mortality in patients with CKD.[141]

HF and CKD often co-exist. Nearly one-third of patients with HF have concomitant CKD stage 3 or worse.[142,143] CKD also carries a significant risk for the development of HF. Among CKD patients starting dialysis therapy, 36% have HF, and an additional 7% develop HF while receiving dialysis.[144]

HF and CKD both carry significant risk for SCD, hospitalisation and mortality; when these two conditions co-exist they markedly increase the risk of morbidity and mortality.[143,145] Almost 60% of cardiac deaths in the dialysis population can be attributed to SCD.[145,146] In addition, both HF and CKD are independently associated with multiple cardiac risk factors known to decrease survival.

There is paucity of randomised data to adequately address the benefit of ICD therapy in patients with CKD. In most trials, patients with renal dysfunction were excluded or there was significant heterogeneity across studies in their stratification of CKD i.e. use of estimated glomerular filtration rate (eGFR) versus blood urea nitrogen (BUN) versus creatinine. Most of the data of ICD in CKD patients is derived from retrospective cohorts, registries and models.

In patients with Stage 1 and 2 CKD, the most robust data came from Goldenberg et al. who performed a retrospective analysis of the outcome associated with renal dysfunction in patients enrolled in the MADIT-II.[147] They showed that those with stage 1 and 2 CKD patients tend to have similar survival benefit after ICD therapy as those without CKD.

The clinical benefits and cost-effectiveness of ICD implantation on patients with stage 3,4 and 5 CKD remain less robust. The data relating to increased mortality in these CKD patients is consistent. However, the degree to whether ICD modifies the adverse effect of CKD to the patient overall survival is unknown. For those patients with ESRD or stage 5 CKD, the median survival after primary prophylactic ICD implantation was estimated at 21 months. The risk of

death within 1 year was significantly greater than those with CKD stage 1 patients (OR 35, 95% CI 4.2-24.1, p<0.0001).[148] A secondary analysis from MADIT-II showed no mortality benefit from ICD implantation in patients with eGFR<35mL/min/1.73m^2 (Stage 3b) (all-cause mortality HR 0.95, p=0.95).[147] A recent study on the ESRD patients showed that the ICD use in dialysis patients was increasing but the rates of all-cause and cardiovascular mortality remain high despite ICD implantation.[149] Device infections are unfortunately common in these patients. Although they occurred most frequently during the first year after implantation, the infection rate remained high throughout follow-up. Diabetes (HR, 1.15; 95% CI, 1.08-1.23), infection within the past 60 (HR, 2.42; 95% CI, 2.25-2.62) or 61-365 (HR, 1.49; 95% CI, 1.39-1.59) days, and peripheral vascular disease (HR, 1.14; 95% CI, 1.07-1.20) were associated independently with the risk of any infection after implantation.[149]

The subcutaneous implantable cardioverter-defibrillator (S-ICD) was designed to eliminate complications related to transvenous leads.[150] It offers a potentially attractive alternative to the transvenous ICD in ESRD patients on haemodialysis, thus limiting the risk of central vein stenosis and endovascular infection. There remains limited data on the safety and efficacy of S-ICD in dialysis patients. In a single-centre retrospective study, 27 (34%) of 79 patients receiving S-ICD on haemodialysis had higher incidence of primary endpoint (death, HF hospitalisation or appropriate S-ICD shocks) (23.8%/year) driven mainly by higher rate of appropriate shocks consistent with the increased risk of SCD in ESRD patients.[151] However, there was a low rate complication rate in the dialysis cohort, in particular the absence of any device-related infections.

A feature that distinguishes the S-ICD from the transvenous ICD is the inability to terminate arrhythmias with antitachycardia pacing (ATP), but only with an electrical 80 J shock.[150] Moreover, bradycardia pacing is limited only to the immediate post-shock period (50 bpm for 30s). Therefore, patients with pacing indication (bradycardia pacing, CRT, and ATP for

recurrent monomorphic VT) should not receive an S-ICD[150]. A recent study in CKD patients on haemodialysis who have preserved LV function, demonstrated that the vast majority of SCD were due to bradycardia and asystole, rather than malignant ventricular arrhythmias.[152] These observations mean the role of the S-ICD in ESRD patients remains limited, with those most likely to benefit being a much smaller part of the population and hard to identify.

These findings align with previous studies, suggesting a substantially increased mortality in patients with CKD, which reasonably leads one to question the benefit of ICD therapy in these high-risk patients. The risk of device-related complications needs to be carefully weighed against the benefit in this group of patients,

Cost effectiveness and safety of primary prevention implantable cardioverter defibrillator in heart failure patients

A recent meta-analysis of all the pivotal primary prevention ICD trials provide strong evidence supporting the beneficial effect of ICD therapy on survival of patients with LVEF ≤35% due to ischaemic cardiomyopathy or NICM.[153] There is a suggestion across studies that the beneficial effect of ICD on SCD may increase beyond 2 or 3 years post implant.[154] There is strong evidence that ICD use as primary prevention for HF patients who meet the current criteria reduces the risk of SCD.

At present the effectiveness of ICD in settings outside of randomised clinical trials is less clear. Because clinical trial participants are carefully selected and have close follow-up, results of clinical trials may not always apply to real-world clinical setting. Real world recipients of ICDs generally have more non-cardiac co-morbidities.[155,156] In patients with chronic HF, the early post-discharge period after an acute admission is associated with a high risk of mortality, during which progressive HF is the most likely cause of death.[157] The tipping point of benefit vs. futility of ICD therapy in many HF patients remain ambiguous.

Given the large number of potential HF patients who are eligible for prophylactic ICD, a careful analysis of ICD cost-effectiveness is appropriate. Sanders et al. showed that prophylactic implantation of an ICD has a cost-effectiveness ratio below $100,000 per quality-adjusted life-year (QALY) gained in populations in which a significant device-related reduction in mortality has been demonstrated.[158] In the recent Health Technology Assessment report, ICD reduced all-cause mortality in patients at increased risk of SCD, including patients with ischaemic cardiomyopathy/NICM and LVEF ≤ 35%. The addition of ICD to optimal medical treatment was cost-effective at a willingness-to-pay (WTP) threshold of £30,000.[159] In HF patients at risk of SCD who met the criteria for CRT, CRT-D reduced the risk of all-cause mortality and HF hospitalisation, and improved other outcomes, compared with ICD alone.[159] However, complications were more common in CRT-D. The incremental cost effectiveness ratio (ICER) for CRT-D compared with ICD, but not CRT-D compared with optimal medical treatment, was < £30,000 per QAYL, and the costs and QALYs for CRT-D and CRT-P were similar.[159]

Although the peri-operative risks of new ICD implants are generally low, one should not ignore the long-term risk for device-related complications and reoperations. A large Italian study including 4829 patients from 117 centres reported rates of reoperations for complications at 4 years of 4%, 9% and 14% for single-chamber, dual-chamber and CRT-D devices.[160] Another observational cohort study from the NCDR ICD registry that involved 114884 patients showed that there were 6.1 (CI, 6.0 to 6.2) ICD-related complications per 100 patient-years that required reoperation or hospitalisation.[128] Younger age at implantation (65 to 69 vs. >85 years) (HR 1.55 [CI, 1.43 to 1.69]), CRT-D (HR, 1.38 [CI, 1.31 to 1.45]) versus a single-chamber ICD, female (HR, 1.16 [CI, 1.12 to 1.21]), and black race (HR, 1.14 [CI, 1.05 to 1.23]) were associated with the greatest increased risks for ICD-related complications.[128]

Conclusion

High morbidity and mortality are associated with clinical HF and accounts for an increasing health care burden in many countries. There is no question that ICD therapy has had a major impact on the management of selected HF patients. There remains significant limitations and challenges to the appropriate application of the available evidence for primary prevention ICD or CRT-D in HF patients. A carefully thought-out, case-by-case approach should be utilized when considering implanting ICD or CRT-D in selected HF patients to maximise the benefits of these complex devices. Longer term registry or trial data is needed to address the subgroups that are particularly under-represented in clinical trials but make up a substantial proportion of the patients seen in routine clinical practice.

Chapter 2 CARDIAC RESYNCHRONISATION THERAPY

2.1 INCIDENCE OF LEFT BUNDLE BRANCH BLOCK IN HEART FAILURE

Left bundle branch block (LBBB) diagnosis on surface electrocardiogram (ECG) is defined as QRS duration ≥120 ms in adults, broad notched or slurred R wave in leads I, aVL, V5, and V6 and an occasional RS pattern in leads V5 and V6 attributed to displaced transition of QRS complex.[161] The incidence of LBBB increases progressively with advancing age.[75] Hypertension, ischaemic heart disease, left ventricular hypertrophy, ST-T abnormalities on surface ECG, and an increased cardiothoracic ratio on chest x-ray were associated with LBBB.[76]

LBBB is a common finding in patients with HF. In the large Italian Network on Congestive HF Registry of outpatients referred to cardiology centres for evaluation and treatment of congestive HF showed that complete LBBB develops in as many as 25% of patients with HF of any origin.[162] LBBB affects the myocardial contractile efficiency. Kerwin et al showed that patients with NICM with LBBB is associated with significant ventricular contraction abnormalities during sinus rhythm.[163] These contraction abnormalities exist as multiple levels of dyssynchrony, leading to poor systolic performance of the failing heart.[163] Similarly, Rao et al reported that left ventricular dyssynchrony is present up to 72% in HF patients with complete LBBB.[164] In dog studies, dyssynchrony of left ventricular contraction induced by abnormal electrical activation resulted in a depressed left ventricular contractile response.[165] Additionally, LBBB prolongs mitral regurgitation by increasing pre-ejection and relaxation times.[166] This directly impairs diastolic function by shortening the time available for the left ventricle to fill to an extent likely to limit cardiac stroke volume.

Similar to atrial fibrillation (AF), a deleterious effect of complete LBBB on left ventricular function in HF patients has been established. Luliano et al demonstrated that a prolonged QRS from baseline ECG is an independent predictor of increased total mortality and SCD among

patients with known cardiomyopathy and HF symptoms enrolled in the Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT) trial.[167] LBBB patients showed a trend toward worsened survival (p=0.006) but not SCD.[167] In the large Italian Network on congestive HF Registry, LBBB was associated with a 70% increase in the univariate risk of all-cause mortality rate at 1-year.[162] In the Multicenter Unsustained Tachycardia Trial (MUSTT), the relationship between ECG abnormalities and occurrence of arrhythmic and total mortality have been evaluated.[168] In this study, patients with LBBB or intraventricular conduction delay (IVCD) had lower LVEF and a higher prevalence of HF than those without these abnormalities. The presence of LBBB and IVCD was associated with an 1.5-fold–increased risk of cardiac arrest and total mortality.[168]

2.2 ROLE OF CARDIAC RESYNCHRONISATION THERAPY (CRT) IN HEART FAILURE PATIENTS

Cazeau et al. first described cardiac resynchronisation therapy (CRT) in 1994.[169] In this case report, 4 chamber pacing in patients with evidence of IVCD provides a mechanical activation sequence closer to the natural one.

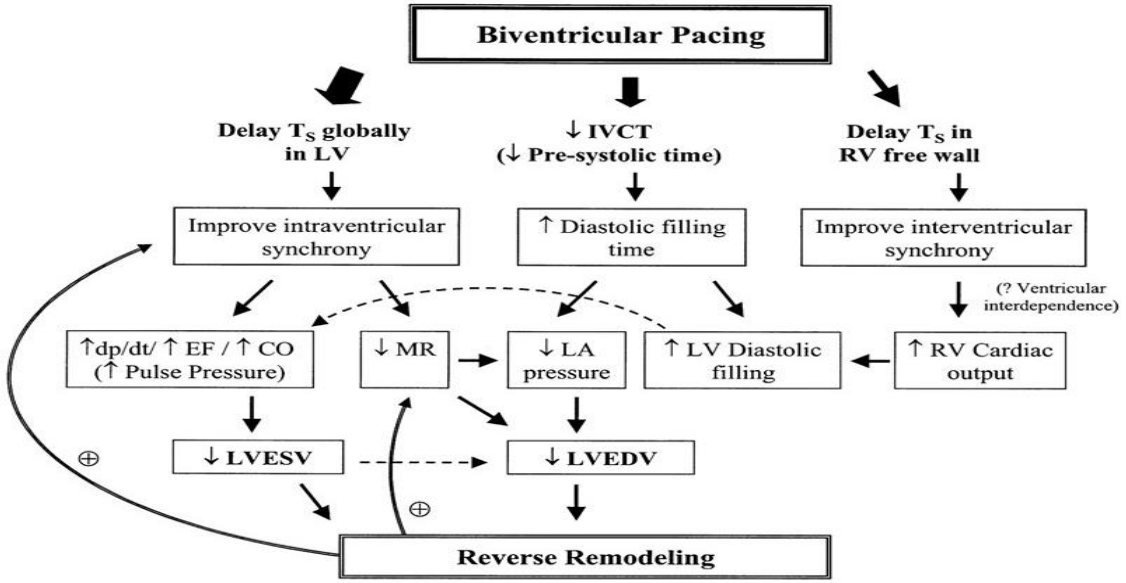
Subsequent to this case report, Leclercq et al performed acute haemodynamic study to assess the potential benefit of biventricular dual chamber pacing (DDD) by comparison with no ventricular pacing and with conventional single-site right ventricle DDD pacing in patients with normal sinus rhythm, severe HF and surface ECG evidence of major IVCD.[170] It demonstrated that biventricular DDD pacing compared with intrinsic rhythm and single-site right ventricle DDD pacing, may significantly improve cardiac performance in patients with major IVCD and severe HF with significant left ventricular dysfunction.[170] Similarly, another haemodynamic study by Saxon et al. showed that simultaneous right and left ventricular apical pacing results in acute improvements in global ventricular performance in 11 patients with depressed left ventricular function.[171]

These acute studies led to the development of randomised studies evaluating the effect of CRT on quality of life/symptom and functional capacity of patients with HF. The European and Canadian InSync Study was designed to demonstrate the efficacy and safety of CRT in HF using these endpoints.[172] CRT system was implanted in 103 patients and significant improvements in exercise capacity, NYHA functional class, and quality-of-life score were noted at 1, 3, 6 and 12 months after implantation.[172]

Prevention of cardiac remodelling is important to improve prognosis of HF patients. Study from Yu et al. showed that CRT can result in reverse cardiac remodelling.[173] In this study, 25 patients with NYHA class III-IV HF and QRS duration >140ms who received CRT showed improvement of LVEF, reduction of mitral regurgitation, increase in diastolic filling time as

well as improvement in NYHA functional class at 3 months follow-up after implantation.[173] The proposed mechanisms of benefit by CRT were due to improvements in the intraventricular synchrony, atrioventricular synchrony and interventricular synchrony (**Figure 2**).

Figure 2: Proposed Mechanisms of Benefit of Biventricular Pacing



Reproduced with permission from Yu CM, Chau E, Sanderson JE, et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. Circulation 2002; 105:438-45.

Abbreviations:

CO: cardiac output: dP/dt: the rate of pressure rise in systole; EF: ejection fraction; IVCT: *isovolumic contraction time ; LA: left atrial; LV: left ventricular; LVEDV: left ventricular end-diastolic pressure and volume; LVESD: left ventricular end-systolic volume ;MR: mitral regurgitation; RV: right ventricle; T_S: the time to peak myocardial sustained systolic velocity (SM)*

Subsequent to these studies, the two landmark studies, Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) and Cardiac Resynchronization- Heart Failure (CARE-HF), established the medium- to long-term morbidity and mortality benefits of CRT in HF patients.[83,84]

A total of 1520 patients who had advanced HF with NYHA class III or IV symptoms due to ischaemic cardiomyopathy (ICM) or NICM and a QRS duration of at least 120 msec were randomly assigned in a 1:2:2 ratio to receive optimal pharmacologic therapy alone or in combination with cardiac-resynchronisation therapy with pacemaker (CRT-P) or a CRT–defibrillator (CRT-D) in COMPANION trial.[84] CRT-D was associated with a significant decrease in all-cause mortality (relative risk reduction: 36%; p=0.003), while the 24% relative risk reduction in mortality associated with CRT-P was nearly statistically significant (p=0.059).[84]

In CARE-HF, a total of 404 patients were assigned to receive medical therapy alone and 409 to receive medical therapy plus CRT-P. The mean duration of follow-up was 29.4 months (range, 18.0 to 44.7). There were 82 deaths in the CRT group, as compared with 120 in the medical- therapy group (20% vs. 30%; hazard ratio 0.64; 95% confidence interval, 0.48 to 0.85; p<0.002).[83] This resulted in a 36% relative reduction in the risk of death (p< 0.002) observed in those who received CRT-P. As compared with medical therapy, CRT also reduced the interventricular mechanical delay, the end-systolic volume index, and the area of the mitral regurgitant jet; increased the LVEF and improved symptoms and the quality of life (p<0.01 for all comparisons).[83]

These trials established the clinical indications for CRT in selected HF patients, which form the basis for current consensus international guidelines.[85]

2.3 USE OF CARDIAC RESYNCHRONISATION THERAPY – CHANGE OF CLINICAL SETTING

Preface

Cardiac resynchronisation therapy (CRT) has been shown in multiple studies to improve HF symptoms, quality of life and survivals.[80-84] Ongoing studies aim to expand the use of CRT in patients with asymptomatic or minimal symptoms from left ventricular dysfunction.

The following research provides a comprehensive review on the expanding clinical indications of CRT. Some of these are not well known, for example HF patients with narrow QRS complexes, mechanical dyssynchrony alone, HF patients with chronic kidney disease (CKD) and cost-effectiveness of these devices. This review highlights the need for more research in this area to guide appropriate management in this group of patients. Similarly, for cost-effectiveness study, because of current economic situation, it is important to balance the incremental benefits and costs of CRT with the possible increases in complications and morbidity related to CRT.

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Contribution of Candidate

Khang-Li Looi was involved in conception of the review paper. She developed the structure and arguments for the paper and wrote the manuscript for publication. She also wrote critical revisions during the review stage of the manuscript prior to publication.

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Abstract

Current guidelines recommend cardiac resynchronisation therapy (CRT) for patients with severe left ventricular dysfunction (left ventricular ejection fraction [LVEF] ≤ 35%), QRS duration of ≥ 120-150ms (Class IA and IB indications) on surface electrocardiogram (ECG) and New York Heart Association (NYHA) class III or IV heart failure (HF) symptoms. Ongoing studies aim to expand the use of CRT in patients with asymptomatic or minimal symptoms left ventricular dysfunction. There have been studies that have shown benefit of CRT extended to this group of patients. Three have also been different implications of the role of CRT in patients with atrial fibrillation (AF), patients with narrow QRS duration or with right bundle branch block (RBBB) on surface ECG as well as patients with end-stage renal failure on dialysis therapy. This article aims to review the current body of evidence of expanding use of CRT in these populations.

Introduction

Heart failure (HF) is a growing and major health burden in western countries. The prevalence of HF is estimated at 1–2% in the western world and the incidence approaches 5–10 per 1000 persons per year.[7] Cardiac resynchronisation therapy (CRT) has been shown in multiple studies to improve HF symptoms, quality of life and improve survivals.[80-84] The 2 landmark studies, the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) and the Cardiac Resynchronization–Heart Failure (CARE-HF) trials, established the clinical indications for CRT, which form the basis for consensus international guidelines.[83,84,174] These two trials which randomised 2333 patients in sinus rhythm (SR) with QRS prolongation on surface electrocardiogram (ECG) (≥ 120ms), New York Heart Association (NYHA) functional class III and ambulatory class IV HF and a persistently reduced left ventricular ejection fraction (LVEF), despite optimal medical treatment. The trials showed that CRT reduced the risk of death from any cause and hospital admission for worsening HF.[83,84] The effect of left ventricular reverse remodelling from CRT was sustained over time.[175] This has significant clinical implications and has led to the development of hypothesis that implanting CRT in patients at earlier stage of HF and different characteristics of patients with HF may prevent the disease progression, and lead to improve clinical outcomes. This article reviews the use of CRT in the changing and new clinical setting and the implications for daily clinical practice.

Cardiac resynchronisation therapy (CRT) in patients with mild heart failure: The evidence

The earliest evidence of CRT in NYHA class I-II patients came from CONTAK CD and Multicenter InSync ICD II (MIRACLE ICD) trials.[82,176]

In CONTAK CD, 490 patients with implantable cardioverter defibrillator (ICD) were randomised to either CRT on or no CRT.[82] All patients were in NYHA class II to IV at the time of entry into the study. However many patients demonstrated significant symptomatic improvement with medical treatment during this period. Thus, 227 patients were in NYHA class III/IV and 263 were in NYHA class I/II when the randomized therapy was initiated. At 6 months, CRT was linked to a significant reduction in left ventricular dimensions ($p < 0.001$) and improvement in LVEF (5.1% vs.2.8%, $p=0.020$).[82] However, the reduction in HF progression and changes in NYHA class as well as quality of life were not statistically significant. Many patients responded positively once medical treatment was optimised before randomisation. This improvement in clinical status made it more difficult to show benefit in healthier patients. Importantly, this trial showed that CRT improves left ventricular reverse remodelling.

Likewise, in the Multicenter InSync ICD II (MIRACLE ICD) trial all the 186 patients with secondary indication for ICD were randomised either to CRT-on or CRT-off.[176] CRT resulted in significant improvement in cardiac structure and function and clinical HF composite endpoint over 6 months but did not alter exercise capacity. It appeared that CRT offers important benefits to optimally medically managed, mildly symptomatic NYHA class II HF patients with ventricular dyssynchrony and an indication for an ICD. The study showed the potential of CRT to limit disease progression even in patients with mild HF symptoms.

These studies provided a preview of the much larger trials such as REVERSE, MADIT-CRT and RAFT studies in this group of patients with asymptomatic or mildly symptomatic HF.

The Resynchronization Reverse Remodelling in Systolic Left Ventricular Dysfunction (REVERSE) trial was the first large randomised controlled trial that included 610 patients with NYHA class I and II symptoms, QRS $\geq$120ms and LVEF $\leq$40%.[177]. At 12 months of follow-up, only 16% of patients with CRT device on worsened compared to 21% of those with CRT-

off (p=0.10).[177] However, CRT was associated with a significant improvement in left ventricular dimensions (p<0.0001). The reduction of left ventricular dimensions was particularly prominent in those patients with non-ischaemic cardiomyopathy, those with larger left ventricular end systolic volumes and those with a broader QRS on surface ECG (≥152ms). The time to the first HF-hospitalisation was also significantly delayed in those with CRT-on (HR 0.47, p=0.03).[177] Although CRT appeared to slow the HF disease progression in this study, the impact of clinical outcome was only modest. It is worthy to note that the patients in REVERSE trial were on optimal medical treatment. This might be a potential explanation for these "negative" results. Also, this trial has a short follow-up of 1 year. The treatment effect of CRT might require a prolonged period and therefore, not be surprising that a 1-year trial of CRT including asymptomatic patients with HF was too short to demonstrate the efficacy of CRT.

The sub-analysis of the European data of REVERSE trial provided further insights into the role of CRT in 262 mildly symptomatic HF patients. Over the 24 months period, 19% of those with CRT-on vs. 34% of those with CRT-off patients worsened (p=0.01).[178] Furthermore CRT was associated with a significant reduction in the left ventricular end systolic volume index (p<0.0001). The time to first HF-hospitalisation was significantly delayed in those with CRT-on (p=0.03).[178] These results provided additional data to support the use of CRT in delaying HF progression.

The Multi-center Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy (MADIT CRT) study demonstrated a 34% reduction in the risk of death or nonfatal HF among the mild HF patients with CRT-D as compared to those in the ICD only group (p=0.001).[86] This benefit was mainly driven by the 41% reduction in the risk of HF events and there was no difference between the patients with ischaemic or non-ischaemic cardiomyopathy. Furthermore, there was clear improvements in the left ventricular mechanical indexes with

reduction in the left ventricular volumes ($p<0.001$) and increase in LVEF ($p<0.001$), reiterating the reverse remodelling effect of CRT that was observed in REVERSE.

Another large study that compared ICD with CRT-D in patients with mildly symptomatic HF was the Resynchronization/Defibrillator for Ambulatory Heart Failure Trial (RAFT). Among the 1798 patients with LVEF ≤30%, QRS durations ≥120ms and NYHA class II or III HF, the primary outcome of death or hospitalisation for HF occurred in 33.2% of those with CRT-D, compared to 40.3% in those with ICD only ($p<0.001$).[87] The time to the occurrence of the primary outcome was significantly delayed in the CRT-D group (HR 0.75, $p<0.001$). The time to death was also significantly prolonged in the CRT-D group (HR 0.75, $p=0.003$).[87]

A recent meta-analysis of the above 5 randomised trials was performed. At pooled analysis, there was a significant decrease in mortality with CRT (odd ration [OR] 0.78, $p=0.024$) and this benefit was largely driven by the RAFT study. CRT was shown to reduce HF events (OR 0.63, $p<0.001$) and induced significant left ventricular reverse remodelling ($p<0.001$).[88] The analysis also showed that CRT was associated with a delay progression of HF symptoms (OR 0.54, $p=0.026$) and a significant improvement in exercise tolerance ($p<0.001$).[88]

With the additional findings from the above trials, the relative magnitude of the benefits of CRT in patients with NYHA class II symptoms is similar to those observed in patients with NYHA class III symptoms. Therefore, the European Society of Cardiology (ESC) Task Force agreed to give a new recommendation for patients with NYHA class II HF. In the 2013 ESC Guidelines on cardiac pacing and cardiac resynchronisation therapy, CRT preferably a CRT-D is a class IA indication for NYHA class II HF patients with LVEF ≤35% and QRS duration ≥150ms.[174] However, the evidence for recommending CRT in patients with NYHA class I remain inconclusive due to the low number of patients enrolled in randomised trials.

Special considerations and new/future indications of cardiac resynchronisation therapy

Cardiac Resynchronisation Therapy and patients with atrial fibrillation

Atrial fibrillation (AF) is a common arrhythmia and its prevalence increases in the presence of HF. Additionally, the development of AF in HF patients may significantly affect the outcomes. Population data from Framingham Study suggests that new onset AF after a HF diagnosis conferred a hazard ratio for death of 1.6 in men and 2.7 in women.[179] The role of CRT in patients with AF is less well-established. The evidence of CRT in patients with AF predominantly came from observational case studies.[105,180,181] The first prospective and randomised trial that evaluated the role of CRT in patients with permanent AF and severe HF is the Multisite Stimulation In Cardiomyopathies (MUSTIC) AF trial which included 131 patients, at least half was in permanent AF and in need of ventricular pacing. However only patients with a biventricular pacing rate >85% did show a slight but significant improvement in functional status at 1 year follow-up.[182] In RAFT study, 229 patients (12.7%) had permanent AF at baseline. There was no clear reduction in clinical events and patients with permanent AF appeared to gain minimal benefit from CRT-D compared with a standard ICD.[183] Despite apparently good rate control of AF before randomisation, the delivery of CRT remained suboptimal because of a low percentage of biventricular pacing. A recent meta-analysis including 23 observational studies and followed a total of 7,495 CRT patients, 25.5% with AF, for a mean of 33 months found that AF was associated with an increased risk of non-response to CRT (34.5% vs. 26.7%; pooled relative risk [RR] 1.32; p =0.001) and all-cause mortality (10.8% vs. 7.1% per year, pooled RR 1.50, p = 0.015).[184]

The benefits of CRT appear to be attenuated in patients with AF. Indeed, the presence of AF affects the effective delivery of biventricular pacing. In patients with AF, phases of effective biventricular capture alternate with phases of competing AF rhythm which causes spontaneous,

fusion, or pseudo-fusion beats.[104] This suggests that the global effective CRT delivery may be markedly reduced compared with atrial-synchronous rhythm with a short AV interval as is achieved during SR. Moreover, in AF patients, during exertion, spontaneous ventricular rate tends to override biventricular pacing rates, resulting in further reduction of paced beats precisely when patients are most in need of having biventricular capture, thus greatly limiting exercise tolerance. For this aspect, the indication of CRT for patients in AF with NYHA class III or IV, QRS duration ≥ 130ms and LVEF ≤35% remains Class IIA in the recent 2013 ESC Guidelines.[174]

In most patients with AF with intact intrinsic conduction, adequate biventricular pacing could only be achieved with atrioventricular (AV) nodal ablation. The use of AV nodal ablation was highly variable in majority of CRT trials. In RAFT, AV nodal ablation was only used in 1 patient.[183] A recent meta-analysis of 6 studies that enrolled 768 CRT-AF patients including 339 patients who underwent AV nodal ablation showed that AV nodal ablation conferred an RR of 0.42 and 0.44 for overall mortality and for cardiovascular mortality, respectively.[185] AV nodal ablation was also shown to improve NYHA functional class in patients with AF. The current 2013 ESC Guidelines recommend a Class IIA indication for CRT in patients with AF, QRS duration ≥120ms and LVEF ≤35%, provided that AV nodal ablation is added to these patients with incomplete (<99%) biventricular capture and those who are candidates for AV nodal ablation for rate control. A randomised controlled trial, Cardiac Resynchronisation Therapy and AV Nodal Ablation Trial in Atrial Fibrillation Patients (CAAN-AF) (http://clinicaltrials.gov/ct2/show/NCT01522898) is currently enrolling and aimed to determine if AV nodal ablation combined with CRT in CRT-eligible AF patients will result in significant reductions in mortality and HF events compared to patients treated with CRT alone.

Cardiac Resynchronisation Therapy and patients with chronic kidney disease

Renal impairment is common in patients with HF. In a systematic review of heart failure population, a total of 63% of patients had any renal impairment, and 29% had moderate to severe impairment.[186] Adjusted all-cause mortality was increased for patients with any renal impairment (HR 1.56; p<0.001) and moderate to severe impairment (HR 2.31; p<0.001).[186]

The effect of CRT on renal function has not been studied in large randomised trials. A retrospective study showed the survival rate among those with standard ICD alone (88 patients) and CRT-D patient (787 patients) within glomerular filtration rate (GFR) < 30mL/min/1.73 m^2 and GFR ≥ 60mL/min/1.73m^2 groups was similar, whereas CRT-D patients with GFR 30–59 (moderate renal impairment) had significantly better survival compared to those with ICD alone (HR 2.23, p=0.002).[187] This survival benefit was associated with improved renal and cardiac function. However, among patients with a baseline GFR < 30 mL/min/1.73 m^2, a group largely ignored in most CRT trials, survival was limited.[187] It might imply that the CRT implantation procedure itself had no lasting impact on renal function.

Many patients with chronic kidney disease (CKD) have concomitant cardiac disease with indications for device therapy but majority of the trials have excluded this group of patients. Recently, a study 482 CKD patients treated by CRT reported higher survival in those with normal or mild renal impairment than in those with CKD (defined as a GFR of ≤ 60 mL/min/1.73 m2) (72% vs. 57% at 3 years, p<0.01).[188] This study has excluded patients on dialysis.

There is also a paucity of data on the role of CRT in patients with CKD on dialysis therapy. Based on current limited data, the benefits and risks should be taken into consideration when considering the implantation of a CRT device in a dialysis patient. More research in this field is warranted to guide appropriate clinical decision in this group of patients.

Cardiac Resynchronisation Therapy and patients with heart failure but a narrow QRS complex

Previous studies have shown that approximately 30% of HF patients have narrow QRS duration <120ms and thus these patients will not qualify for CRT according to current guidelines.[189] Yet these patients have depressed left ventricular systolic function and exhibit left ventricular mechanical dyssynchrony as assessed by echocardiography.[190,191]

Several small studies have reported HF patients with narrow QRS had demonstrated a substantial echocardiographic and clinical improvement following CRT.[192-194] Based on these encouraging outcomes of the smaller observational studies, the Cardiac Resynchronization Therapy with Heart Failure and Narrow QRS (RethinQ) study was conducted to evaluate the efficacy of CRT in patients with standard indication for ICD, NYHA class III HF, a QRS duration <130ms and evidence of mechanical dyssynchrony on echocardiography.[195]. At the end of follow-up, there was no difference between those with narrow and wide QRS patients. However, this study was of too short duration to observe any effects on morbidity and mortality. Recently, The Evaluation of Resynchronization Therapy for Heart Failure (LESSER-EARTH) trial that assessed whether CRT improves exercise capacity and left ventricular reverse remodelling outcomes in patients with LVEF ≤35%, symptoms of HF and a QRS duration <120ms was interrupted prematurely after 85 patients were randomised. The trial showed that CRT did not improve clinical outcomes or left ventricular reverse remodelling in those with a narrow QRS duration <120ms.[196] In fact, there was an associated with a non-significant trend toward an increase in HF-related hospitalisation.

Similarly, the Echocardiography Guided Cardiac Resynchronization Therapy (EchoCRT) study was recently terminated early due to futility of CRT in this population. The mean QRS duration was 105.0 ms for the CRT group. The primary outcome, death from any cause or hospitalisation for worsening HF, occurred in 28.7% in the CRT group, as compared with 25.2%

in the control group (HR with CRT, 1.20; p=0.15).[197] There was an excess of deaths due to cardiovascular causes in patients randomly assigned to CRT (37 deaths, vs. 17 in the control group; p=0.004). There was also a non-significant trend toward an increase in mortality related to HF. [197]

Despite the hypothesis that CRT might be beneficial to those with HF but narrow QRS duration, the current published studies have consistently failed to demonstrate a benefit in this group of patients. The current guidelines do not recommend CRT in patients with chronic HF with QRS duration <120ms (Class IIIB evidence).

Cardiac Resynchronisation Therapy and patients with right bundle branch block

Left bundle branch block (LBBB) has been shown to have detrimental effect in patients with HF. Short term mortality rates for the subgroups of patients with decompensated HF with QRS<120 ms, RBBB and LBBB were 46.1%, 56.8% and 57.7%, respectively (p<0.0001).[198] Another population-based study of HF patients, those with LBBB had features consistent with more severely decompensated HF. Furthermore, even after accounting for these baseline factors and validated predictors of mortality, a LBBB on the presentation ECG conferred a 10% increased risk of death and a 32% increase in HF rehospitalisation in long-term follow-up.[79]

In patients with LBBB, the normal sequence of electrical activation is reversed leading to significant electromechanical coupling delay. On the other hand, patients with RBBB might have minimal electrical or electromechanical coupling delay unless left fascicular hemiblock is present.[199] A study using 3-dimensional non-fluoroscopic electroanatomic contact mapping system (3D-Map) showed that patients with RBBB, compared to LBBB, have a greater right-sided conduction delay, while the degree of left ventricular delay is not significantly different between the two groups.[200] These findings seem to suggest that in HF patients with RBBB, CRT should benefit those in whom an underlying left-sided intraventricular conduction delay is masked by RBBB.

The number of patients with right bundle branch block (RBBB) included in large randomised controlled trials of CRT was low. A single-centre registry of 636 CRT patients with only 59 patients with RBBB (9.3%) found that the composite end point of death, heart transplantation, or ventricular assist device implantation occurred in 147 patients (23.0%), most frequently in the RBBB group (p=0.004).[201] The highest symptomatic NYHA response rate was observed in those with LBBB, whereas few patients with RBBB responded (p<0.001). This differential response remained significant after controlling for baseline differences among groups (p=0.02).[201]

Similarly, a pooled data from the MIRACLE and CONTAK-CD trials showed that patients with RBBB had no evidence of improvement in symptoms, 6-minute walk test or quality of life scores at 6 months.[202] A meta-analysis of 4 publications from five studies reported data on patients with RBBB showed no favourable outcomes of CRT in patients with RBBB.[203] In a recent post hoc analysis of the MADIT-CRT trial, patients with RBBB and a non-left anterior fascicular block had improvement in left ventricular volumes and function. However there was no difference in the 3-year probability of death or HF admissions among those with RBBB or ICD only (p=0.962 and p=0.374).[204]

At this stage, those with non-LBBB with QRS >150ms the indication remains as Class IIB for CRT device.[174] Physicians and patients should be aware of the likely reduced benefit from CRT in patients with RBBB, and this should be factored into decision making. However, until more data are available it is too early to change guidelines.

Cardiac Resynchronisation Therapy and patients with mechanical dyssynchrony

The hypothesis of CRT in narrow QRS with ventricular dyssynchrony cannot be neglected, albeit the evidence remains weak so far. Similar question remained for patients with mechanical dyssynchrony and wide QRS: how do we select the right patients for CRT? The Predictors of Response to CRT (PROSPECT), a prospective, multicenter, nonrandomised

study was unable to find a single echocardiographic measure of dyssynchrony through which patient selection for CRT could be improved even though up to 12 echocardiographic parameters have been used.[205] The recent study using apical rocking (ApRock) as a surrogate marker for LV dyssynchrony in patients with wide QRS implies that patients with an increase in myocardial contractile reserve resulting in more dyssynchrony may derive a greater benefit from CRT. The Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fraction (PARAMOUNT) Trial suggested that dyssynchrony may play a pathophysiologic role in HF patients with preserved LVEF.[206] However strong evidence for the usefulness of echocardiography for patient selection in CRT is still lacking. Despite these well-presented and convincing data, the answer at this point in time clearly is physicians will only implant CRT in those meeting current guideline criteria, irrespective of echocardiographically measured dyssynchrony.

Safety and Cost-effectiveness issues:

With the current progress in research, the clinical applications for CRT are expanding. However, the cost, invasiveness and morbidity (e.g. infection) of CRT need to be considered carefully.

Cost effectiveness

The cost-effectiveness study from the European cohort of REVERSE indicated that CRT in mildly symptomatic HF has a similar cost-effectiveness ratio as in moderate to severe HF. Compared with CRT-OFF, 0.94 life years or 0.80 quality-adjusted life years (QALYs) were gained in the CRT ON group at an additional cost of €11 455, yielding an incremental cost-effectiveness ratio of €14.278 per QALY gained.[207]

The 2007 Health Technology Assessment found that CRT-P and CRT-D devices reduce mortality and hospitalisations due to HF, improve quality of life and reduce sudden cardiac death in those with NYHA classes III and IV, and evidence of dyssynchrony. Compared with

optimal medical treatment, the devices are estimated to be cost-effective at a willingness-to-pay (WTP) threshold of £30,000 per QALY; CRT-P is cost-effective at a WTP threshold of £20,000 per QALY.[208] However the estimated net benefit from CRT-D is less than with the other two strategies, until the WTP threshold exceeds £40,160/QALY.[208] The cost of CRT-P devices is already substantial; the addition of ICD will be more expensive since the latter technology involved will be more sophisticated. The hypothesized incremental benefits in survival from CRT-D would need to be balanced by possible increases in morbidity owing to, for example, device-related complications and inappropriate shocks.

Safety

CRT implantation is an invasive procedure and the implant often takes considerably longer than other pacemaker and ICD procedures, and is undertaken in a patient group at increased risk of haemodynamic compromise because of the underlying HF and poor LVEF. Overall perioperative complication rates range from 4% in more recent trials to as high as 28% in earlier CRT trials.[177,209]

The success rate of LV lead implantation in REVERSE was 97%, which is higher than those reported in previous studies.[177] The rate of LV lead dislodgement was 8% at 1 year. However, all the centres participated in the REVERSE had a long experience with CRT implantations, suggesting that these procedures should be limited to centres with high volumes and excellence. In MADIT-CRT trial, serious device-related adverse events occurred with a frequency of 4.5 per 100 device-months in the CRT–D group and of 5.2 per 100 device-months in the ICD-only group.[86] Although the adverse events were infrequent in both groups, they could not be completely ignored.

The rate of adverse events within 30 days after device implantation was significantly higher among patients in the CRT-D group than among those in the ICD group in RAFT study. There were 118 device- or implantation-related complications among the 888 patients receiving CRT-

D, as compared with 61 of 899 patients in the ICD group ($p<0.001$).[87] The adverse events reported were consistent with the rates in other studies.[209,210] LV lead dislodgement and an increased rate of infection remain significant problems. Although many of these adverse events did not have substantial long-term consequences, they may prolong hospitalisation.

With the increasing number of CRT device implantation, infection becomes a major challenge that implanting physician has to face. The first large prospective study analysing both incidence and prevalence of CRT device-related infection showed that the risk of CRT infection is twice that of a standard pacemaker implant risk. The prevalence was close to 4.3% at 2.6 years, an incidence of 1.7% per annum.[211] Four independent predictive factors were identified: procedure time ($p=0.002$); dialysis ($p=0.0001$); re-intervention ($p=0.006$); and procedure type (CRT-D vs. other procedures; $p=0.01$).[211] These factors should be considered carefully in the evaluation of patients selected for CRT implantation.

Conclusion

CRT has demonstrated favourable survival and symptom benefits in prior trials, especially those with highly symptomatic HF, LVEF $\leq$ 35% and QRS $\geq$ 120ms. The issue of whether CRT might be extended to other patient populations has been raised. Ongoing clinical randomised trials will provide stronger evidence for any potentially new indications. Considering the cost and safety issues of CRT, one has to be cautious of translating all the trial findings into wider and routine use of CRT.

Chapter 3 CARDIAC RESYNCHRONISATION THERAPY: PACEMAKER VERSUS INTERNAL CARDIOVERTER-DEFIBRILLATOR IN PATIENTS WITH IMPAIRED LEFT VENTRICULAR FUNCTION

3.1 PREFACE

CRT has been proven to reduce the risk of mortality and hospitalisation from HF in patients with either a CRT-D or CRT-P.[80-84] However, the incremental benefits in survival from CRT-D would need to be balanced by possible increases in morbidity and complications. The choice of appropriate device remains unanswered.

The aims of the research presented in this chapter were:

- To identify the long-term outcome of patients with either CRT-D or CRT-P in routine clinical practice
- To identify any potential risk factors that would identify the patient population most likely benefit from CRT-D.

This research showed that the survival benefit in CRT-D was highest in the first year, but this benefit appeared to be attenuated by the second year and became insignificant by the end of follow-up. This information has an important impact on patient management, especially when selecting the appropriate device in patients with multiple comorbidities.

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Contribution of Candidate

Khang-Li Looi was involved in the data collection, analysis and interpretation of the results. She developed the structure and arguments for the paper and wrote the manuscript for publication.

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3.2 ABSTRACT

Objective: Studies have shown beneficial effects of cardiac resynchronisation therapy (CRT) on mortality among heart failure patients. However, the incremental benefits in survival from CRT with a defibrillator (CRT-D) are unclear. The choice of appropriate device remains unanswered.

Method: This is a single-centre observational study in a tertiary cardiac centre, patients (n=500) implanted with CRT-P (n=354) and CRT-D (n=146) were followed for at least 2 years (mean 29 months, SD 14 months). The primary end point was all-cause mortality.

Results: A total of 116 deaths (23.2%) were recorded: 88 (24.8%) and 28 (19.2%), in the CRT-P, and CRT-D groups respectively. At 1 year there was a trend favouring CRT-D (HR 0.54, 95% CI: 0.27 to 1.07, p=0.08) but this was attenuated by the second year and became insignificant at the end of follow-up (HR 0.76, 95% CI: 0.50 to 1.170, p=0.21). There was no survival benefit from having an ICD if patients were deemed non-responders to CRT. 27% of the CRT-P patients with ischaemic cardiomyopathy met indications for potential ICD implantation for primary prevention. These were older patients with poorer baseline function in comparison to CRT-D patients with devices for primary prevention. Once these differences were adjusted for, there was no difference in outcome between the groups.

Conclusion: CRT-D did not offer additional survival advantage over CRT-P at longer term follow-up, as the clinical benefit of a defibrillator attenuated with time. Further work is needed to define which subset of patients benefit from CRT-D.

3.3 INTRODUCTION

Cardiac resynchronisation therapy (CRT) has become an acceptable treatment modality for patients with medically refractory congestive heart failure (CHF). The clinical effects of long term CRT have been proven to reduce mortality and hospitalisation from heart failure, resulting in clinically important improvements in exercise capacity and health related quality of life (QOL).[82-84] Patients may receive a CRT device with a defibrillator (CRT-D) or CRT with pacing alone (CRT-P).

The 2013 European Society of Cardiology (ESC) guideline suggests that CRT is recommended in CHF patients with left ventricular ejection fraction (LVEF) ≤35% who remain in New York Heart Association (NYHA) functional class II, III and ambulatory IV; despite adequate medical treatment.[174] It is also recommended that when an internal cardioverter defibrillator (ICD) is planned for either primary or secondary prevention of sudden cardiac death (SCD), CRT is recommended when indicated. In the United Kingdom, the National Institute for Health and Clinical Excellence (NICE) recommended CRT with a pacing device (CRT-P) as a treatment option for people with CHF fulfilling similar criteria on optimal pharmacological treatment.[212] However, they suggest CRT-D may be considered for people who fulfil the criteria for implantation of a CRT-P device and who also separately fulfil the criteria for the use of an ICD. Many patients may be eligible for both treatments, but it does not necessarily follow that such patients would obtain additional benefit from the combined treatment over one treatment alone, particularly in the longer term.

A meta-analysis found that CRT-D was associated with significant reductions in all-cause mortality as compared to an ICD alone.[213] The risks of lead problems and coronary dissection were significantly higher in patients who received CRT-D which remained a concern.[213] A recent systematic review showed some benefits of CRT-D over CRT-P in the all-cause death rate after one-year follow-up.[214] However, the crucial question regarding the choice of

appropriate device in the longer-term remains unanswered and deciding which patients may benefit from the added defibrillator device is challenging.

This study aimed to assess the long-term outcome of patients with either CRT-D or CRT-P in routine clinical practice and to identify any potential risk factors that would identify the patient population most likely benefit from CRT-D.

3.4 METHODS

This study was a single centre, retrospective observational study with prospective follow-up. A total of 500 consecutive patients implanted with either CRT-D or CRT-P at a tertiary referral centre (Papworth Hospital, Papworth, UK) from June 2006 to June 2010 were included. Initial choice of device (CRT-P vs. CRT-D) was based on NICE guidance but then modified (as needed) after discussion between implanting physician and individual patients, taking into account their preferences. The devices were implanted using standard protocols after written consent was obtained. All the patients were followed up in the pacing and general clinics. Patient information and data were retrospectively retrieved and analysed at the end of the follow-up period. Response to CRT was defined as improvement in NYHA functional class. The primary endpoint of the study was all-cause mortality.

3.5 STATISTICAL ANALYSIS

Continuous variables are presented as mean ± standard deviation, and categorical data as counts or percentages. Analysis and comparisons of continuous data were performed using ANOVA, whilst the χ^2 test was used to compare categorical data. Fisher's exact test was used if χ^2 assumptions were not met.

Survival was estimated using Kaplan Meier analyses. Cox proportional-hazards-models were used to explore univariate and multivariate predictors of events. Initial exploratory co-variates of age, gender, atrial fibrillation, aetiology of heart failure, diabetes, hypertension, QRS morphology, QRS duration, LVEF, serum sodium, and serum creatinine were used.

Multivariate models for mortality included terms with *p*-value of <0.1 at univariate analysis along with type of device. Interaction terms between device choice and covariates were used to identify predictive factors by assessing whether there was a significant difference in the hazard ratio for death between subgroups. A two-sided probability level of <0.05 was considered significant. All calculations were performed using SPSS 20.0 (IBM Software, USA).

3.6 RESULTS

A total of 500 consecutive patients were enrolled. Overall mean age was 69±10 years with 78% being men. Mean follow-up was for 29±14 months. CRT-D was implanted in 146 patients (29.2%), while the remaining 354 patients (70.8%) received CRT-P. The mean LVEF was 25±7.5%. The baseline characteristics of the two groups are shown in **Table 2**. Compared to the patients who received CRT-P, those who had CRT-D implanted were younger, more likely to be male and have ischaemic cardiomyopathy, and with milder symptoms. They also received more amiodarone compared to those who had CRT-P.

Table 2: Baseline characteristics of CRT-P and CRT-D patients

Variable	**CRT-P (n=354)**	**CRT-D (n=146)**	***p*-value**
Mean age – years ± SD	70 ± 9.9	67 ± 9.3	0.002*
Male (%)	252 (72.6)	133 (91.1)	<0.001*
Ischaemic heart disease (%)	168 (48.3)	96 (65.8)	0.001*
Hypertension (%)	25 (7.1)	10 (6.8)	0.92
Diabetes Mellitus (%)	57 (16.1)	20 (13.7)	0.48
History of AF (%)	71 (20.0)	21 (14.4)	0.21
AVN ablation (%)	27 (7.6)	2 (1.4)	0.003*
LVEF - % ± SD	25.3 ±7.7	23.9 ± 7.1	0.06
NYHA Class III/IV (%)	333 (94.1)	128 (87.7)	0.019*
QRS duration – ms ± SD	159 ± 25.4	161 ± 30	0.50
Use of an ACEI/ARB (%)	321 (90.1)	134 (91.2)	0.40
Use of a β-blocker (%)	244 (69.5)	110 (76.9)	0.10
Use of mineralocorticoid antagonists (%)	216 (62.6)	84 (56.4)	0.23

Use of diuretics (%)	317 (92.2)	133 (89.3)	0.21
Use of digitalis (%)	62 (18)	24 (16.1)	0.80
Use of amiodarone (%)	34 (9.7)	25 (17.5)	0.016*
Use of anticoagulation (%)	93 (27.6)	36 (25.2)	0.74
Baseline biochemistry and haematology			
Haemoglobin - g/dL	13.1 ± 1.6	13.5 ± 1.5	0.005*
Sodium - mmol/L	136 ± 7.9	137 ± 3.3	0.27
Urea - mmol/L	10.8 ± 8.6	9.9 ± 5.4	0.23
Creatinine - µmol/L	128 ± 48.5	131 ± 43.8	0.47
Albumin - g/L	38 ± 4.6	38 ± 4.4	0.24
ALT - U/L	27 ± 16	35 ± 43	0.12
ALP - U/L	95 ± 50	96 ± 48	0.84

Two-sided p<0.05

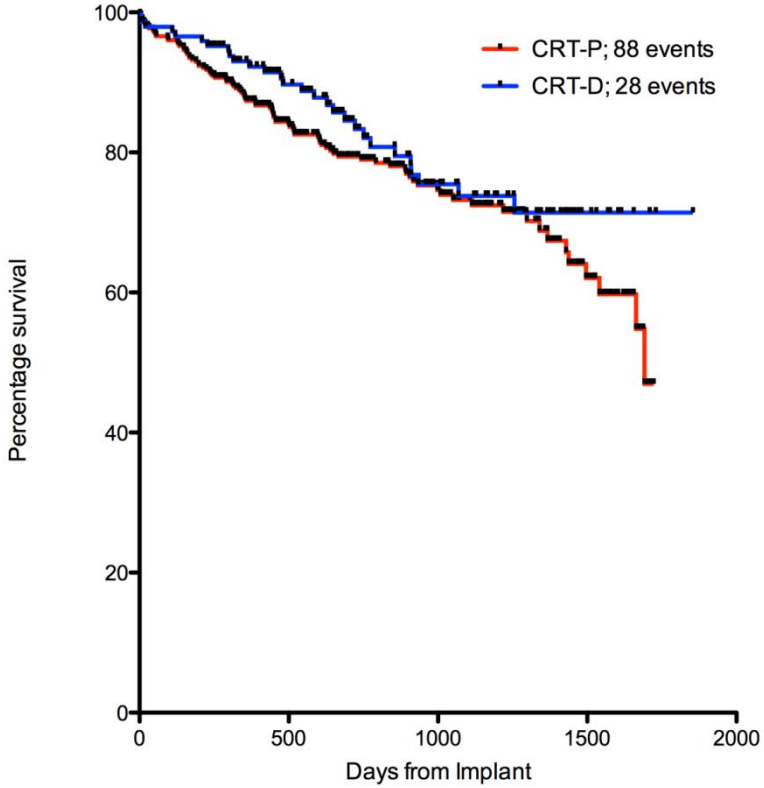
Abbreviations:
ACEI/ARB: angiotensin-converting enzyme inhibitors or angiotensin receptor blockers; AF: atrial fibrillation; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AVN: atrio-ventricular node; CRT-D: cardiac resynchronisation therapy with a defibrillator device; CRT-P: cardiac resynchronisation therapy with biventricular pacing; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; SD: standard deviation

CRT-P versus CRT-D

The mean duration of follow-up was 887±416 days in the CRT-P group and 876±441 days in the CRT-D group [95% confidence interval (CI) for difference: -103 to 81 days, *p*=0.82]. There was a significant functional improvement in NYHA class, with only 29.3% having class III / IV symptoms at last follow-up compared with 92.3% previously. Overall, there were a total of 116 deaths (23.2%): 88 (24.8%) in the CRT-P group and 28 (19.2%) in the CRT-D group. The mean time to death from implantation was 513±420 days overall, 499±435 days in the CRT-P group, and 554±374 days in the CRT-D group (95% CI for difference: -136 to 218 days, *p*=0.54).

Although not significant, at 1 year there was a trend to benefit in the CRT-D group (hazard ratio (HR) for CRT-D: 0.54, 95% CI: 0.27 to 1.07, *p*=0.08). At follow-up of 2 years, the survival benefit afforded by CRT-D was attenuated and insignificant (HR for CRT-D 0.71, 95% CI: 0.43 to 1.17, *p*=0.18) and this continued until the end of all follow-up (HR for CRT-D: 0.76, 95% CI: 0.50 to 1.17, *p*=0.21, **Figure 3**). Adjusting for baseline differences, the HR for CRT-D remained insignificant at all-time points.

Figure 3: Kaplan-Meier survival curve for all-cause mortality across whole study stratified by device type. CRT-P: cardiac resynchronisation therapy with pacing; CRT-D: cardiac resynchronisation therapy with a defibrillator



Number at Risk

Day	0	250	500	750	1000	1250	1500	1750
CRT-P	354	319	240	179	112	69	32	2
CRT-D	146	136	100	68	52	34	11	2

Responders vs. non-responders

In the CRT-D and CRT-P groups, the response rate was 68.3% and 73.4% respectively. There were no differences in the baseline characteristics between responders and non-responders other than slightly more frequent amiodarone use in the non-responders. At 1 year and at 2-year follow-up, non-responders had a higher mortality (HR for death at 1 year 3.85, 95% CI: 1.370 to 10.81, p=0.011 and HR for death at 2 years 2.06, 95% CI: 1.02 to 4.18, p=0.04). Over all follow-up, there was no difference in the survival between the groups (HR for death for non-responders 1.32, 95% CI: 0.73 to 2.39, p=0.36).

Stratifying by device showed that amongst people receiving CRT-P, non-responders did worse at 1 year (HR for death 3.31, 95% CI: 1.01 to 10.86, p=0.048) and at 2 years (HR for death 2.21, 95% CI: 1.01 to 4.88, p=0.049) but not overall. No mortality differences were found between responders and non-responders in the CRT-D group. Comparing the survival of non-responders alone by device (CRT-P vs. CRT-D) revealed no survival differences at any time point.

Factors predicting survival

Table 3 shows results of the univariate and multivariate survival analysis. Younger age, dilated cardiomyopathy, hypertension, higher sodium, lower creatinine, use of angiotensin converting enzyme inhibitors (ACE) or angiotensin receptor blockers (ARB), and the use of β-blockers, all predicted survival. In multivariate analysis, younger age, female gender, hypertension, a higher serum sodium, lower creatinine and β-blocker use were significant predictors of survival. There were no differences in univariate and multivariate factors predicting survival when stratified separately by CRT-P and CRT-D.

Table 3: Univariate and Multivariate predictors of mortality

Predictors	**HR**	**Univariate 95% CI**	***p*-value**	**HR**	**Multivariate 95% CI**	***p*-value**
Age	1.03	1.01 – 1.05	0.003*	1.03	1.00 – 1.05	0.03*
Age >75 years old	1.23	0.82 – 1.85	0.32			
Male Gender	1.62	0.98 - 2.68	0.06	2.09	1.18 – 3.71	0.012*
Atrial Fibrillation	1.40	0.92 – 2.14	0.12			
Ischaemic (vs. dilated) cardiomyopathy	1.46	1.01 – 2.12	0.048*	1.14	0.76 – 1.72	0.52
Diabetes Mellitus	0.86	0.50 – 1.48	0.58			
Hypertension	0.33	0.12 – 0.91	0.032*	0.31	0.12 – 0.86	0.02*
Left Bundle Branch Block	0.65	0.38 – 1.11	0.12			
QRS Width	0.99	0.99 – 1.00	0.61			
Pre-procedure LVEF	0.98	0.96 – 1.00	0.11			
Sodium	0.98	0.97 – 0.99	<0.001*	0.90	0.86 – 0.94	<0.001*
Creatinine	1.01	1.01 – 1.02	<0.001*	1.004	1.007 – 1.009	0.02*
ACEI/ARB use	0.50	0.29 – 0.88	0.016*	0.65	0.35 – 1.20	0.17

β-blocker use	0.63	0.43 – 0.92	0.015*	0.61	0.41 – 0.91	0.014*
Spironolactone use	0.72	0.48 – 1.08	0.11			
CRT-D (vs. CRT-P)	0.76	0.50 – 1.17	0.21	0.76	0.48 – 1.12	0.23

Two-sided p<0.05

Abbreviations:
ACEI/ARB: angiotensin-converting enzyme inhibitors or angiotensin receptor blockers; CI: confidence interval; CRT-D: cardiac resynchronisation therapy with a defibrillator device; CRT-P: cardiac resynchronisation therapy with biventricular pacing; HR: hazard ratio; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association

NICE guidance for ICD implantation

Of the 146 patients that had CRT-D - 49% were for primary prevention and 51% for secondary prevention indications. Virtually all patients (99.3%) with an ICD met NICE guidelines for its implantation. There was no survival difference between those who had CRT-D for either primary or secondary prevention reasons. There was also no survival difference between those with ischaemic or non-ischaemic cardiomyopathy for primary or secondary indications for ICD. Among the 354 patients who received CRT-P, 95 patients (27%) strictly met primary prevention indications for ICD according to NICE guidance. The baseline characteristics of these patients and those who received CRT-D for primary prevention are shown in **Table 4**. Compared to those who received CRT-D, this group of patients were generally older with higher NYHA functional class and poorer baseline status. As expected, there was higher number of deaths in the CRT-P group (HR for death 1.88, 95% CI: 1.15 to 3.08, p=0.01). However, once baseline variables were controlled for, there was no difference in mortality between the groups (HR for CRT-P 1.31, 95% CI: 0.41 to 4.17, p=0.65).

Table 4: Baseline characteristics of CRT-P patients who met primary prevention indications for ICD, and those who received CRT-D for primary prevention

Variable	CRT-P (n=95)	CRT-D (n=74)	*p*-value
Mean age – years ± SD	74 ± 8.1	66 ± 8.6	<0.001*
Male (%)	78 (82.1)	66 (89.2)	0.20
Ischaemic heart disease (%)	95 (100)	46 (62.2)	<0.001*
Hypertension (%)	5 (5.3)	3 (4.1)	0.76
Diabetes mellitus (%)	21 (22.1)	8 (10.8)	0.06
History of AF (%)	13 (13.7)	7 (9.5)	0.40
LVEF - % ± SD	22.2 ± 5.5	23.4 ± 6.1	0.18
NYHA class III (%)	95 (100)	55 (74.3)	0.001*
QRS duration – ms ± SD	160 ± 25	156 ± 28	0.24
Use of ACEI/ARB (%)	84 (88.4)	74 (98.7)	0.02*
Use of β-blocker (%)	69 (72.6)	59 (79.7)	0.34
Use of mineralocorticoid antagonist (%)	57 (60)	42 (56.8)	0.29

Use of diuretics (%)	91 (95.8)	66 (89.2)	0.05
Use of digitalis (%)	17 (17.9)	12 (16.2)	0.75
Use of amiodarone (%)	5 (5.3)	8 (10.8)	0.19
Use of anticoagulation (%)	16 (16.8)	16 (21.6)	0.45
Baseline biochemistry and haematology			
Haemoglobin - g/dL	13.0 ± 1.4	13.6 ± 1.5	0.02*
Sodium - mmol/L	137 ± 3.4	137 ± 2.9	0.80
Urea - mmol/L	11.4 ± 6.4	9.7 ± 5.1	0.06
Creatinine - µmol/L	138 ± 51.2	125 ± 42.4	0.09
Albumin - g/L	37 ± 4.9	39 ± 3.7	0.03*
ALT - U/L	27 ± 16.1	26 ± 14.8	0.94
ALP - U/L	93 ± 45.2	95.0 ± 56.7	0.82

Two-sided p<0.05

Abbreviations:
ACEI/ARB: angiotensin-converting enzyme inhibitors or angiotensin receptor blockers; AF: atrial fibrillation; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AVN: atrio-ventricular node; CRT-D: cardiac resynchronisation therapy with a defibrillator device; CRT-P: cardiac resynchronisation therapy with pacemaker; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; SD: standard deviation

3.7 DISCUSSION

Our single-centre observational study suggests that a potential survival benefit of CRT-D over CRT-P at one year was not significant after longer-term follow-up. Response to CRT predicted survival, but non-responders did not survive longer if they had a CRT-D over a CRT-P device. Multivariate analysis of survival suggested that older men with hyponatraemia and renal dysfunction had the poorest survival, independent of other risk factors, including presence or absence of an ICD. The presence of hypertension suggests good cardiac output and therefore this could account for the improved survival in the multivariate analysis. In our cohort, patients who did not receive an ICD for primary prevention despite meeting NICE guidance for implantation, had a poorer prognosis than those receiving an ICD, but the difference was explained by poorer baseline functional status.

ICDs in patients with heart failure

ICD implantation has escalated over the past 10 years. Observational data from early drug trials in patients with HF suggested that they had a high risk of sudden cardiac death.[215,216] The Sudden Cardiac Death in Heart Failure (SCD-HeFT) trial was the first to show that ICD reduced all-cause mortality in patients with both ischaemic and non-ischaemic cardiomyopathy.[63] In the COMPANION (Comparison of Medical Therapy, Pacing and defibrillation in Heart Failure) trial, all-cause mortality and all-cause hospitalisation were reduced by both CRT-D and CRT-P compared to medical therapy.[84] Although there was some suggested superiority of CRT-D due to the short follow-up, a post-hoc analysis subsequently showed no significant survival differences between CRT-D and CRT-P arms.[89] One of the most important mechanisms of action for the benefit of CRT is reverse remodelling, which takes time to evolve.[217] Given enough time, one may expect a significant reduction in mortality with CRT-P implanted patients and there is currently no robust evidence that the potential early benefit conferred by an ICD is durable.[86,175,177,218]

Studies have demonstrated that in CHF patients who received either ICD or CRT-D for primary or secondary prevention, the most common cause of death was progressive heart failure.[91,92,219] In the prospective study of Thijssen et al that examined the modes of death in 2859 ICD and CRT-D patients over a 14-year period , the annual mortality rate was 5%.[92] The proportion of patients who died suddenly was low and comparable for both primary and secondary ICD and CRT-D patients.[92] The 8-year cumulative incidence of SCD was 2.1% (95% CI 0.3%–4.0 %) in primary prevention ICD patients, 3.2% (95% CI 1.6%–4.8%) in secondary prevention ICD patients, and 3.6% (95% CI 1.8%–5.3%) in CRT-D patients (log rank p = 0.026).[92] A recent small study involving a subgroup of patients post myocardial infarction (MI) with severe left ventricular dysfunction that have a negative electrophysiologic study (EPS) showing no inducible ventricular tachycardia (VT) can do without the protection of an ICD with low rates of arrhythmias or death.[220]

In our study, the potential advantage of a CRT-D device over CRT-P was attenuated after one year. It suggests that in individuals with severe and worsening CHF due to systolic LV dysfunction, CHF complications other than ventricular tachy-arrhythmias contribute importantly to duration of survival. Selected patients may be better served by CRT-P with more aggressive medical treatment enhancing QOL in the longer term. Although CRT-D is still the device of choice for reducing the mortality in the early years of implant, downgrading to a CRT-P at generator change may be a viable option.

CRT-P versus CRT-D: Which device to implant?

Our multivariate analysis suggested that age, gender, blood pressure, serum sodium and serum creatinine were important predictors of outcome. Co-morbidities, such as myocardial infarction (MI) and renal failure play a pivotal role in the prognosis of a patient with CRT-D.[221] Hyponatraemia has also been recognised as an independent predictor of outcome in patients with LV dysfunction and an ICD. Factors such as age, and underlying co-morbidities should

all be taken into account before the decision regarding the type of device to be implanted is made. Existing evidence has showed that the benefits of ICDs in the elderly as well as in women are not well established.[222-225] A recent large prospective registry of ICD patients showed that elderly patients are at increased risk of death compared with their younger counterparts, but the absolute mortality risk was modest when patients are carefully selected.[226] These results may serve as a guide for discussion when elderly ICD candidates are evaluated.

Just over a quarter of our CRT-P patients met NICE indications for implantation of an ICD for primary prevention. An ICD was not implanted on the basis of a discussion between the patient and the physician in charge of their care. As expected, this group of patients had poorer baseline status compared to those who received CRT-D, and thus, a higher number of deaths were observed. However, once baseline co-morbidities were adjusted for; there was no survival difference between the two groups.

Studies have shown that as the severity of heart failure increases, the proportion of sudden cardiac death compared to heart failure-related deaths decreases.[215,216] Newer guidance highlights the lack of data comparing CRT-D and CRT-P directly, and suggests that ICD therapy is favoured in younger patients with life expectancy estimated at greater than a 1 year, who has milder symptoms and less co-morbidity.[174] Our results add weight to these recommendations. Consideration of co-morbidities and known predictors of mortality will help to identify patients who are most likely to derive relative benefit of from different devices.

Cost-benefit

A large cost-effectiveness meta-analysis comparing medical therapy, CRT-P, and CRT-D, estimated implantation of a new CRT-P system to cost just over £5000, and a CRT-D system to cost over £17000. It suggested that CRT-P was cost-effective at a threshold of £20,000 per quality adjusted life year (QALY), but that CRT-D was effective only at a threshold of £40,000 per QALY.[208] A Belgian cost benefit-analysis concluded that although there may be a survival

benefit from CRT-D over CRT-P, the incremental clinical benefit appeared too marginal to warrant a three-fold higher device price for CRT-D.[227] Identifying the patients most likely to benefit from a CRT-D device is essential. The higher number of CRT-P implants in our study reflects the reimbursement situation in UK, and thus will be difficult to translate to countries like the USA or Germany, where the majority of the implanted devices are CRT-D.

3.8 LIMITATIONS

This is a single centre retrospective study with prospective follow-up. Device prescription was not randomised and patients with poor functional status and limited expected survival were likely implanted preferentially with CRT-P. This opens the door for bias, although we did try to control for this statistically. We did not define the mode of death in all patients or identify CRT-D associated complications (e.g. inappropriate shocks). The lack of survival difference between CRT-D and CRT-P shown by our study may be confounded by underlying patients' characteristics. For example, the use of ACE-I, ARB, or β-blockers which had been shown to prevent worsening CHF and SCD may reduce the survival differences between the two groups.[55] However, 'all-cause mortality' has been used widely as an endpoint in CRT trials.

The main strengths of our study were the long-term follow-up of a mean of 29 months, and the representation of 'real-world' practice. We defined 'CRT responders' as those who underwent an improvement in NYHA functional class at the end of follow-up. The definition of response to CRT varies widely between studies. A recent analysis of the most-cited publications on CRT suggested that agreement between different methods defining CRT response was poor 75% of the time, and strong only 4% of the time.[228] In a practical setting, the definition of CRT response should extend to measure patient outcomes; i.e. improvement in symptoms, QoL, and duration of life.

The issue of whether to implant CRT-P or CRT–D remains controversial, and a definitive randomised trial comparing these treatments may never be conducted. An observational study

with prospective follow-up such as ours provides a useful perspective for both clinicians deciding on an individual patient basis, and for health policy decisions and funding.

3.9 CONCLUSIONS

In our real-world observational study of 500 patients with CHF, CRT-D did not offer an additional survival advantage over CRT-P at longer term follow-up; as the clinical benefit of a defibrillator apparently attenuated with time. Our results add to existing literature suggesting that CRT-D confers an early survival benefit, but this was lost in the longer-term. Balancing patients' co-morbidities and the potential for device related complications against the potential benefit from the defibrillator is recommended on a case-by-case basis.

Chapter 4 APPLICABILITY OF A RISK SCORE FOR PREDICTION OF THE LONG-TERM BENEFIT OF THE IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR IN PATIENTS RECEIVING CARDIAC RESYNCHRONIZATION THERAPY

4.1 PREFACE

Data from major randomised trials have shown that the ICD provides a meaningful and significant reduction in mortality in patients with ICM and NICM and LVEF ≤30% - 35% as part of primary prevention strategy.[60-63,67,84] All patient candidates for CRT are theoretically indicated for an ICD. Therefore, the addition of the ICD can also potentially decrease the risk of SCD in CRT patients.[87]

To date, there are no randomised controlled trials that directly compare CRT-P to CRT-D. It remains to be determined which CRT patients get the highest benefit from the ICD. In routine clinical practice, 37% of primary-prevention ICD patients experience potentially lifesaving ICD intervention in the first 5 years after implantation, but the remaining 63% did not require ICD intervention.[229] Therefore, different risk scores capable of estimating mortality risk of ICD patients have been developed to identify the patients who will actually benefit from ICD treatment.[93,137,138,230,231]

The aims of the research presented in this chapter were:

- To assess whether the Goldenberg score can accurately predict all-cause mortality risk of patients receiving CRT
- To identify CRT patients who are more likely to benefit from the addition of the ICD

The study showed that patients with standard indication for CRT with a low Goldenberg risk score are more likely to benefit from the presence of the ICD. The benefit of the ICD in low-risk-score CRT patients is most obvious in the first few years after implantation but attenuates over time. The benefit of the ICD in addition to CRT in patients with a high Goldenberg risk score or severe renal dysfunction is limited. HF patient due for CRT implantation should be made aware that the benefit of adding ICD decreases with increasing number of comorbidities to a point where patients will cease to benefit from it.

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Contribution of Candidate:

Khang-Li Looi was involved in the data collection and analysis, as well as in developing arguments and writing of the manuscript for publication.

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4.2 ABSTRACT

Aims: The Goldenberg risk score, comprising five clinical risk factors (NYHA class>2, atrial fibrillation, QRS duration>120 ms, age>70 years, urea>26 mg/dL), may help identify patients in whom the survival benefit of the defibrillator may be limited. We aim at assessing whether this score can accurately predict the long-term all-cause mortality risk of patients receiving cardiac resynchronisation therapy (CRT), and identify those who are more likely to benefit from the defibrillator.

Methods: In this retrospective observational cohort study, 638 patients with ischaemic or non-ischaemic dilated cardiomyopathy who had CRT-D (n=224) versus CRT-P (n=414) implantation were prospectively followed-up for survival outcomes. The long-term outcome of patients with CRT-D vs. CRT-P was compared within risk score categories and in patients with severe renal dysfunction. Mean follow-up in surviving and deceased patients was 62.7 and 32.5 months, respectively.

Results: This score showed higher discriminatory performance in CRT-D vs. CRT-P patients (AUC 0.718±0.041 vs. 0.650±0.032, respectively, p=0.001). In those with scores 0-2, a CRT-D device decreased mortality rates in the first four years of follow-up compared with CRT-P (11.3% vs. 24.7%, p=0.041), but this effect attenuated with longer follow-up duration (21.2% vs. 32.7%, p=0.078). In this group, the benefit of CRT-D during follow-up was seen after adjusting for traditional mortality predictors (HR 0.339, p=0.001). No significant differences in mortality rates were seen in patients with score ≥3 (57.9% with CRT-D vs. 56.9%, p=0.8) and those with severe renal dysfunction (92.9% in CRT-D vs. 76.2%, p=0.17). Similar results were seen following propensity score matching.

Conclusion: A simple risk stratification score comprising five clinical risk factors may help identify CRT patients who are more likely to benefit from the presence of the defibrillator.

4.3 INTRODUCTION

Cardiac resynchronisation therapy (CRT) is an accepted treatment for patients with medically refractory congestive heart failure (CHF).[83,84,86,87,177] Although the CRT-defibrillator (CRT-D) has been shown to decrease mortality risk and CHF events compared with the implantable cardioverter-defibrillator (ICD) alone in patients with standard indications for CRT,[83,84,87,177] the benefit of the CRT-D compared with CRT-pacemaker (CRT-P) has not been properly evaluated. A post-hoc analysis of the COMPANION trial showed no significant survival difference between CRT-D and CRT-P patients in New York Heart Association (NYHA) class IV[89], whilst a more recent systematic review suggested some benefits of CRT-D over CRT-P in the reduction of 1-year all-cause death rate.[214] A recent observational study did not show any significant survival advantage of CRT-D compared with CRT-P at relatively long-term follow-up.[90]

Multiple risk scores have been developed to estimate mortality rates of potential ICD recipients.[93,137,138,230,231] Goldenberg et al. suggested that a simple risk score can identify patients who will probably not benefit from the ICD despite fulfilling implantation criteria.[93,230] In their post-hoc analysis of MADIT-II, those patients with 0-2 risk factors demonstrated a clear survival benefit from the ICD whereas in those with ≥3 risk factors the survival benefit was non-existent.[93,230] The benefit in those with zero risk factors was only seen in the long-term.[230]

Our study aims at assessing whether the Goldenberg score can accurately predict all-cause mortality risk of patients receiving CRT and identify those who are more likely to benefit from the addition of the defibrillator. We hypothesize that CRT patients with a low Goldenberg score are more likely to benefit from the defibrillator, in accordance with the findings of Goldenberg et al. in a non-CRT context.[93]

4.4 METHODS

Study design

Single-centre retrospective observational cohort study of patients with ischaemic or non-ischaemic dilated cardiomyopathy having CRT-D or CRT-P implantation between January 2005 and December 2011, with prospective follow-up. The indication for CRT-P vs. CRT-D was based on the National Institute for Health and Care Excellence (NICE) guidance [https://www.nice.org.uk/guidance/ta120] (**Table 5)**.

However, the final choice was modified, as needed, according to the preference of the patient following a discussion with the attending physician on the pros and cons of having a defibrillator and respective implications. Survival data were assessed. The Goldenberg score was obtained by summing the risk factors identified in each patient, as explained by Goldenberg et al[93]: NYHA functional class >2, presence of atrial fibrillation (AF, identified at the time of admission for the procedure), QRS duration >120 ms, age >70 years and blood urea nitrogen >26 mg/dL. Patients were divided into two groups: those with a risk score 0-2 and those with a score ≥3. This cut-off was used based on the findings of Goldenberg et al, who found a significant benefit of the ICD in patients with a risk score 0-2 but no benefit in those with a score ≥3. The long-term outcome of patients with CRT-D and CRT-P was assessed and compared within risk categories and in very high risk patients, defined as those with creatinine ≥2.5 mg/dL and/or urea ≥50 mg/dL, as performed by Goldenberg et al.[93] This study complies with the *Declaration of Helsinki* and was approved by our institutional ethics review board.

Table 5: Indications for ICD and CRT treatment for people with heart failure who have left ventricular ejection fraction ≤35%, according to NICE UK guidelines (as seen in https://www.nice.org.uk/guidance/ta120)

	NYHA class			
QRS interval	**I**	**II**	**III**	**IV**
<120 ms	ICD if there is a high risk of sudden cardiac death			ICD and CRT not clinically indicated
120-149 ms without LBBB	ICD	ICD	ICD	CRT-P
120-149 with LBBB	ICD	CRT-D	CRT-P or CRT-D	CRT-P
≥150 ms with or without LBBB	CRT-D	CRT-D	CRT-P or CRT-D	CRT-P

Abbreviations:
CRT-Cardiac resynchronisation therapy; ICD-Implantable cardioverter-defibrillator; LBBB-Left bundle branch block

Patients' eligibility criteria and follow-up

Between January 2005 and December 2011, 638 patients with ischaemic or non-ischaemic dilated cardiomyopathy were submitted to CRT implantation at our tertiary centre: CRT-D in 224 and CRT-P in 414. Left ventricular lead location was uniform between groups: the most frequent location was the lateral branch of the coronary sinus (approximately half of the cases in both groups), followed by the anterolateral and posterolateral branches, respectively. Patients with CRT-D had their devices programmed at the discretion of the operating physician. Follow-up visits were performed at 1 and 3 months after CRT implantation and, in general, every 6 months thereafter. Unscheduled visits and/or remote ICD interrogations were performed in case of ICD shocks in patients with CRT-D devices. CRT optimisation was routinely performed in all patients in the first month after implantation.

Data Collection

The following data were collected: group characterization with information on complete medical history, medication, clinical and echocardiographic data, and blood tests performed at the time of admission for CRT implantation, and device characteristics; follow-up all-cause mortality.

Parameters included in the Goldenberg risk score

In our cohort, 21% of patients had atrial fibrillation at admission, 51.1% were ≥70 years old, 42% had blood urea nitrogen levels >26 mg/dL, 91.4% were in NYHA class >2 and 91.4% had QRS duration >120 ms.

The Goldenberg risk model was originally derived from a primary prevention ICD cohort. However, all criteria were still considered meaningful in a CRT context, despite the fact that we would expect the majority of CRT patients to have a QRS duration >120 ms and to be in NYHA class >2.

In fact, although most patients who receive CRT treatment have a QRS duration in excess of 120 ms, CRT implantation still represents a class IIa indication for heart failure patients with QRS duration <120 ms, reduced ejection fraction and expected high percentage of ventricular pacing in order to decrease the risk of worsening heart failure.[85] There were 55 patients in our cohort (8.6%) who fulfilled these criteria. These were patients in complete heart block who required standard pacing but were given a CRT due to significant left ventricular systolic dysfunction. It is unknown whether this specific group of patients is at high risk of ventricular arrhythmias and therefore it remains to be determined whether they should receive a CRT-D rather than a CRT-P.

Furthermore, results of the REVERSE and MADIT-CRT trials, published in 2008 and 2009, respectively, demonstrated the usefulness of CRT in patients in NYHA functional class I and II. As such, although the majority of our patients were in NYHA class ≥3 (automatically fulfilling one of the criteria of the Goldenberg score), 8.6% of the cohort received CRT despite being in class I or II. These procedures were performed in 2010 and 2011, following the publication of the previously mentioned studies. The relevance of this parameter is further highlighted by the fact that NYHA class III patients did not get any survival benefit from the ICD in the largest primary prevention ICD trial ever conducted – the Sudden Cardiac Death in Heart Failure (SCD-HeFT) Trial.

Study Endpoints

The primary endpoint of this study was all-cause mortality during follow-up. Analysis was performed according to the intention-to-treat principle.

4.5 STATISTICAL ANALYSIS

Statistical analysis was done using *IBM SPSS Statistics*, v.22. When needed, baseline characteristics are described with mean ± standard deviation for continuous data and counts and proportions for categorical data. The Kolmogorov-Smirnov test was used to test the normal

distribution of continuous variables. The Chi-square test, Student's t-test and non-parametric equivalent tests were used when appropriate. Calibration of the Goldenberg model was evaluated through the Hosmer and Lemeshow goodness-of-fit test, while its discriminatory power in the overall cohort and both study groups was assessed by calculating the area under each operating characteristic curve (ROC). ROC curves were compared using Medcalc Software for Windows. Univariate analysis was carried out to compare mortality rates in CRT-D vs. CRT-P patients according to the Goldenberg score (0-2 vs. ≥3) and Kaplan-Meier curves were created to illustrate and compare unadjusted cumulative all-cause mortality between device groups according to their baseline risk score, with p-values by the log-rank test. Proportional hazards regression was performed to assess the impact of the type of device on mortality rates when adjusted for traditional mortality predictors. In addition, to further reduce potential treatment selection bias and differences in baseline characteristics between patients with CRT-D and CRT-P, propensity score matching was performed separately in patients with a Goldenberg score 0-2 and those with a score ≥3. A logistic regression model was used to calculate the propensity score using the following variables: age, gender, aetiology (ischaemic vs. non-ischaemic), NYHA class, LV ejection fraction, blood urea nitrogen, glomerular filtration rate, haemoglobin, atrial fibrillation, treatment with beta-blockers and angiotensin converting enzyme inhibitors or angiotensin receptor blockers. P values <0.05 (two-sided) were considered statistically significant.

4.6 RESULTS

Patients were followed for an average of 48.9±27 months (median 50 months; range 1-116 months). Mean follow-up in the 347 surviving patients (54.4%) was 62.7±22.6 months, whereas survival time in the 291 who died (45.6%) was 32.5±23.3 months. **Table 6** shows the baseline characteristics of all CRT-D and CRT-P patients. **Table 7** and **Table 8** compare the

baseline characteristics of CRT-D and CRT-P patients based on the Goldenberg score (0-2 and ≥3).

Table 6: Baseline characteristics of entire cohort (638 patients)

	CRT-D (n=224)	CRT-P (n=414)	P value
Age (years)	66	69.8	<0.001
Male gender	88.4%	72.9%	<0.001
LV ejection fraction (%) *	24.5	25.7	0.051
NYHA class ≥3	85.8%	94.7%	<0.001
Ischaemic aetiology	60.8%	47.7%	0.002
Atrial fibrillation	20.1%	21.5%	0.7
Diabetes Mellitus	19.2%	27.5%	0.061
QRS duration (ms)	157.2	159.2	0.4
AV node ablation	2.4%	7.5%	0.01
Left bundle branch block pattern	94.2%	90.3%	0.13
Haemoglobin at admission (g/dL)	13.5	13.1	0.026
GFR at admission (mL/min)	53.7	51.5	0.15
BUN at admission (mg/dL)	26.6	30.3	0.019

Sodium at admission (mmol/L)	136.8	136.3	0.4
Albumin at admission (g/L)	38.3	37.7	0.2
Very high risk**	8.5%	12.0%	0.17
Beta-blockers	79.4%	69.3%	0.012
ACEI/ARA-II	94.1%	92%	0.4
Response to CRT	67.5%	65.5%	0.7
Mean follow-up (months)	49.2	48.7	0.8

**LV function was assessed within three months of implantation*

***Defined as creatinine ≥2.5 mg/dL and/or blood urea nitrogen ≥50 mg/dL*

Abbreviations:
ACEI-angiotensin-converting-enzyme inhibitor; ARA-II–type 2 angiotensin receptor antagonists; BUN–Blood urea nitrogen; GFR–Glomerular filtration rate; LV–Left ventricular

Table 7: Baseline characteristics of patients with Goldenberg score 0-2 (214 patients)

	CRT-D (n=99)	CRT-P (n=115)	P value
Age (years)	59.4	61.5	0.11
Male gender	83.5%	67.3%	0.011
LV ejection fraction (%) *	23.7%	26.6%	0.011
NYHA class ≥3	70.9%	84.7%	0.033
Ischaemic aetiology	46.8%	33%	0.061
Atrial fibrillation	3.8%	5.9%	0.5
Diabetes Mellitus	9.8%	23.3%	0.06
QRS duration (ms)	152.4	148.2	0.34
AV node ablation	2.5%	4.7%	0.5
Left bundle branch block pattern	94.2%	91.4%	0.54
Haemoglobin at admission (g/dL)	13.6	13.5	0.4
GFR at admission (mL/min)	64	67.3	0.15
BUN at admission (mg/dL)	19.5	18.1	0.11

Sodium at admission (mmol/L)	137	137.4	0.45
Albumin at admission (g/L)	38.3	38.9	0.55
Very high risk**	0%	0%	-
Beta-blockers	81%	73.8%	0.27
ACEI/ARA-II	98.7%	94%	0.11
Response to CRT	61.5%	68%	0.4
Mean follow-up (months)	58.4	54.6	0.3

**LV function was assessed within three months of implantation*

***Defined as creatinine ≥2.5 mg/dL and/or blood urea nitrogen ≥50 mg/dL*

Abbreviations:
ACEI-angiotensin-converting-enzyme inhibitor; ARA-II–type 2 angiotensin receptor antagonists; BUN–Blood urea nitrogen; GFR–Glomerular filtration rate; LV–Left ventricular

Table 8: Baseline characteristics of patients with Goldenberg score ≥3 (424 patients)

	CRT-D (n=125)	CRT-P (n=299)	P value
Age (years)	71.4	73.4	0.025
Male gender	91.6%	75.1%	<0.001
LV ejection fraction (%) *	24.9	25.6	0.43
NYHA class ≥3	96%	99.2%	0.044
Ischaemic aetiology	72.7%	52.6%	0.001
Atrial fibrillation	33.3%	28.3%	0.35
Diabetes Mellitus	26.9%	28.2%	0.8
QRS duration (ms)	159	163.1	0.16
AV node ablation	2%	9.3%	0.018
Left bundle branch block pattern	93.2%	89.3%	0.31
Haemoglobin at admission (g/dL)	13.4	12.8	0.007
GFR at admission (mL/min)	44	45.2	0.5
BUN at admission (mg/dL)	33	35.1	0.44
Sodium at admission (mmol/L)	137	136	0.3

Albumin at admission (g/L)	38.6	37.2	0.047
Very high risk**	16%	16.9%	0.85
Beta-blockers	78.8%	69.4%	0.071
ACEI/ARA-II	93.9%	91.9%	0.52
Response to CRT	70.3%	64.5%	0.4
Mean follow-up (months)	42.5	46.7	0.18

**LV function was assessed within three months of implantation in all patients*

***Defined as creatinine ≥2.5 mg/dL and/or blood urea nitrogen ≥50 mg/dL*

Abbreviations:
ACEI-angiotensin-converting-enzyme inhibitor; ARA-II–type 2 angiotensin receptor antagonists; BUN–Blood urea nitrogen; GFR–Glomerular filtration rate; LV–Left ventricular

In those with a risk score 0-2, patients implanted with a CRT-D compared with CRT-P were more often males, had a significantly lower LV ejection fraction and lower NYHA class. There was a trend towards a lower incidence of Diabetes Mellitus and a higher incidence of ischaemic cardiomyopathy in this group. Among patients with a risk score ≥3, those given a CRT-D were two years younger on average and more often males, had a higher incidence of ischaemic cardiomyopathy, higher haemoglobin values and had had AV node ablation less often.

All-cause mortality prediction with the Goldenberg score

This score's discriminatory power was assessed by calculating the area under the curve for follow-up all-cause mortality in the overall cohort - 0.677±0.022, $p<0.001$ – and both study groups - 0.718±0.041, $p<0.001$ in CRT-D patients, and 0.650±0.032, $p=0.001$ in those with CRT-P ($p=0.001$ for comparison). The higher discriminative performance of the Goldenberg score in CRT-D patients, compared with CRT-P, was seen at the end of the first and fourth year of follow-up. This confirmed the ability of the model to assign a higher probability of mortality to non-survivors than to survivors, especially in CRT-D patients. The *p*-value for the Hosmer-Lemeshow goodness-of-fit test confirmed the good calibration of the Goldenberg score for all-cause mortality prediction in the entire cohort ($p=1.0$), indicating that the overall model fit was good and confirming the agreement between predicted and true probabilities of mortality.

All-cause mortality in CRT-D vs. CRT-P patients

Incidence of the primary endpoint according to risk category (Goldenberg score 0 to 5) in the overall cohort and both study groups (CRT-D and CRT-P) is described in **Table 9**. As expected, patients with higher Goldenberg score had higher mortality rates.

Table 10 reports all-cause mortality rates in CRT-D vs. CRT-P patients in the sub-groups with a Goldenberg score 0-2 and ≥3, respectively, and in very high-risk patients.

Table 9: Incidence of the primary and secondary endpoints with increasing risk score

Overall cohort (n=638)							
Risk score	**0**	**1**	**2**	**3**	**4**	**5**	**p-value**
n	**2**	**45**	**168**	**212**	**172**	**39**	
Follow-up all-cause mortality	0%	11.1%	32.4%	50.5%	60.5%	76.9%	<0.001
1-year mortality	0%	2.2%	5.4%	11.7%	14.6%	28.2%	0.001
4-year mortality*	0%	7.4%	21.8%	41.8%	52.4%	60%	<0.001
CRT-D patients (n=224)							
Risk score	**0**	**1**	**2**	**3**	**4**	**5**	**p**
n	**2**	**20**	**77**	**65**	**50**	**10**	
Follow-up all-cause mortality	0%	5%	25.9%	53.8%	58%	80%	<0.001
1-year mortality	0%	0%	2.6%	12.3%	12%	20%	0.161
4-year mortality*	0%	0%	14.3%	52.3%	54%	77.8%	<0.001
CRT-P patients (n=414)							
Risk score	**0**	**1**	**2**	**3**	**4**	**5**	**p**
n	**0**	**25**	**91**	**147**	**122**	**29**	
Follow-up all-cause mortality	-	13.6%	37.4%	48.9%	61.4%	76.9%	<0.001
1-year mortality	-	4.5%	7.3%	11.3%	15.6%	30.8%	0.016
4-year mortality*	-	13.5%	27.1%	37.6%	52.4%	53.8%	0.001

**Analysis performed for patients who were followed for at least four years or who died in the first four years of follow-up*

Table 10: All-cause mortality rates and device-related complications in CRT-D vs. CRT-P patients in the sub-groups with a Goldenberg score 0-2 and ≥3

Goldenberg score 0-2			
	CRT-D	**CRT-P**	**P-value**
All-cause mortality	21.2%	31.7%	0.078
1-year mortality	2.4%	6.7%	0.16
4-year mortality*	11.3%	24.7%	0.041
Goldenberg score ≥3			
	CRT-D	**CRT-P**	**P-value**
All-cause mortality	57.9%	56.9%	0.8
1-year mortality	13.1%	14.9%	0.65
4-year mortality*	54.7%	45.6%	0.13

**Analysis performed for patients who were followed for at least four years or who died in the first four years of follow-up*

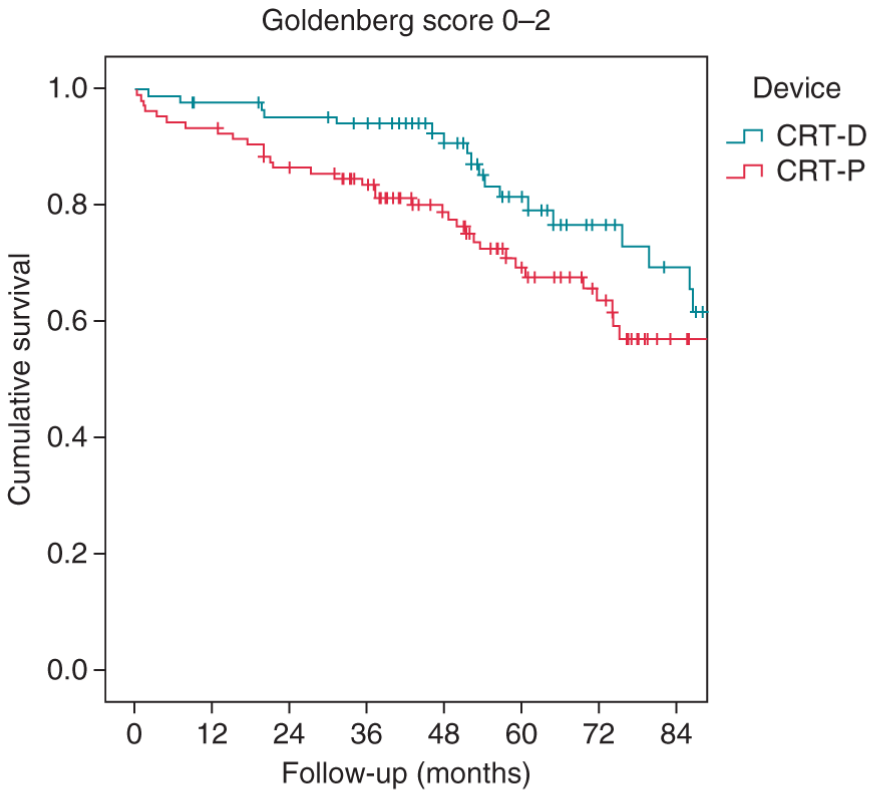
In those with scores between zero and two, a CRT-D device decreased mortality rates in the first four years of follow-up compared with CRT-P (11.3% vs. 24.7%, p=0.041), but this effect attenuated with longer follow-up duration (21.2% vs. 32.7%, p=0.078). No significant differences in mortality rates were seen in patients with score ≥3 (57.9% with CRT-D vs. 56.9%, p=0.8) and those with severe renal dysfunction (92.9% in CRT-D vs. 76.2%, p=0.17). **Figure 4** illustrates unadjusted cumulative all-cause mortality between patients with CRT-D vs. CRT-P according to their baseline risk score (0-2 and ≥3).

In patients with a Goldenberg score of 0-2, implanting a CRT-D device rather than a CRT-P decreased mortality rate even after adjusting for traditional mortality predictors. The corresponding proportional hazards regression model included the type of device (CRT-D vs. CRT-P, HR 0.339, 95% CI 0.178-0.642, p=0.001), left ventricular ejection fraction (HR 0.939, 95% CI 0.898-0.982, p=0.006), aetiology (ischaemic vs. non-ischaemic, HR 1.978, 95% CI 1.054-3.710, p=0.034) and glomerular filtration rate (HR 0.978, 95% CI 0.959-0.998, p=0.033), excluding age, gender and NYHA class. The type of device (CRT-D vs. CRT-P) did not influence mortality rates in those with a Goldenberg score ≥3. Likewise, very high-risk patients had very high mortality rates regardless of the type of device (92.9% in CRT-D vs. 76.2% in CRT-P, p=0.17).

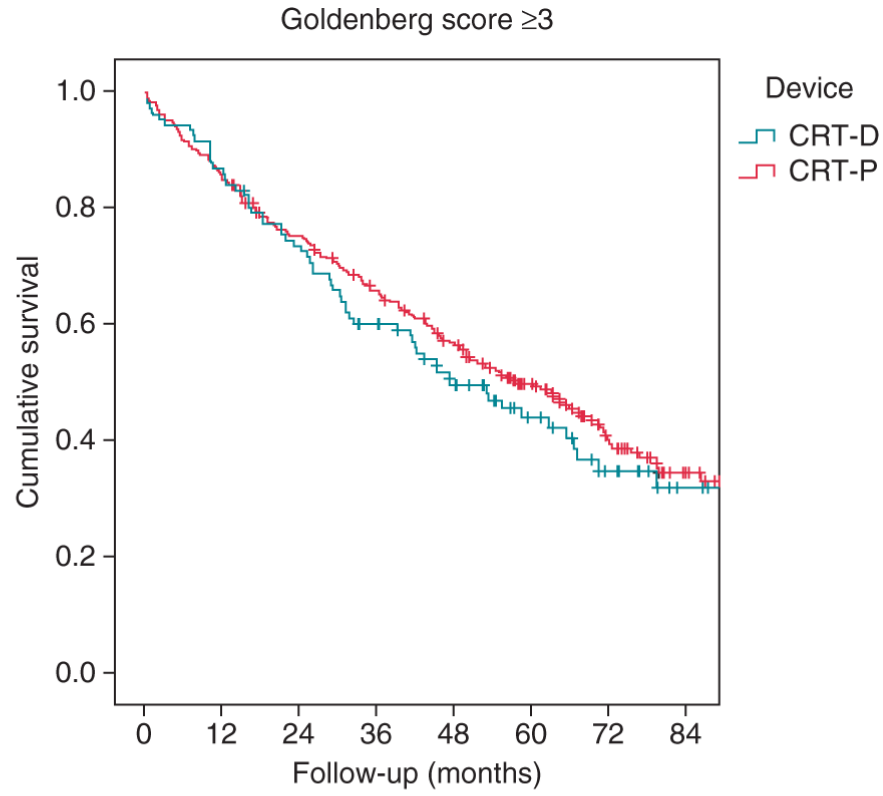
After propensity score matching, the study cohorts consisted of 55 CRT-D vs. 55 CRT-P patients with a Goldenberg score 0-2, and 89 CRT-D vs. 89 CRT-P patients with a risk score ≥3. In both Goldenberg score groups, the difference in mean probability of receiving a defibrillator between CRT-D and CRT-P patients was lower than one per cent. There were no significant differences in baseline characteristics between propensity-matched CRT-D and CRT-P patients in both Goldenberg risk score groups, indicating that they were properly balanced (**supplementary data Table 11 and Table 12**). In those with a Goldenberg risk score 0-2, CRT-D patients had a lower follow-up mortality rate compared with those receiving CRT-

P (20% vs. 38.2%, p=0.036). Furthermore, the type of device (CRT-D rather than CRT-P) was still included in the proportional hazards regression model after adjusting for the probability of receiving a defibrillator, in addition to the parameters mentioned previously (HR 0.375, 95% CI 0.187-0.751, p=0.006). However, in those with a higher risk score, no significant differences in mortality rates were seen (56.2% in CRT-D patients vs. 50.6%, p=0.45).

Figure 4: Cumulative all-cause mortality in patients with risk score 0-2 (log-rank p-value 0.084) and ≥3 (log-rank p-value 0.44) according to device: CRT-D vs. CRT-P



Number at risk							
Months	12	24	36	48	60	72	84
CRT-D	82	79	75	54	38	23	18
CRT-P	97	88	80	63	44	32	21



Number at risk							
Months	12	24	36	48	60	72	84
CRT-D	93	76	62	44	27	15	7
CRT-P	228	196	167	136	95	57	31

4.7 DISCUSSION

Main findings

We showed that a simple risk score can help us identify patients who are more likely to benefit from the addition of the defibrillator. In fact, patients with 0-2 risk factors had a significant mortality benefit in the first four years of follow-up if implanted with a CRT-D rather than CRT-P, while patients with ≥3 risk factors did not get any additional mortality benefit. Likewise, patients with creatinine values ≥2.5 mg/dL and/or urea ≥50 mg/dL had very high mortality rates regardless of the type of device. The benefit of the CRT-D (vs. CRT-P) in those with low risk score was independent of other traditional predictors such as age, gender, aetiology, LV ejection fraction, NYHA class, and renal function, and was also seen after propensity score matching. Our findings were consistent with those reported by Goldenberg *et al.*[93,230] This study further suggests that the benefit of the ICD in CRT patients attenuates over time, as attrition rates in those receiving CRT-D accelerated after the first four years of follow-up.

CRT-D vs. CRT-P: is the defibrillator always of added value?

The ICD is an effective treatment for the prevention of sudden cardiac death (SCD) and the addition of the ICD can potentially decrease the risk of SCD in CRT recipients.[84,87] However, it remains to be determined which patients get the highest benefit from the defibrillator and whether some patients fulfilling implantation criteria do not get any benefit at all. Previous investigators developed risk scores capable of estimating all-cause mortality risk of ICD recipients.[93,137,138,230,231] In a sub-analysis of MADIT-II, Goldenberg *et al.* have shown that a simple risk score constructed as a count of five risk factors could differentiate between patients who would benefit from the ICD vs. those who would not.[93,230] Our current data suggests this risk model may be also useful for identifying patients who should have a defibrillator in

addition to CRT vs. those who should be treated with a CRT-P even when fulfilling ICD implantation criteria. In fact, long-term mortality rates in patients with ≥3 risk factors and those with severe renal dysfunction were high regardless of the ICD. Although this does not constitute unequivocal evidence in itself that the ICD did not prolong their lives, it does suggest that, if it did, it did so to a minimum extent.

There has not been any randomised clinical trial comparing CRT-D vs. CRT-P and it is not likely that such trial will ever be performed. Although the COMPANION trial suggested that the addition of a defibrillator to CRT incrementally increased the survival benefit, as compared with optimal pharmacologic therapy,[84] a post-hoc analysis of this trial has shown that CRT-P was not significantly different from CRT-D for either time to sudden death or CHF death in NYHA class IV patients.[89] A systematic analysis to assess the therapeutic effects of CRT vs. CRT-D in 3403 patients with LV impairment and CHF suggested that CRT-D reduced all-cause death by 8.42% compared with CRT, a benefit that was only seen after 1-year follow-up.[214] We corroborate their findings, as the benefit of the ICD in addition to CRT in those with lower risk score only became significant after the first year in the present study. A recent study compared the long-term prognosis of 266 CRT-D vs. 108 CRT-P patients and concluded that CRT-D may be preferable (mortality rate 6.6 vs. 10.4%/year in CRT-D vs. CRT-P, respectively),[232] yet there were substantial differences between groups that could have affected the analysis. These findings were contradicted by Schuchert et al.[100] Moreover, other studies suggested that in patients with CHF who receive either ICD or CRT-D for primary or secondary prevention, the most common cause of death is progressive heart failure rather than SCD.[91,92] As the benefit of the CRT is enhanced as reverse remodelling occurs, especially in those with non-ischaemic dilated cardiomyopathy,[177,217] and patients who demonstrate recovery of LV function from CRT may be at lower risk of arrhythmic mortality,[233] it is debated whether ICD therapy will have a persistent effect on late survival in responders to CRT. In our cohort, the

addition of the ICD still associated with lower 4-year mortality risk (p=0.026) in those with a Goldenberg score 0-2 and response to CRT (defined as an improvement in NYHA class), but this benefit attenuated with time (p=0.149 for the whole duration of follow-up) and no such benefit was seen in CRT-responders with a higher Goldenberg score.

Physicians should be aware that the benefit of the ICD decreases with increasing number of comorbidities to a point where patients may cease to benefit from it.[234] This consideration is particularly relevant given the higher cost of the CRT-D and the higher risk of device-related complications, in particular infection and lead dysfunction.[100]

4.8 LIMITATIONS

The long duration of follow-up is the main strength of our study. However, this investigation shares the common limitations of all retrospective studies. As therapy prescription (CRT-D vs. CRT-P) was not randomised, differences in mortality risk between groups may have been confounded by patients' characteristics. Also, physicians are often more likely to recommend CRT-P rather than CRT-D to patients who have a higher comorbidity burden or frailty index. Confounders and selection bias should therefore be kept in mind when interpreting the results of our study. However, as a randomised study comparing CRT-D vs. CRT-P is very unlikely to be performed, all studies comparing these two devices will share this limitation given their non-randomised nature. Nevertheless, the lack of consensus regarding the benefit, or lack thereof, of the ICD in addition to CRT in previous observational studies comparing CRT-D vs. CRT-P may in fact support the feasibility of a randomised study on this subject. We tried to mitigate this limitation by performing propensity score matching and multivariate analysis, which suggested the choice of device (CRT-D rather than CRT-P) was associated with lower mortality rate in those with lower *Goldenberg* risk score independently of traditional mortality predictors such as age, gender, aetiology, LV ejection fraction, NYHA class and renal function.

4.9 CONCLUSIONS

A simple risk score comprising five clinical risk factors can be used to identify CRT patients who would benefit from the addition of the defibrillator vs. those in whom the additional survival benefit of the ICD may be limited or non-existent. The validation and potential optimisation of this score in future studies may have an impact on patient selection for these therapies.

4.10 SUPPLEMENTARY DATA

Table 11: Baseline characteristics of CRT-D vs. CRT-P patients with a Goldenberg score 0-2 after propensity score matching

	CRT-D (n=55)	CRT-P (n=55)	P value
Age (years)	59.4	60.8	0.4
Male gender	80%	85.5%	0.4
LV ejection fraction (%) *	24.4	25	0.6
NYHA class ≥3	85.5%	81.8%	0.6
Ischaemic aetiology	45.5%	47.3%	0.8
Atrial fibrillation	3.6%	9.1%	0.2
QRS duration (ms)	154	147	0.2
Haemoglobin at admission (g/dL)	13.6	13.8	0.3
GFR at admission (mL/min)	66	66	0.8
BUN at admission (mg/dL)	6.7	6.5	0.7
On beta-blockers	80%	80%	1.0
On ACEi/ARA-II	100%	96.4%	0.4
Follow-up duration (months)	59.1	56	0.5

Abbreviations:
ACEI-angiotensin-converting-enzyme inhibitor; ARA-II–type 2 angiotensin receptor antagonists; *BUN–Blood urea nitrogen; GFR–Glomerular filtration rate; LV–Left ventricular*.

Table 12: Baseline characteristics of CRT-D vs. CRT-P patients with a Goldenberg score ≥3 after propensity score matching

	CRT-D (n=89)	CRT-P (n=89)	P value
Age (years)	59.8	60.9	0.9
Male gender	94.4%	96.6%	0.5
LV ejection fraction (%) *	25	24	0.6
NYHA class ≥3	97.8%	100%	0.2
Ischaemic aetiology	75.3%	76.4%	0.9
Atrial fibrillation	31.5%	25.8%	0.6
QRS duration (ms)	159	164	0.2
Haemoglobin at admission (g/dL)	13.5	13.2	0.2
GFR at admission (mL/min)	44	44	0.8
BUN at admission (mg/dL)	11.6	11.9	0.7
On beta-blockers	78.7%	78.7%	1.0
On ACEi/ARA-II	94.4%	95.5%	0.6
Follow-up duration (months)	42.7	54	0.007

Abbreviations:
ACEI-angiotensin-converting-enzyme inhibitor; ARA-II–type 2 angiotensin receptor antagonists; *BUN–Blood urea nitrogen; GFR–Glomerular filtration rate; LV–Left ventricular*

Chapter 5 USE OF DEVICE THERAPIES IN HEART FAILURE PATIENTS IN NEW ZEALAND

5.1 USE OF ICD AND CRT IN HEART FAILURE PATIENTS IN THE WORLD

Despite the recommended guidelines, the implant rates in ICDs and CRT devices in HF patients are variable in the "real-world" clinical practice.

In the United States, ICD implantation per million population is 5x higher than in other Western European countries. In year 2000, approximately 40,000 patients (185 ICD implants per million) received prophylactic ICDs in the United States compared to only 13,160 ICDs (31 ICD implants per million) in Western Europe.[235] In 2005, the United States Centres for Medicare Service (CMS)s have approved and expanded their coverage for primary ICD implantation based on best practice guidelines. Subsequent to this, the American Heart Association and the American College of Cardiology (AHA/ACC) have summarised current Class I indications for primary ICD implantation as following[236,237]:

- Patients with LVEF ≤35% due to prior MI who are at least 40 days post-MI and are in NYHA functional class II or III (Level of evidence A)
- Patients with NICM who have LVEF ≤ 35% and who are in NYHA functional Class II or III (level of evidence B)
- Patients with LV dysfunction due to prior MI who are at least 40 days post- MI, have an LVEF ≤ 30% and are in NYHA functional class I. (level of evidence A)
- Patients with nonsustained ventricular tachycardia (NSVT) due to prior MI, LVEF ≤ 40%, and inducible VF or sustained VT at electrophysiological study. (level of evidence B).

This expansion of guidelines has been accompanied by rapid growth of implantations of ICDs and CRT-Ds. The National Cardiovascular Data Registry's (NCDR) ICD Registry assessed the temporal trends in patient characteristics and outcomes among patients aged ⩾65 years with LVEF ⩽35% who underwent primary prevention ICD implantation, including those receiving concomitant CRT between 2006 and 2010 showed the proportion of patients aged ⩽75 years

increased from 47.4% to 48.5% and those aged ⩾85 years increased from 6.5% to 7.6% ($p<0.001$).[238] The proportion of women undergoing ICD implantation increased modestly (27.3% to 28.4%, $p=0.001$) during these times. More CRT-D devices and fewer single chamber ICDs were used over time.[238] Between 2006 and 2010, there were also noted significant improvements in all outcomes, including 6-month all-cause mortality (7.1% in 2006, 6.5% 2010; adjusted odds ratio[OR], 0.88; 95% confidence interval [CI], 0.82–0.95), 6-month rehospitalisation (36.3% in 2006, 33.7% in 2010; adjusted OR, 0.87; 95% CI, 0.83–0.91), and device-related complications (5.8% in 2006, 4.8% in 2010; adjusted OR, 0.80; 95% CI, 0.74–0.88).[238]

However, some specific patient populations, such as those patients in the early timeframe following MI, do not benefit from ICD implantation, despite being at high risk for SCD.[239,240] Given the high cost of ICD devices, payers and policymakers have an obligation to ensure ICD implantations are placed appropriately. A recently published study by Al-Khatib et al. has raised the concerns that up to 22.5% of patients did not meet evidence-based criteria for ICD implantation in the NCDR ICD Registry.[241] Indeed, in 2010, the Department of Justice (DOJ) began investigating ICD implantations based on the medical necessity and timing of the procedures. The findings reported by the researchers in combination with the DOJ investigations has resulted in a dramatic decline in the number of patients undergoing ICD implantation in the United States.[242,243]

Usually new treatment modalities are implemented gradually, and usage increases further when such treatments are included in published guidelines. However, the EuroHeart survey has shown that implementation of device therapy for patients with HF in Europe occurred slowly.[244] In addition, there are often unexplained differences in the use of proven therapies for chronic HF between European countries. [245] These differences may be partly explained by financial constraints.

From year 2004-2008, the Eucomed Registry showed that the rates of implantation of devices for HF have markedly increased but there are large differences between European countries.[246] More specifically, implantation rates of ICD and CRT-D have increased enormously. When all CRT implants are considered, the proportion of patients that receive CRT-D (instead of CRT-P) has increased as well[246]. The findings are in line with data from the United States for the period 1997–2004, in which a steady increase in the use of devices for HF was observed.[247] There remained large differences observed between European countries in the rates of device implantation. In Germany the ICD implantation rate in 2008 was 264/million, compared with only 63/million in Spain.[248] One may also question the low numbers in some European countries since device therapy is recommended by the current HF Guidelines. There may indeed be a big gap between the number of patients who fit the criteria for ICD implantation and the number who actually get such a device. One recent data showed that low use of device therapy may be more common in women, blacks, and elderly patients.[249] In addition, recent data from a large European CRT survey showed that the mean age of HF patients in whom a CRT-D device is implanted is markedly lower than those in whom a CRT-P is implanted (68 vs. 75 years) indicating that the decision about which device to implant is partly determined by age.[250] Similarly, in the 2014 European Heart Rhythm Association (EHRA) White Book, it was reported that a total of 51,274 CRT devices were implanted in 1701 national centres in year 2013.[251] There was a decrease in both absolute numbers of implants and the rate of implants per million population compared with 2012, whereas a steady growth had been witnessed from 2009. The ratio of CRT-D/CRT-P implants was 2.6 with a mean of 44 CRT-Ds and 17 CRT-Ps per million population.[251] Italy had the highest implantation rates of CRT-D, followed by Israel, the Czech Republic, and Germany.[251] Denmark had the highest rate of CRT-P implantations and the United Kingdom (UK) had the second highest.[251]

By comparison with the ACC/AHA guidelines, the National Institute for Health and Clinical Excellence (NICE) guideline in the United Kingdom (UK) is more conservative. The 2006 UK NICE guidelines recommended ICD implantation in patients who had sustained MI) at least 40 days previously with an LVEF ⩽30% with QRS duration on 12-lead ECG ⩾120 ms.[252] It was also advised that patients with an LVEF ⩽35% and non-sustained ventricular tachycardia on ambulatory ECG and a positive electrophysiological test should also receive an ICD.[252] This published NICE guidance was drawn up before the findings of the SCD-HeFT trial could be assimilated and thus only address primary prevention in ICM and not NICM.[252]

Subsequently the 2008 European and North American guidelines support prophylactic ICD implantation in NICM patients with LVEF<35% and NYHA class II-III HF symptoms leading to increasing implantation in NICM patients.[253] The 2012 European Society of Cardiology guidelines for HF do not differentiate their recommendations on the basis of the aetiology of the LV impairment.[55] The updated UK NICE technology appraisal (TA314) guidance published in 2014 now base stratification of HF patients with LVEF ⩽35% on QRS duration and NYHA functional class, with ICD implantation being recommended in patients in NYHA class I–III and QRS duration >120ms.[254] It is also recommended that where patients meet LVEF and NYHA criteria, but have QRS <120ms, they should receive an ICD if there is high risk of SCD. Importantly, the updated guidelines no longer exclude patients with NICM during the decision-making process.[254]

In the first National Report of Pacemaker, ICD and CRT: Two Year National Survey for 2003 and 2004, the implantation rates for ICDs and CRT in the UK were amongst the lowest in Western Europe.[255] Since then the use of ICD in HF patients due to reduced LVEF is now a mainstay of treatment with >5000 devices implanted during 2012, a rise of >10% from 2009.[256] Cubbon et al. assessed the ability of NICE TA314 guidelines in >1000 HF patients and found that between 30% and 60% of unselected HF patients were now eligible to receive an ICD,

depending on the attribution of high-risk status to patients with narrow QRS interval.[257] The 11th annual report for the National Cardiac Rhythm Management (CRM) Device Audit showed that from April 2015 to March 2016 the overall ICD and CRT-D implant rate in UK is gradually increasing, but remains one of the lowest in Europe.[258] In contrast, the overall implant rate for CRT is increasing steadily, and currently the UK has the third highest CRT implant rate in Europe.[258] Implant rates vary considerably between the UK nations. Scotland implants approximately half the number of ICDs and CRT devices per head compared to England, Wales and Northern Ireland.[258]

In Asia, there has been controversy about benefits of ICD. When criteria from the MADIT-II trial were applied to a Japanese cohort, eligible patients who did not undergo ICD implantation had better survival than the historical Western MADIT-II population.[259] In a subgroup analysis of Western data on SCD, Asian Americans were at lower risk of SCD compared with White Americans.[260] These studies have contributed to the perception that Asians may be at lower risk of SCD and thus less likely to benefit from ICD therapy. Indeed, limited published crude implantation rates suggest a low and heterogeneous uptake within Asia, with ICD implantation rates per million inhabitants ranging from 0.5 in Philippines to 45.9 in Japan.[261]

Regional differences in healthcare systems and the availability of government reimbursement for primary prevention ICD implantation could influence ICD implant rates in Asia.[262] Other factors may also contribute to the disparity in ICD utilisation in Asia. Socioeconomic barriers or cultural differences in device knowledge or perception may limit the application of device therapy in Asia, even in the face of proven outcome benefits. In the ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) registry, 5276 patients with symptomatic HF and reduced LVEF from 11 Asian regions and across 3 income regions (high: Hong Kong, Japan, Korea, Singapore, and Taiwan; middle: China, Malaysia, and Thailand; and low: India, Indonesia, and Philippines) were studied.[263] In this registry, ICD implantation was found to be associated with

reduced risks of both all-cause mortality and SCD but ICD utilisation within Asia is low (12%) with marked disparity across geographic regions and socioeconomic status.[263] Higher ICD utilisation was directly related to higher socio and national economic status, presumably reflecting in part, the cost burden of ICD devices. Lack of knowledge about device therapy was a barrier to patients' acceptance of ICD implantation, underscoring the need for better patient education.[263]

ICD and CRT are expensive therapies, and not all HF patients who qualify based on the published guidelines should necessarily receive such a device. Indeed, health-care systems and governmental bodies are increasingly conscious of the associated costs of this device therapy. Targeted educational efforts are also warranted to improve both physicians' and patients' understanding of the preventive role of ICDs as lifesaving devices, particularly in enabling patients to make an informed decision about its usage.

5.2 TRENDS OF USE OF ICD/CRT IN NEW ZEALAND

New Zealand is a developed country and geographically comprises two main landmasses - the North Island and the South Island. In June 2016, the population of New Zealand was estimated at 4.69 million and was increasing at a rate of about 2.1% per year.[264]

While the clinical indications for ICD therapy to reduce mortality in a wide range of patients at increased risk of SCD are now widely accepted, it is not clear that clinical practice is consistent with these guidelines. Currently there are four tertiary referral hospitals (Auckland City Hospital, Wellington Hospital, Waikato Hospital and Christchurch Hospital) and 2 regional cardiac centres (North Shore Hospital and Tauranga Hospital) in New Zealand that offer ICD and CRT implantation. The ICD and CRT implant rates remain low in New Zealand with treatment gaps and variations. The current ICD implant rate in New Zealand (41/million population) is significantly lower compared with Australia (145/million), the United States (577/million), and Western Europe (140/million).[265-268]

A retrospective audit was conducted by Larsen et al. to address the use of ICDs in two of the four tertiary referral hospitals offering this service in New Zealand over the period from 2000 to 2007.[265] Over the 8-year study period, there were 702 patients received their first ICD either at Wellington Hospital or Auckland City Hospital. The follow-up time was 40 months (interquartile range 18–64 months). Less than a third of these devices were implanted for primary prevention (439 patients, 27%) and these primary prevention patients were younger (mean age 49 years vs. 54 years, p=0.001), and included more females (p=0.02).[265] Patients receiving devices for primary prevention were more likely to have either NICM (p=0.0001) or a hypertrophic cardiomyopathy (p=0.003), and were more likely to have LVEF <30% (p=0.0001).[265]

There was a marked increase in both number and rate of new implants across the study period. The implant number and rate both peaked in 2004 at 123 devices and 44 devices per million respectively[265]. After inclusion of Christchurch Hospital and Waikato Hospital implant figures, the national implant rate increased from 18 per million in 2000 to 49 per million in 2006.[265] The national data showed that the implant rate in Auckland and Wellington was slightly lower than in the other two centres. The percentage of implants for primary prevention ICDs showed an increase across the study period, from 24% in 2000 to 37% in 2007.[265] Over the study period, 74% of implanted devices were single chamber ICDs, 23% were dual chamber and 3% were CRT devices. CRT devices were first implanted in 2003, and while the percentage of these devices being implanted increased, they still accounted for < 5% of new implanted devices in 2006 and 2007.[265]

In recent years, CRT has emerged as a key player in the treatment of HF. Based on clinical evidence of efficacy and effectiveness, indications for CRT are clearly defined in consensus guidelines on HF management.[269,270] However, the implementation of such indications is hampered by the high upfront costs of CRT devices, among other factors. In New Zealand, a

large number of HF patients would potentially fulfil international guidelines criteria for these devices. Considering current workforce and funding constraints, the published 2010 New Zealand guidelines have more restrictive recommendations. These guidelines currently recommends primary prevention ICD in patients with ICM of at least 1 month after acute MI or NICM present for at least 3 months, LVEF ⩽30% measured ⩾3 months after optimal HF treatment and at least 3 months remote from any revascularisation procedure.[271] This is different from the international guidelines in terms of the LVEF cut-off point and was based primarily on resource concerns. Additionally, primary prevention ICD is not recommended routinely for patients ⩾ 75 years of age. Other criteria qualifying for CRT-D implantation included LVEF ⩽35% at least >6 weeks of optimal medical HF treatment, whose QRS duration on electrocardiogram (ECG) is >149 ms or is 120–149 ms with two additional criteria for dys-synchrony on echocardiogram (aortic pre-ejection delay >140 ms, interventricular mechanical delay >40 ms, or delayed activation of the posterolateral left ventricular wall), who are NYHA Class II/III, have had no major cardiovascular event in the prior 6 weeks and who are in sinus rhythm. In line with other guidelines, there should be no major comorbidity that would reduce survival to ⩽ 18 months for those considered for CRT-D implantation.[271]

At Christchurch Hospital, a retrospective audit of CRT implants from year 2000 and a prospective assessment of 10 consecutive CRT implants through to year 2007 identified only 78 cases.[272] In Auckland, the first CRT implant occurred at Green Lane Hospital (GLH) in the year 2000, and until 2003 a single physician performed device implantation. The service was relocated from Green Lane Hospital to Auckland City Hospital in 2004, and since then the service has expanded. The referral catchment for device implantation includes Auckland District Health Board (DHB), Counties Manukau DHB, Northland DHB, and until mid-2012 Waitamata DHB and Hawke's Bay DHB, with a combined population of approximately 1.79

million. Between year 2000 and April 2011, 159 CRT procedures were performed on 139 patients. Of all the procedures 63% had new device implants, and 23% were upgraded from a pacemaker or ICD to CRT and this represented the largest series of CRT procedures published in New Zealand.[273]

The New Zealand Cardiac Implanted Device Registry is built on the All New Zealand Acute Coronary Syndrome – Quality Improvement (ANZACS-QI) platform that uses a web-based data collection platform to collect information on patients receiving implanted devices. From year 2014 to 2015, participation in the registry is voluntary, therefore this dataset does not represent every device implanted during this period at these hospitals. Each participating centre receives a monthly report detailing the number of patients registered in the Device registry and dataset completion rates. Data are entered by medical and cardiac physiology staff at the time of procedure, and included basic demographic details. The primary patient symptom, aetiology and most significant documented ECG finding and the device type are recorded. Perioperative complications defined as within 24 hours of the procedure were also collected. The first description of data on new pacemaker implants between 1st January 2014 and 1st June 2015 from this Registry has been recently published.[274] The proportion of CRT-P devices recorded during this study period was relatively low (n=32, 2%) compared to international registries.[274] The Device registry also collects data on ICD implants but two high volume implanting hospitals were not utilising the Device registry during the study period, therefore those procedures have not been reported.

The Device registry is supported by the New Zealand National Cardiac Clinical Network and Heart Rhythm NZ for use to capture all pacemaker and ICD implants in New Zealand public hospitals. Since 2016, all implant centres in New Zealand have started to capture and report implantation using this registry.

There are limitations with this Device Registry. This registry is voluntary, and there is no routine audit to determine overall levels of accuracy of data entered. In addition, the proportion of patients entered into the registry by participating hospitals is not monitored. This limits the ability to examine implant rates and to examine equity of access to different types of devices across the country. The Device registry allows capture of post-discharge complications, but currently many of the records are incomplete and this data has therefore not been reported.

Complete clinical data for most patients were not available on the Device Registry at the start of this candidature, so a retrospective review of all patients receiving their first ICD/CRT implant at the 4 tertiary hospitals (Auckland City Hospital[ACH], Christchurch Hospital, Waikato Hospital, Wellington Hospital) and 2 regional cardiac centres (North Shore Hospital and Tauranga Hospital) between 1 January 2007 and 31 May 2015 was conducted to understand the ratio of ICD/CRT implant rates across the country. Repatriation of these complex devices' implantation from tertiary to a regional cardiac centre i.e. Tauranga Hospital occurred in year 2009 and in mid-2012 for North Shore Hospital. Ethics approval of the study was obtained from the Central Health and Disability Ethics Committee (Ethics ref: 15/CEN/58/AM02).

Data on indications for ICD/CRT implantation and co-morbidities, details of the type of device, and follow-up details including complications, hospitalisations and deaths were requested from the implanting centres. Prior to the Device Registry each implant centres have their own way of collecting data. **Figure 5**, **Figure 6** and **Figure 7** showed the total number of implants of the 6 centres for ICD, CRT-D and CRT-P in HF patients for the year 2007-2015. These graphs showed a marked increase in number for CRT-D and CRT-P across the study period. However, there was missing records in the number of implants of ICD/CRT-D for year 2007-2008 and in CRT-P for year 2010-2012 at Wellington Hospital. Relevant medical histories, ECGs and relevant echocardiographic parameters including LVEF were also missing in some patients

from Waikato, Wellington and Christchurch Hospitals. This required the candidate to extensively search to source all relevant information. However, these were also incomplete despite the candidate has contacted each implant centres. This is especially relevant to the study findings, because determination of number of implants was based on completeness and accuracy of this documentation.

Given the limitations, the candidate concentrated the recruitment and selection of HF patient cohorts, clinical data and outcomes in the Northern Region of New Zealand. All these data were collected through medical charts review. For the clinical outcomes of interest including hospitalisation and mortality, these were identified using the administrative data of Ministry of Health (MoH) and National Minimum Datasets [NMDS] inpatient hospitalisation data via National Health Index (NHI) linkage as well as the New Zealand Mortality Collection Data.

In the following section of this chapter, all the studies presented below described the trends and utilisations as well as outcomes of HF patients with ICD/CRT-D and CRT-P in the Northern Region of New Zealand.

Figure 5: Total number of implantable cardioverter defibrillator (ICD) in heart failure patients from the 6 implant centres: Year 2007-2015

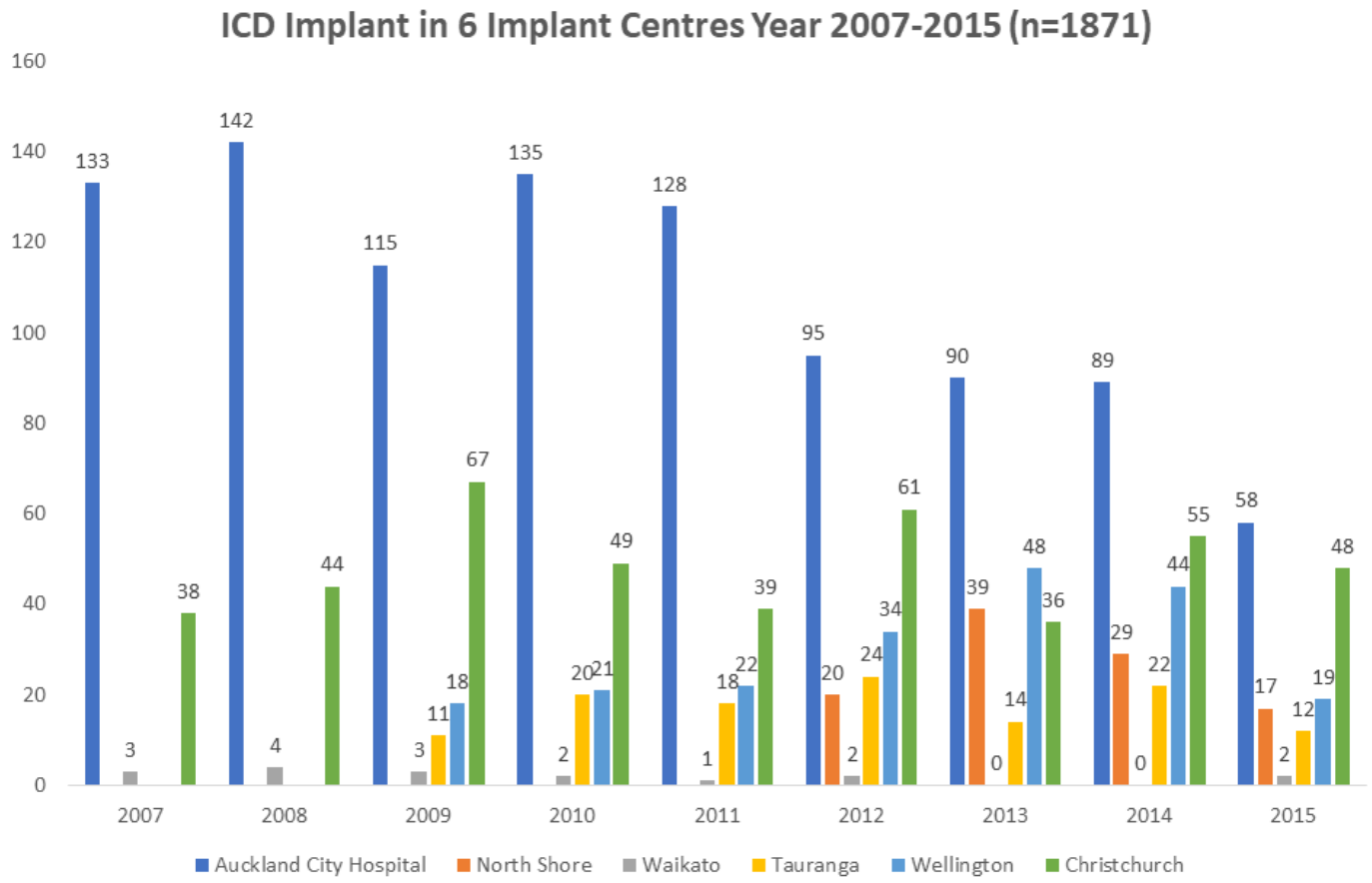


Figure 6: Total number of cardiac resynchronisation therapy with defibrillator (CRT-D) in heart failure patients from the 6 implant centres: Year 2007-2015

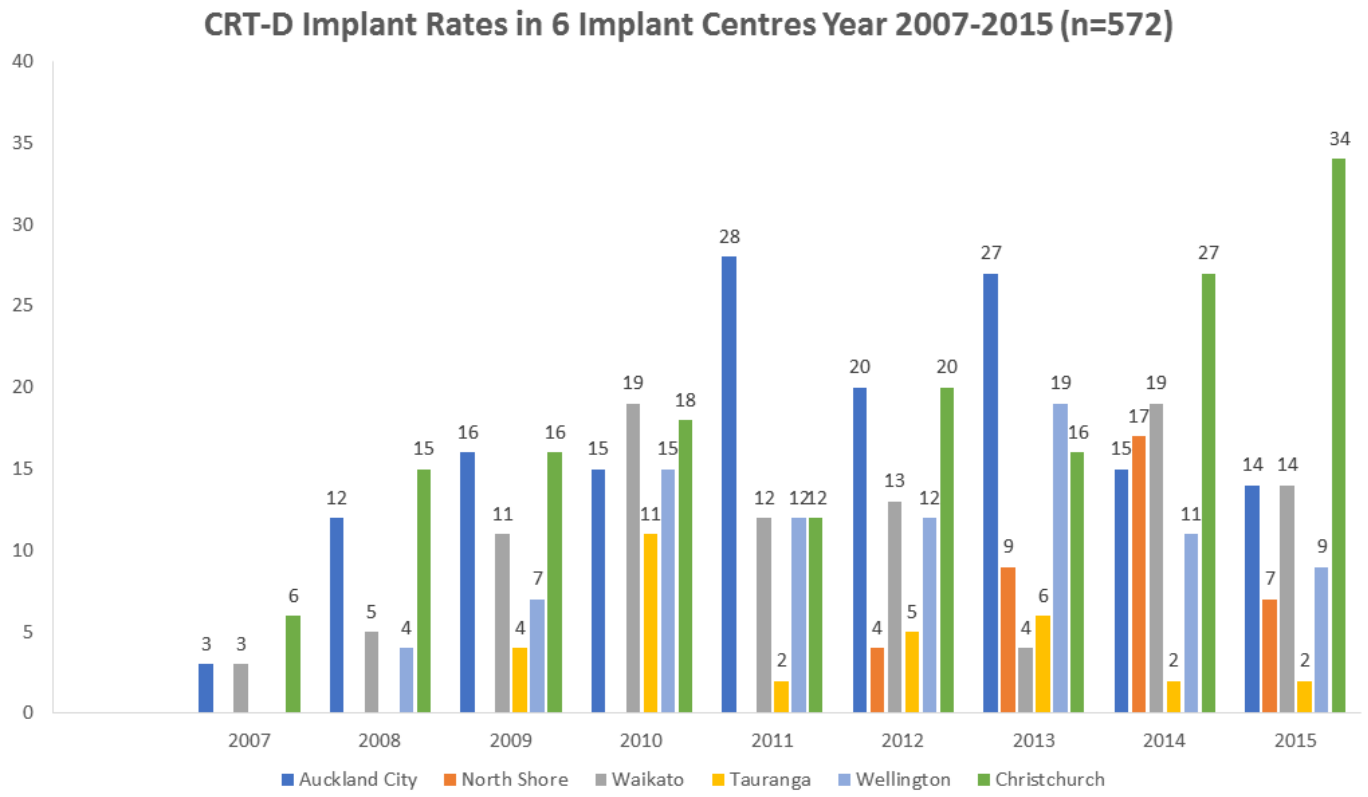
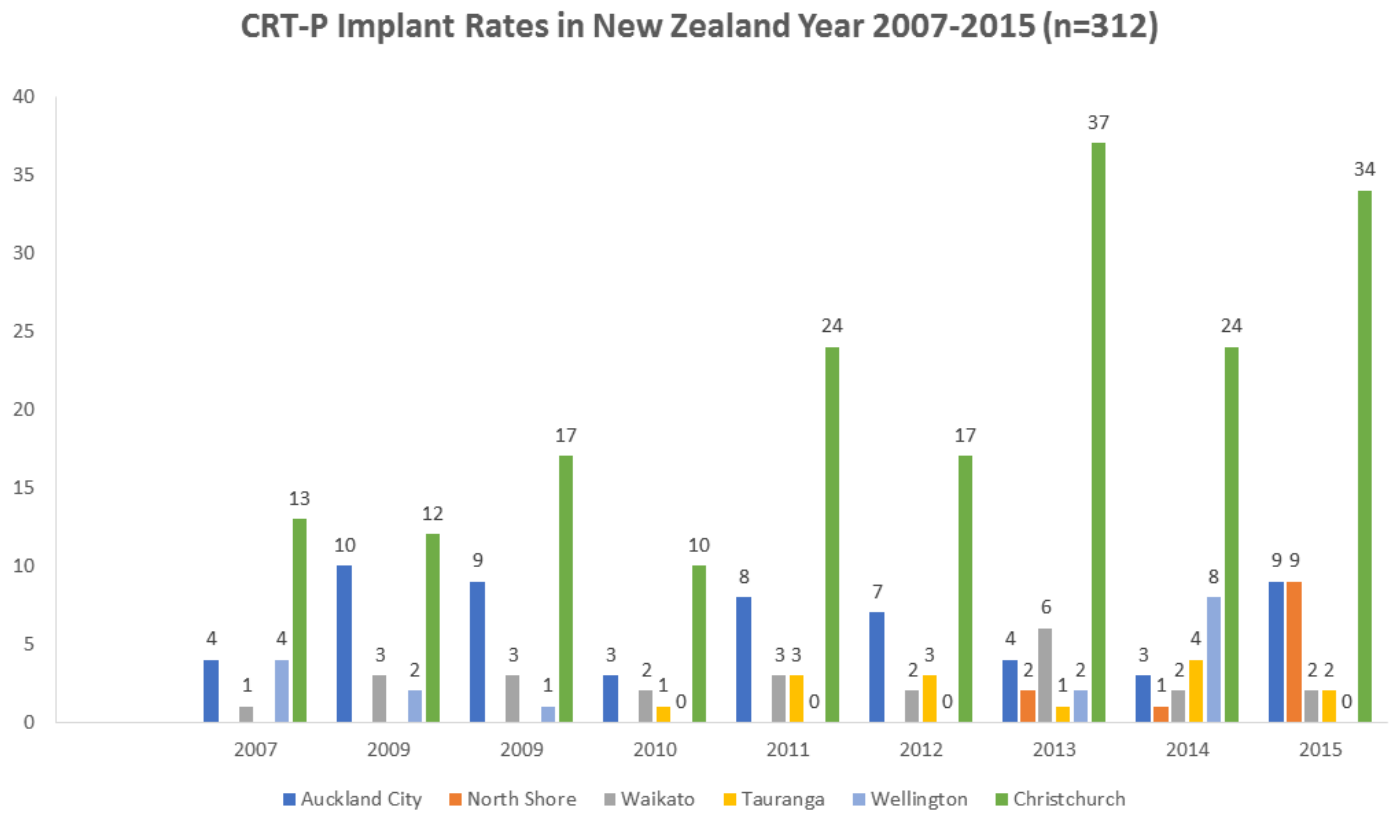


Figure 7: Total Number of Cardiac Resynchronisation Therapy with pacemaker (CRT-P) in Heart Failure Patients from the 6 Implant Centres: Year 2007-2015



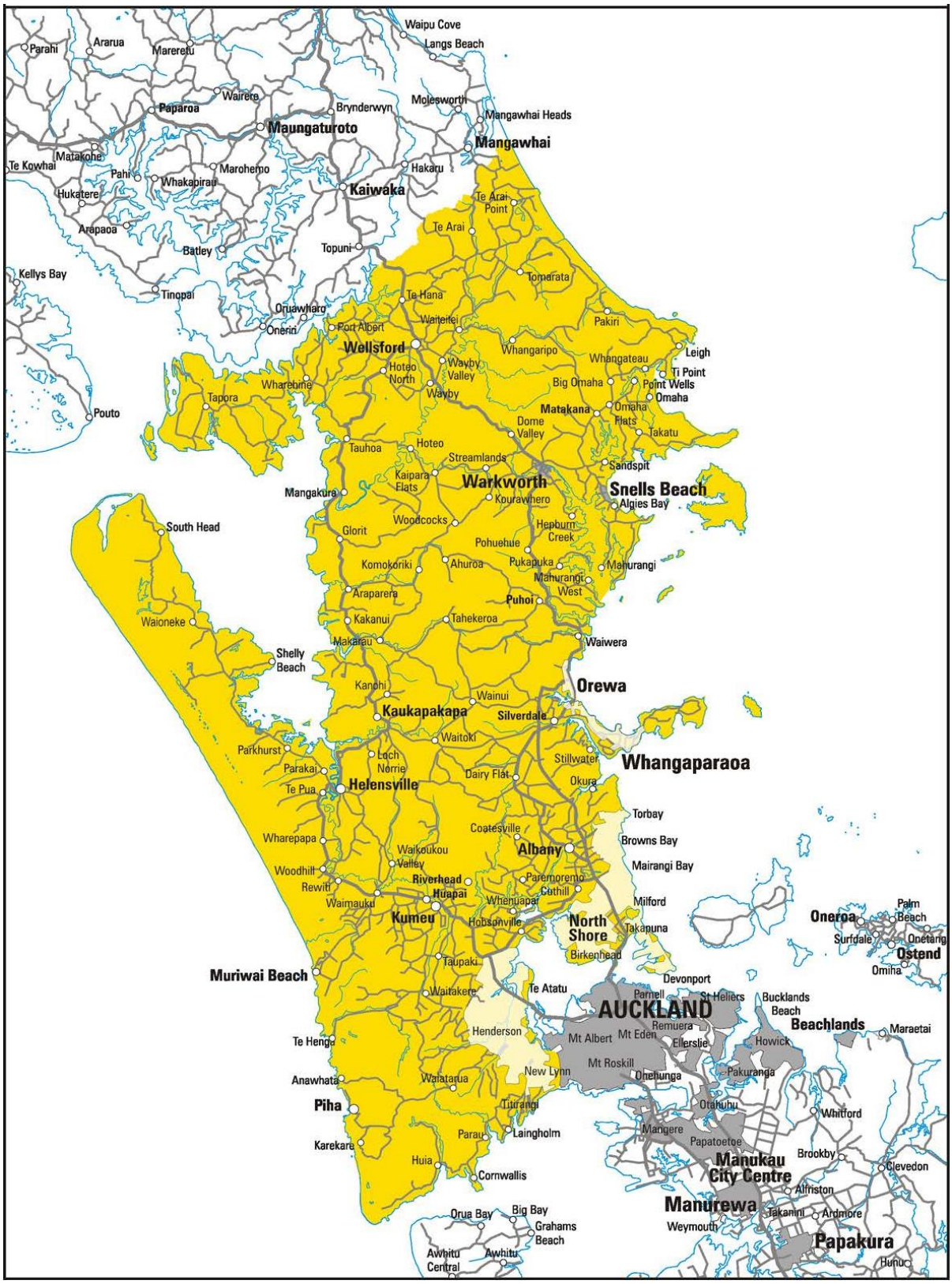
Additional analysis: Implantation of complex cardiac implantable electronic devices: Provision of service at a Regional Cardiac Centre

Due to the limited number of trained healthcare professionals, the implantation of the complex devices such as ICDs/CRTs is usually performed in tertiary cardiac centres. Having understood the trends of ICD/CRT use in HF patients in New Zealand, we sought to examine the impact of repatriating these complex devices implantation from a tertiary hospital to a regional cardiac centre on implant numbers and complications.

Waitemata District Health Board (WDHB) serves the communities of Rodney, North Shore and Waitakere at Auckland (**Figure 8**). With more than 580,000 people, WDHB is the largest New Zealand DHB by population (60% New Zealand European, 18% Asian, 10% Māori, 10% Pacific peoples).

In the past, all WDHB patients who required ICD/CRT would have to be referred to Auckland City Hospital (ACH). From mid-2012 repatriation of these procedures to WDHB occurred after an appointment of an electrophysiologist. We examined the de novo implantation of ICD and CRT, upgrade from pacemaker to ICD and upgrade from pacemaker/ICD to CRT of all WDHB patients from 2007 till mid-2015. The total number of implants and complication rates at both sites were compared. These data were obtained via review of clinical records held on electronic Clinical Record Information System (CRIS).

Figure 8: Waitemata District Health Board (WDHB) Catchment Area



Source: Ministry of Health. https://www.health.govt.nz/new-zealand-health-system/key-health-sector-organisations-and-people/district-health-boards/location-boundaries-map.

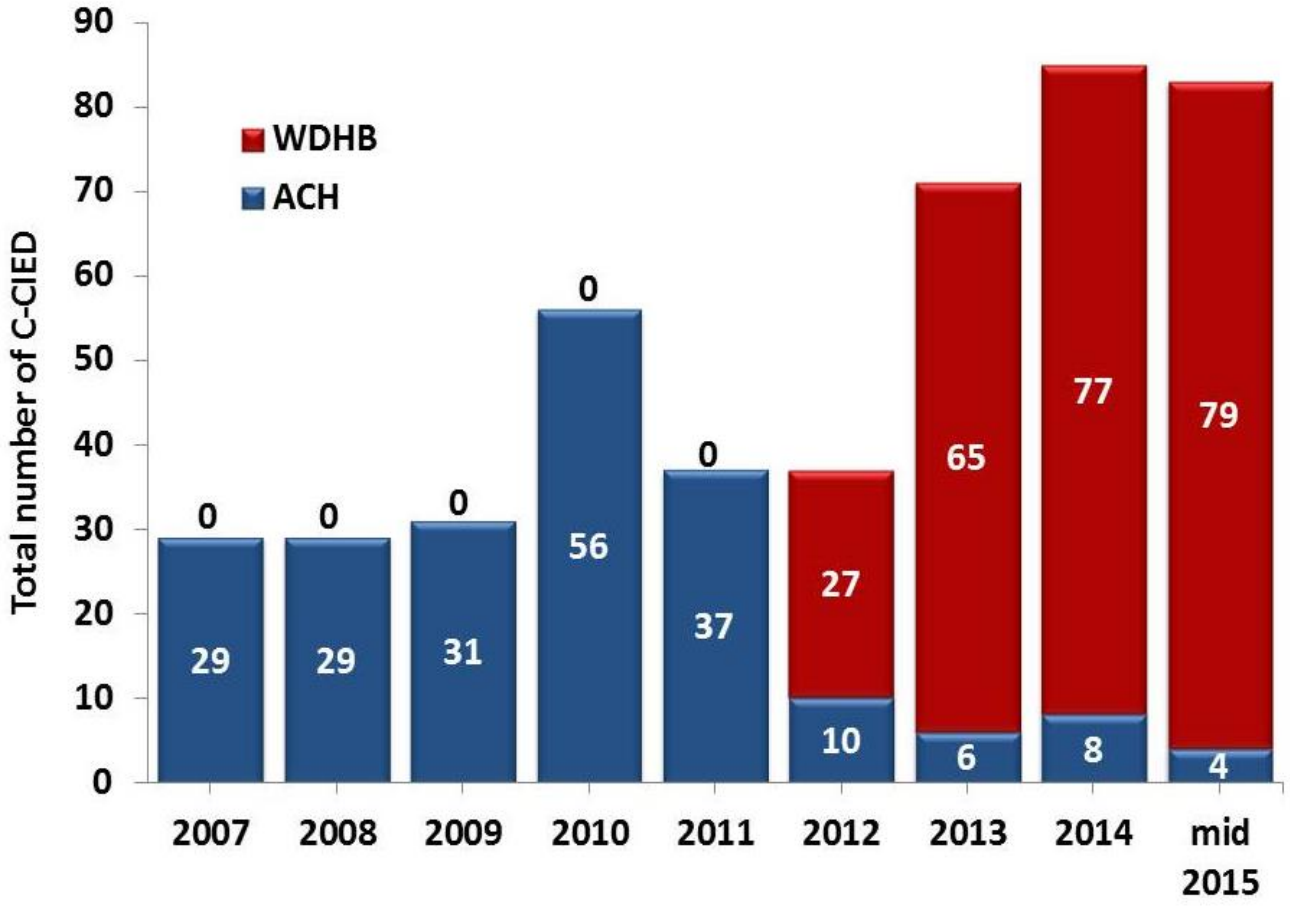
From 2007 to mid-2012, 207 patients from WDHB catchment area underwent ICD/CRT implantation at Auckland. Since mid-2012, WDHB has implanted 247 of these devices (**Figure 9**). There was a trend of increasing number of ICDs/CRT implanted since repatriation. The increasing number of complex devices implanted was mainly due to increased number of referral for primary prevention ICDs/CRT-Ds (**Figure 10)**

The complication rates were no different between the two sites (6.1% vs.10.3% at WDHB and ACH, respectively, p=0.19) (**Table 13**).

Establishment of a complex cardiac implantable electronic devices service at a regional cardiac centre with appropriate facilities and support is feasible, safe and has the potential to improve access to these devices' implantation and management.

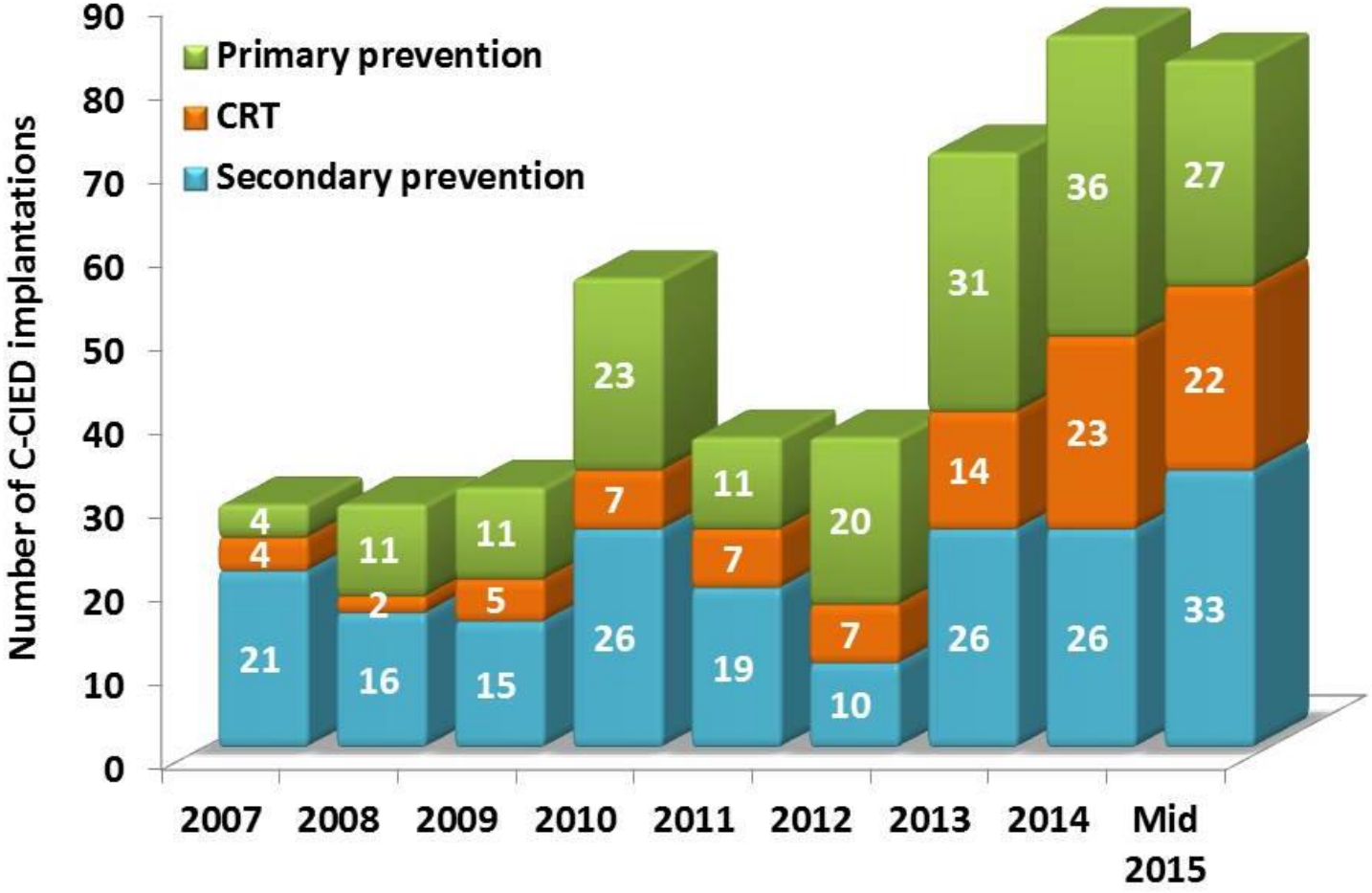
Published abstract: Looi K-L, Cooper L, Sidhu K, Dawson L, Slipper D, Hood M, Lever N, Gavin A: Implantation of Complex Cardiac Implantable Electronic Devices: Provision of Service at a Regional Cardiac Centre. Heart, Lung and Circulation 2016, 25: S26-S27.

Figure 9: Total Number of Complex Devices Implanted at Both WDHB and ACH for WDHB Patients



Abbreviations:
ACH: Auckland City Hospital, WDHB: Waitemata District Health Board

Figure 10: Type of Complex Devices Implanted for WDHB Patients at WDHB and ACH



Abbreviations:
C-CIED: complex cardiac implantable electronic devices; CRT: Cardiac resynchronisation therapy; WDHB: Waitemata District Health Board

Table 13: Procedural complication rates between ACH and WDHB for WDHB residing patients

Year	Total Procedural Complications at ACH n (%)	Total Complications at ACH for WDHB patients n (%)	Total Complications at WDHB n (%)
2007	8 (5.9)	2 (7.7)	-
2008	21 (13.6)	4 (14.3)	-
2009	27 (20.6)	4 (13.8)	-
2010	9 (6)	5 (9.3)	-
2011	16 (10.3)	3 (8.6)	-
2012	15 (12.8)	1 (10)	0
2013	7 (5.9)	0	3 (6)
2014	13 (12.4)	1 (12.5)	5 (10.9)
Mid-2015	1 (3.2)	0	0

Abbreviations:
ACH: Auckland City Hospital; WDHB: Waitemata District Health Board

5.3 LONG TERM OUTCOMES OF HEART FAILURE PATIENTS WHO RECEIVED PRIMARY PREVENTION IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR (ICD): AN OBSERVATIONAL STUDY

Preface

There is no question that ICD therapy has had a major impact on the management of selected HF patients. There remain significant limitations and challenges to the appropriate application of the available evidence for primary prevention ICD or CRT-D in HF patients. New Zealand, traditionally has had low number of ICD implants per million population because of limited resources.

The aim of the research presented in this chapter was:

- To describe the outcomes in HF patients selected for primary prevention device therapy in the Northern region of New Zealand

The research study highlights that even in appropriately selected HF patients there is a very low incidence of arrhythmic death. The incidence of hospitalisation for both ventricular arrhythmias and HF was significantly lower in the CRT-D group suggesting that where appropriate this should be the device of choice in appropriate HF patients. This information has important impact on management approach especially in the current economic era with limited resources and funding.

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Contribution of Candidate:

Khang-Li Looi was involved in the data collection and analysis, as well as in developing arguments and writing of the manuscript for publication.

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Abstract

Background

Implantable cardioverter defibrillator (ICD) therapy is indicated for selected heart failure patients for the primary prevention of sudden cardiac death. Little is known about the outcomes in patients selected for primary prevention device therapy in the Northern region of New Zealand

Method

Heart failure patients with systolic dysfunction who underwent primary prevention ICD/cardiac resynchronisation therapy-defibrillator (CRT-D) implantation between 1st Jan-2007 -1st June-2015 were included. Complications, mortality and hospitalisation events were reviewed.

Results

385 primary prevention devices were implanted (269 ICD, 116 CRT-D). Mean age at implant was 59.1±11.4 years. Mean duration of follow-up was 3.64 ±2.17 years. The commonest cause of death was heart failure (41.8%). Only 2 patients died from sudden arrhythmic death. The 5-year- heart failure mortality rate was 6% whereas the 5-year sudden arrhythmic death rate was 0.3%. Heart failure hospitalisations were commoner in those who received ICD than CRT-D (67.7% vs 25.8%, $p<0.001$). Maori patients have low implant rates (14%) with relatively high rates of admissions with heart failure and ventricular arrhythmias admissions,

Conclusions

Even in appropriately selected heart failure patients who received primary prevention devices, only a small percentage died as a result of sudden arrhythmic death. CRT–D should be the device of choice where appropriate in heart failure patients. Significant challenges remain to improve access to device therapy and maximise benefit to those who do get implanted.

Introduction

Randomised controlled trials have demonstrated the impact of ICD in the primary prevention of sudden cardiac death (SCD) in patients with poor left ventricular function without evidence of documented ventricular arrhythmias.[61-63,67,275] Under current international guidelines, class I indications for ICD implantation for primary prevention of SCD include patients with:[276]

1. Left ventricular ejection fraction (LVEF) ≤35% due to previous myocardial infarction (MI) who are ≥40-days post MI and are in New York Heart Association (NYHA)class II or III,
2. Non-ischaemic cardiomyopathy (NICM) with LVEF ≤35% and who are NYHA class II or III and
3. Pre-exiting ischaemic cardiomyopathy (ICM) with LVEF≤30% and are in NYHA class I

A number of studies in the UK estimated the required ICD implant rate to meet National Institute for Health and Clinical Excellence (NICE) recommendations for primary and secondary prevention vary between 100 and 150/million/year.[277,278] New Zealand, traditionally has had lower numbers of new implants/million population for ICD.[265,266] In 2007, the ICD implant rate in New Zealand was 41/million population compared with Australia (145/million), the United States (577/million), and Western Europe (140/million).[265-268]. 27% of implanted devices were for primary prevention indications.[265] Since then, there was a steady increase in ICD implant rates. In 2013, there was 423 ICDs implanted in New Zealand.[279] The number of new implant/million population was still low at 95.[279]

Several potential barriers to the optimal use of ICD therapy in eligible patients have been reported.[248,280,281] Affordability and capacity are of concern.[282] In New Zealand, there are approximately 12,000 hospital admissions each year; approximately 5,500 patients are for heart failure (HF).[19] A large number of HF patients would potentially fulfil international guidelines criteria for these devices. Considering current workforce and funding constraints, the published 2010 New Zealand guidelines have more restrictive recommendations. These guidelines

currently recommends primary prevention ICD in patients with ICM of at least 1 month after acute MI or NICM present for at least 3 months, LVEF ≤30% measured ≥3 months after optimal HF treatment and at least 3 months remote from any revascularisation procedure.[271] This is different from the international guidelines in terms of the LVEF cut-off point and was based primarily on resource concerns. Additionally, primary prevention ICD is not recommended routinely for patients ≥ 75 years of age. Other criteria qualifying for CRT-D implantation included LVEF ≤35% at least >6 weeks of optimal medical HF treatment, whose QRS duration on electrocardiogram (ECG) is >149 ms or is 120–149 ms with two additional criteria for dys-synchrony on echocardiogram (aortic pre-ejection delay >140 ms, interventricular mechanical delay >40 ms, or delayed activation of the posterolateral left ventricular wall), who are NYHA Class II/III, have had no major cardiovascular event in the prior 6 weeks and who are in sinus rhythm. In line with other guidelines, there should be no major comorbidity that would reduce survival to ≤ 18 months that would be a disqualification for CRT-D implantation.[271]

No data is currently available for CRT-D or ICD implant rates or outcomes in HF patients in the Northern Region of New Zealand who received primary prevention ICD/CRT-D.

Method

This was an observational study that described the medium to long-term outcomes of HF patients who received primary prevention ICD or CRT-D residing in the Auckland (ADHB), Counties Manukau (CMDHB), Northland (NDHB), and Waitemata (WDHB) District Health Boards region (Northern Region). The time period of the study was from 1st of January 2007 to 1st of June 2015. All de novo ICD and CRT-D implants, all pacemakers upgrades to ICD and CRT-D and epicardial lead placement with CRT-D procedures were included. Procedures involving solely ICD and CRT-D pulse generator replacement were excluded.

Patients were identified using an established device database. Data pertaining to the procedure and the post-procedure period were obtained from clinical records and that database. Data collected included patient demographic data, procedure-related data, acute (within 24 hours of implant), early (>24 hours to 2 weeks from implant) and late (≥ 2-weeks after implantation) complications. Appropriate and inappropriate ICD shocks were recorded from the device database during follow-up.

Subsequent hospitalisation events post implant were identified using the administrative data of Ministry of Health (MoH) and National Minimum Datasets [NMDS] inpatient hospitalisation data via National Health Index (NHI) linkage up to December 2015. HF and ventricular arrhythmias hospitalisations were defined using the International Classification of Diseases diagnosis 10 (ICD-10) codes (Appendix A). Mortality data was collected using New Zealand Mortality Collection. The cause of death data was only available up until the end of 2013. For those with no cause of death data accessible from NMDS, review of clinical records was performed to further determine the cause of death.

Mortality was classified as cardiovascular death, HF death, arrhythmic death, malignancy and other non-cardiac death.

Ethics approval of the study was obtained from the Central Health and Disability Ethics Committee (Ethics ref: 15/CEN/58/AM02).

Statistical analysis

Baseline characteristics were summarised as either mean with standard deviation or frequency with percentage depending on the nature of the data. Comparisons between ICD and CRT-D were conducted using either the Wilcoxon rank-sum test, the Chi-Squared test or the two-sample Z test. Survival rates over time were depicted in Kaplan-Meier curves and the differences between survival distributions were evaluated with the log-rank test. Univariate logistic regression was conducted to determine potential independent predictors of all-cause

mortality, cardiovascular mortality and HF mortality. Statistical analyses were performed using the statistical package SAS version 9.3 (SAS Institute, Cary, NC). All p-values resulted from two-sided tests and a p-value of <0.05 was considered statistically significant.

Results

A total of 404 procedures were performed in 385 HF patients. Mean age at implant was 59.1±11.4 years. Majority were male (84.9%) and of European descent (61.6%). Mean follow-up was 3.64±2.17 years with 282 (73.3%) patients having up to 5-years follow-up. ICD was the most common device implanted (69.9%) and the majority of the ICDs were single-chamber devices (53.3%). In the CRT-D group, a left ventricular lead was successfully placed in 104 patients (89.7%%) at the initial procedure. Seven required a second procedure endovascularly. Nine patients had epicardial lead placement. Four patients did not receive CRT because of failed left ventricular lead placement.

The baseline characteristics of the patients is shown in **Table 14**. Compared to the CRT-D patients, ICD patients were younger (58.1±11.9 years vs. 61.1±10.1, p=0.019) and more likely to have ICM (49.1% vs. 22.6%, p<0.0001).

Table 14: Baseline Characteristics of Heart Failure Patients who received primary prevention ICD and CRT-D

	ICD (n=269)	CRTD (n=116)	p
Mean Age (years ±SD)	58.1±11.9	61.1±10.1	0.019
Gender			
Male (%)	234 (87)	92 (80)	0.079
Female (%)	35 (13)	23 (20)	
Ethnicity (%)			
NZ European/Other	147 (54.7)	89 (77.4)	
Maori	48 (17.8)	6 (5.2)	
Pacific Island	29 (10.8)	15 (13.0)	<0.0001
Asian	40 (14.8)	4 (3.5)	
Unspecified	5 (1.9)	1 (0.9)	
DHB's (%)			
Auckland DHB	63 (23.4)	26 (22.4)	
Counties Manukau DHB	74 (27.5)	34 (29.3)	0.867
Northland DHB	25 (9.3)	8 (6.9)	
Waitemata DHB	107 (39.8)	48 (41.4)	
Underlying heart disease (%)			
Ischaemic cardiomyopathy	132 (49.1)	26 (22.6)	<0.0001
Non-ischaemic cardiomyopathy	114 (42.4)	77 (66.9)	<0.0001
Other causes	23 (8.6)	13 (11.2)	0.56
NYHA Class (%)			
I	92 (34.2)	12 (10.4)	
II	145 (53.9)	58 (50.4)	<0.0001
III	32 (11.9)	45 (39.2)	

Mean LVEF (%)	24.6±5.2	23.9±5.7	0.125
Atrial Arrhythmias (%)			
Paroxysmal AF	25 (9.3)	13 (11.3)	0.545
Chronic AF	55 (20.5)	13 (11.3)	0.031
AV node Ablation (%)	0	2 (1.7)	0.089
Diabetes Mellitus (%)	58 (21.6)	26 (22.8)	0.788
Hypertension (%)	81 (30.1)	28 (24.6)	0.271
QRS morphologic type (%)			
RBBB	28 (10.4)	0	<0.0001
LBBB	29 (10.8)	101 (87.8)	
IVC	23 (8.6)	0	
Paced	0	13 (11.3)	
QRS duration (%)			
Intrinsic (RBBB+LBBB+IVC)			
No of patients	80 (29.7)	101 (87.8)	<0.0001
Mean duration	153.3±22.4	175.1±18.3	
Paced			
No of patients	0	13 (11.4)	<0.0001
Mean duration	-	173.5±39.3	
Estimated glomerular filtration rate (eGFR)			
Mean	62.7±14.9	63.1±15.3	0.789

Abbreviations:
ICD: Implantable cardioverter-defibrillator; CRT-D: cardiac resynchronisation therapy-defibrillator; DHB: District Health Board; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; AF: atrial fibrillation; LBBB: left bundle branch block; RBBB: right bundle branch block; IVC: intraventricular conduction delay

Five ICD patients were later upgraded to CRT-D. The mean time of upgrade was 3.2±2.3 years. Indications for upgrade were a composition of worsening HF with deterioration in NYHA class, deterioration of LVEF and/or widening of QRS duration on ECG.

Complications

During the first 24-hours after implantation, there were 12 acute complications. These included lead dislodgements requiring intervention in 6 patients (5.2%) in the CRT-D group and 3 patients (1.5%) in the ICD group (p=0.02) (**Table 15**).

There were 5 device-pocket infections (1.29%) that required removal. Mean duration to infection was 1.79±1.78 months. Mean duration to infection in ICD group was 1.68±2.04 months whereas it was 2.28 months in the CRT-D group (p=N.S).

Device Therapy

During the follow-up, 76 (19.7%) patients had received anti-tachycardia pacing (ATP) and 66 (17.1%) had appropriate ICD shocks. There was no difference in device therapy in the ICD and CRT-D patients (p=0.80 and p=0.14 for ATP and appropriate ICD shocks, respectively). There was no difference in the incidence of appropriate ICD therapy in ICM and NICM patients (p=0.42 and p=0.47, respectively). In our study, 35 (9.1%) patients received inappropriate shocks, most commonly due to atrial fibrillation (71.4%) and regular supraventricular tachyarrhythmias (25.7%). A small number experienced inappropriate therapy because of T-wave over-sensing (2.9%). There was no difference between the two groups in the time to first inappropriate shocks (p=0.74).

Table 15: Acute, early and late complications in ICD and CRT-D patients

Complications	ICD (n=269)	CRT-D (n=116)	P value
Acute	4(1.5%)	8 (6.9%)	0.01
Lead dislodgement	3(1.5%)	6 (5.2%)	0.02
Cardiac tamponade	1 (0.4%)	1(0.9%)	0.28
Coronary sinus dissection	-	1(0.9%)	-
Early	4(1.5%)	1(0.9%)	0.62
Lead Dislodgement	2 (0.7%)	1(0.9%)	0.9
Device pocket haematoma	2(0.7%)	-	-
Late	11 (4.1%)	6(5.2%)	0.64
Lead issues	6(2.2%)	4 (4.3%)	0.38
Device-pocket revision	1(0.4%)	1(0.9%)	0.28
Device-pocket infections	4 (1.5%)	1 (0.9%)	0.62

Abbreviations:
ICD: Implantable cardioverter-defibrillator; CRT-D: cardiac resynchronisation therapy-defibrillator

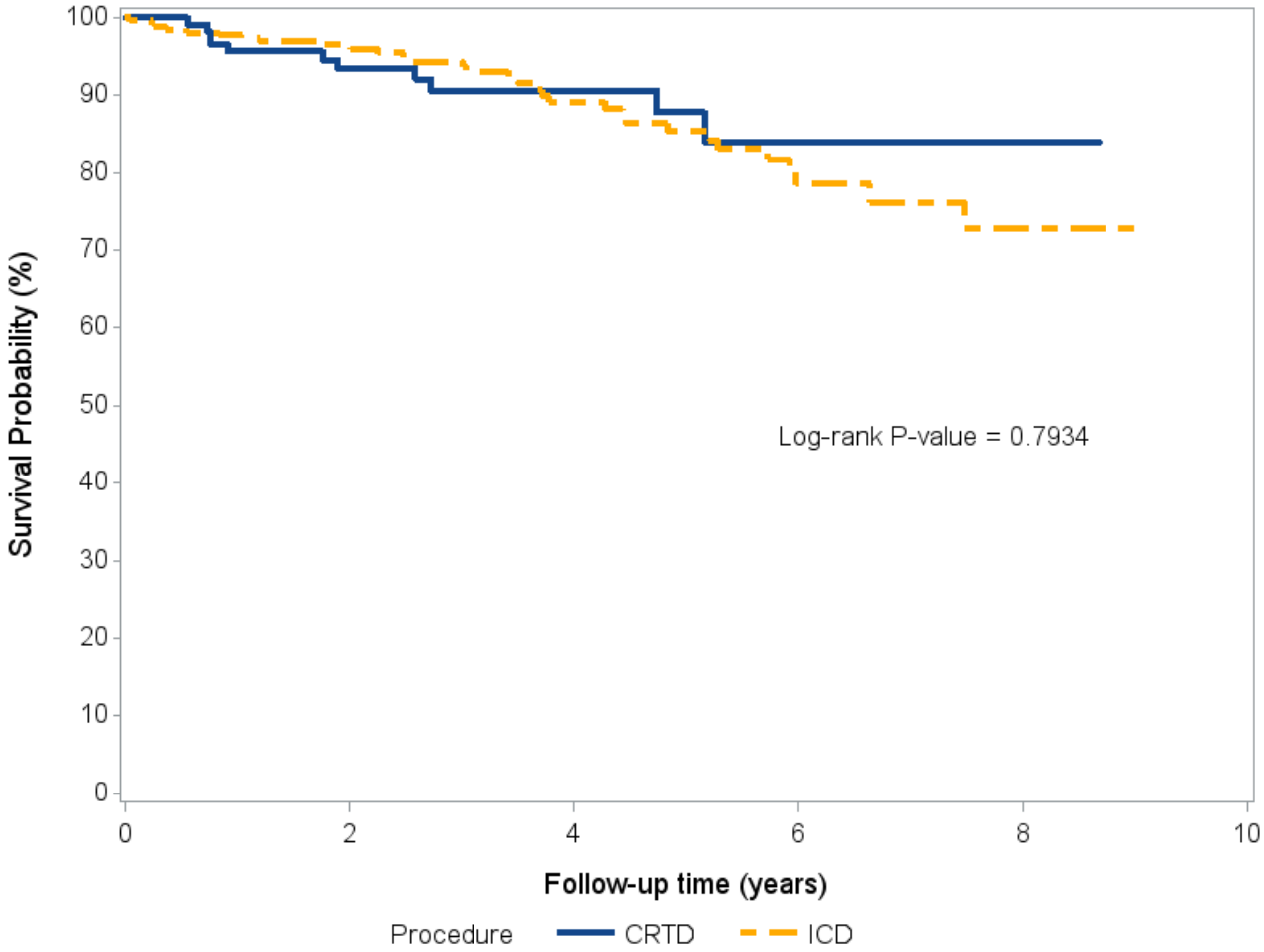
Mortality

At the end of the follow-up, 67 (17.4%) patients had died. Of these deaths, 42 were classified as cardiovascular death, 8 deaths were due to malignancy and 8 from other non-cardiac causes (p=0.88). The remainder 9 were classified as unspecified cause in the community. The 5-year all-cause and 5-year cardiovascular mortality rates were 14% and 9%, respectively.

Of the 42 cardiovascular deaths, 28 were due to HF and 12 deaths were attributable to MI, or cerebrovascular accidents. Only 2 were due to sudden arrhythmic death. These 2 patients had end stage HF for palliative care with slow ventricular arrhythmias below the detection rate programmed in their ICD for which no therapies were delivered. The 5-year- HF mortality rate was 6% whereas the 5-year sudden arrhythmic death rate was low at 0.3%.

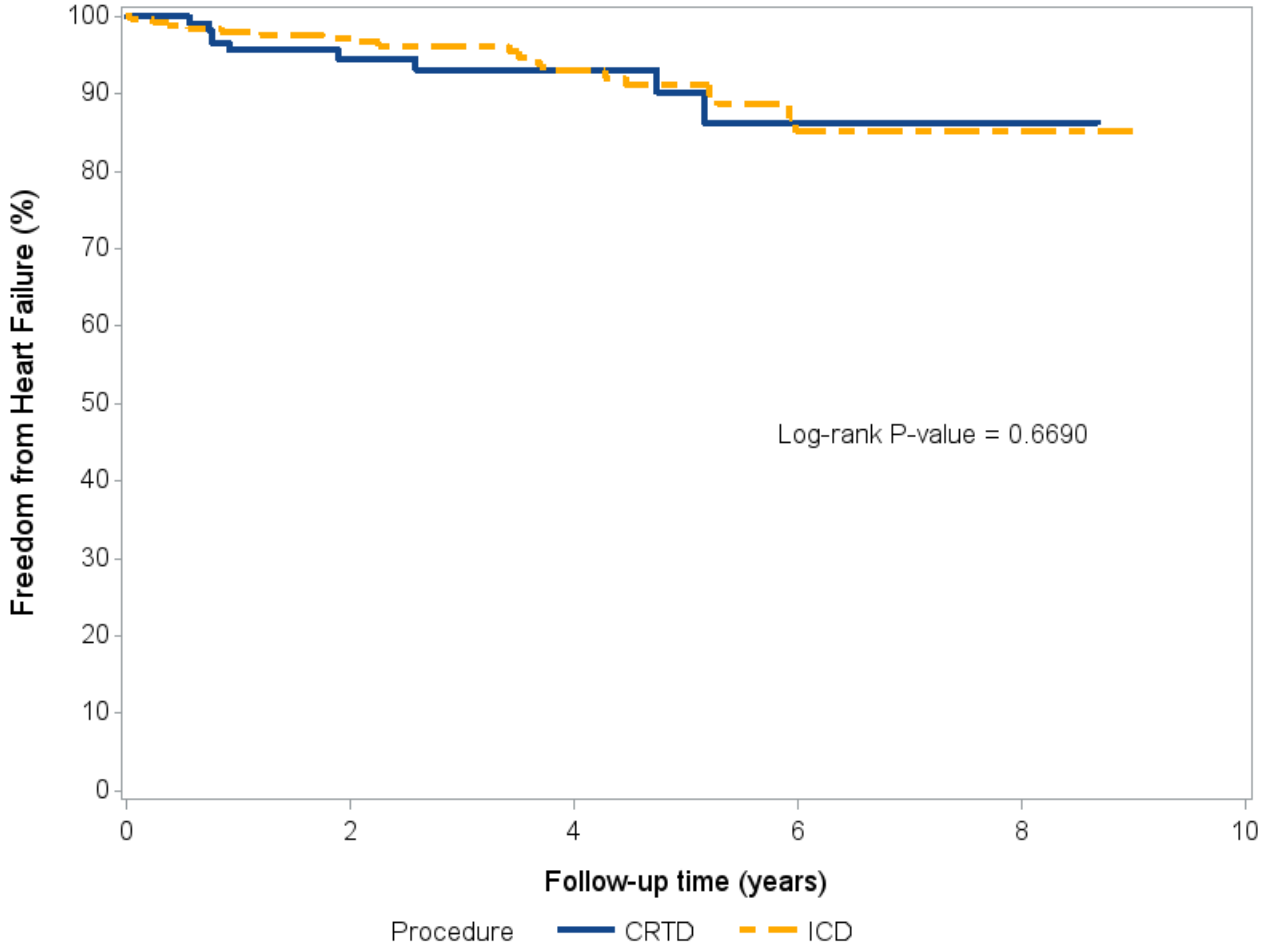
There was no difference in cardiovascular or HF mortality rates in ICD and CRT-D patients (**Figure 11** and **Figure 12**). For ICM and NICM patients, no difference in cardiovascular or HF survival was observed over-time (**Figure 13** and **Figure 14**).

Figure 11: Kaplan-Meier survival curve for cardiovascular mortality in ICD and CRT-D groups



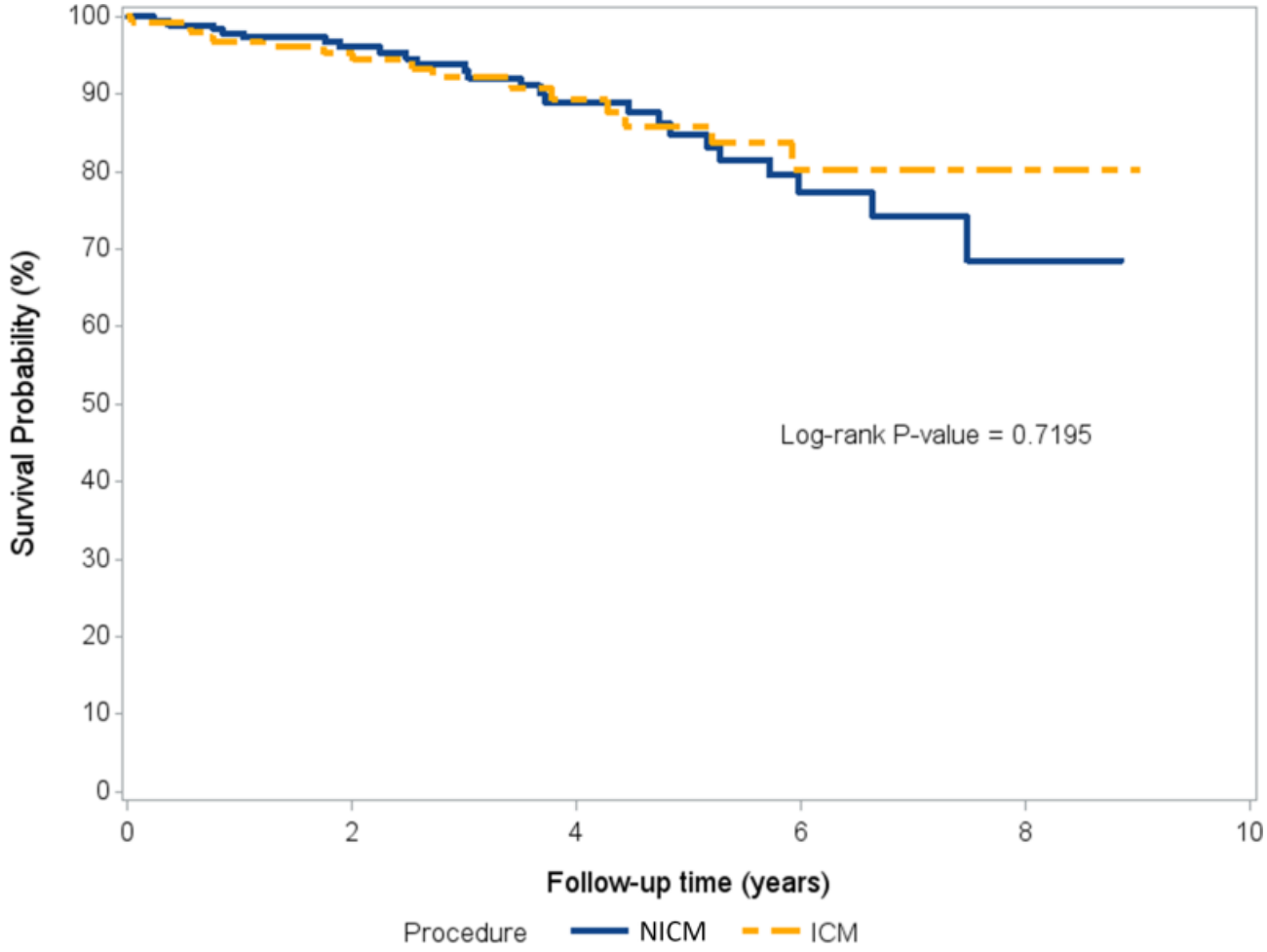
Abbreviations:
CRTD: cardiac resynchronisation therapy with defibrillator; ICD: implantable cardioverter-defibrillator

Figure 12: Kaplan-Meier survival curve for heart failure mortality in ICD and CRT-D groups



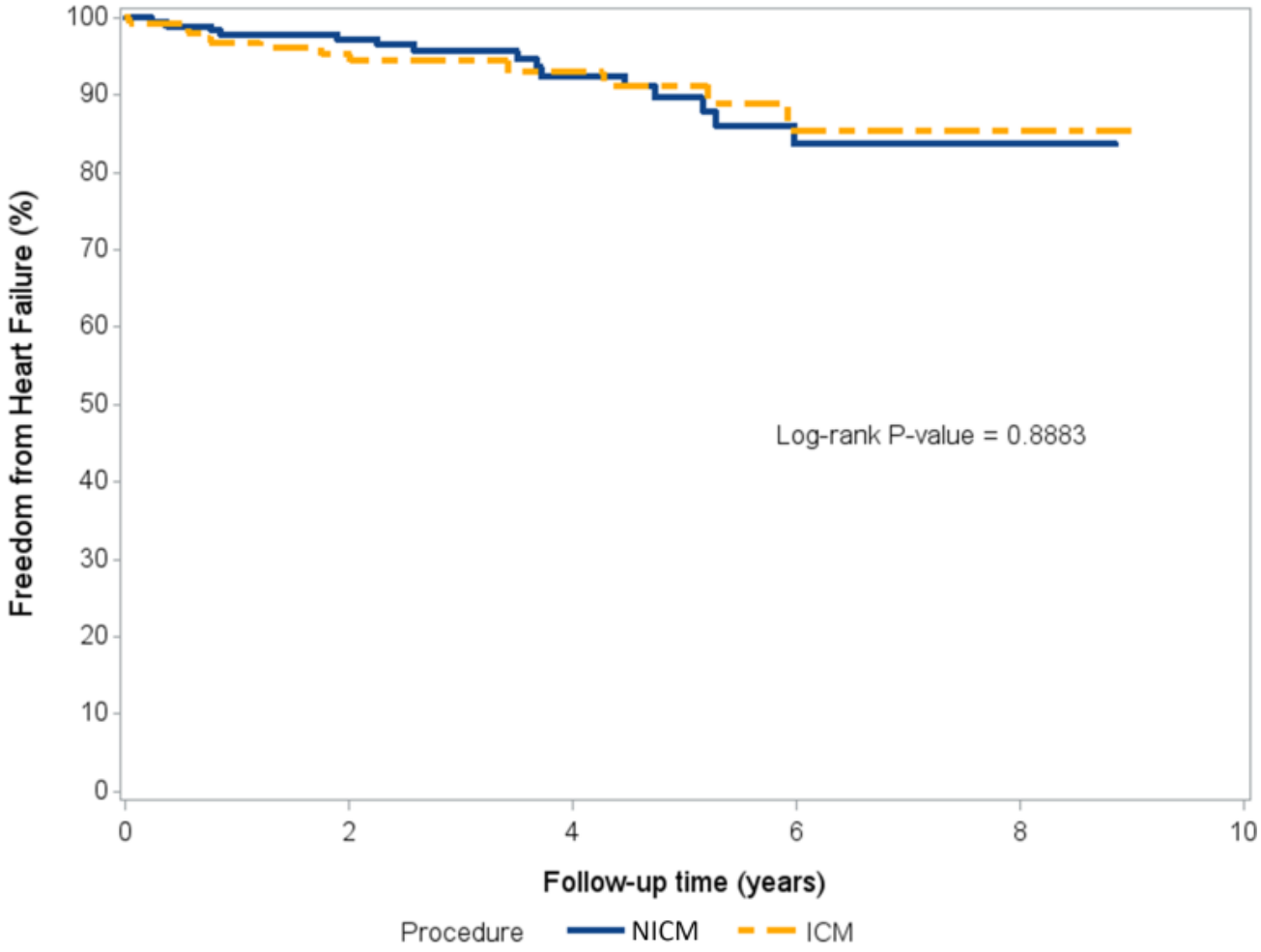
Abbreviations:
CRTD: cardiac resynchronisation therapy with defibrillator; ICD: implantable cardioverter-defibrillator

Figure 13: Kaplan Meier survival curve for cardiovascular mortality in ICM and NICM patients



Abbreviations:
ICM: ischaemic cardiomyopathy; NICM: non-ischaemic cardiomyopathy

Figure 14: Kaplan Meier survival curve for heart failure mortality in ICM and NICM patients



Abbreviations:
ICM: ischaemic cardiomyopathy; NICM: non-ischaemic cardiomyopathy

Using univariant logistic regression analysis, Maori ethnicity, NYHA class III symptoms and LVEF were significant predictors in all-cause and cardiovascular mortalities (**Table 16**). However, only NYHA class III symptoms remained an independent predictor for HF mortality (Odd ratio [OR] 4.2, 95% confidence interval [CI]1.273 - 13.641, p= 0.018).

Hospitalisation Events

Among the 385 patients, 260 patients had 1194 all-cause hospitalisations after implant. Mean duration from implant to subsequent hospitalisation was 9.57±10.85 months. Mean duration from implant to subsequent hospitalisation for ICD patients was 10.39±11.9 months and for CRT-D patients was 7.54±7.26 months, respectively (p=0.026).

Heart Failure Hospitalisations

Of the 1194 hospitalisations, there were 275 HF events in 93 patients (67.7% ICD and 32.3% CRT-D patients respectively) (p<0.001) and 20.4% were Maori. Mean duration from implant to first subsequent HF event was 15.87±14.8 months. For ICD and CRT-D patients, there was no difference in the mean duration to first HF hospitalisation after implant (p=0.40).

Ventricular arrhythmias Hospitalisations

There were 65 ventricular arrhythmias hospitalisations in 43 patients (76.7% ICD and 23.3% CRT-D patients respectively) (p=0.07) and 23.3% were Maori. Mean duration from implant to first ventricular arrhythmias hospitalisation was 18.24±16.53 months. No difference was found in the mean duration from implant to first ventricular arrhythmias hospitalisation in ICD and CRT-D patients (p=0.08).

Table 16: Univariant logistic regression analysis for all-cause mortality and cardiovascular mortality

	All-Cause Mortality			Cardiovascular Mortality		
	Odds Ratio	**95% Confidence Intervals**	**P-value**	**Odds Ratio**	**95% Confidence Intervals**	**P-value**
Age (years)	1.009	0.985 - 1.033	0.4553	0.991	0.965 - 1.018	0.5212
Female (vs. male) Gender	0.503	0.207 - 1.225	0.1302	0.403	0.120 - 1.350	0.1406
Maori	2.843	1.473 - 5.487	0.0018	2.27	1.035 - 4.979	0.0407
QRS Duration	1	0.993 - 1.008	0.9166	1.003	0.994 - 1.012	0.4733
ICM (vs. NICM)	1.008	0.585 - 1.738	0.9759	0.789	0.403 - 1.543	0.4881
NYHA Class						
II	1.351	0.677 - 2.694	0.3932	1.775	0.690 - 4.566	0.2337
III	2.625	1.218 - 5.656	0.0137	4.284	1.590 - 11.544	0.004
LVEF	0.949	0.903 - 0.997	0.0358	0.903	0.850 - 0.959	0.001
QRS Morphology						
LBBB	1.082	0.611 - 1.918	0.7869	1.139	0.579 - 2.239	0.7064

**p<0.05*

Abbreviations:
NICM: non-ischaemic cardiomyopathy; ICM: ischaemic cardiomyopathy; LBBB: left bundle branch block, LVEF: left ventricular ejection fraction; NYHA: New York Heart Association

Discussion

Our study is a "real world" description of the medium to long-term outcomes of HF patients who received primary prevention ICD and CRT-D. In appropriately selected patients, there was a low incidence of arrhythmic death. CRT-D patients have lower hospitalisation rates for both HF and ventricular arrhythmias. We have acceptable complication rates comparable to international published reports for the time.[66,128]

HF is an increasing problem in both developed and developing countries. The Framingham Heart Study showed that HF is associated with increased risk of SCD.[56] However, the most common mode of death in this group of patients remains progressive HF. In a sub-analysis of the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial, pump failure (44.4%) was the most common mode of death followed by SCD (26.5%) in patients with advanced HF.[96] Our findings were concordant with published data demonstrating the most common cause of death is due to worsening HF. Only a small percentage of patients died from sudden arrhythmic death (2.9%) with a 5-year arrhythmic mortality rate of 0.3%. Thus, the commonest mode of death in HF patients, even those at risk for ventricular arrhythmias, is progressive pump failure that cannot be addressed by an ICD alone. In our study, there were 275 HF hospitalisations and 65 ventricular arrhythmias events confirming that patients with HF were at higher risk of worsening HF than ventricular arrhythmias. LVEF was a strong predictor for all-cause and cardiovascular mortality in the univariate analysis. Therefore, optimisation of HF management with the aim of improving LVEF (with the used of CRT devices where appropriate) remains important. Although progressive HF remained the commonest cause of death (41.8%), a significant proportion of patients still died from malignancy (11.9%). These patients have significant co-morbidities resulting in 876 other non-cardiac related hospital admissions.

Maori ethnicity was a significant predictor of all-cause and cardiovascular mortality in our study. In general, Maori are disproportionately represented in adverse health outcomes.[283] The device implantation rates were 14% (n=54) in Maori and only 5.2% (n=6) received CRT-D. They comprised of 20% and 23% of subsequent HF and ventricular arrhythmias admissions. Despite the advances in the management of HF, Maori were about 4-times as likely as non-Maori to be hospitalised for HF (relative risk [RR] 4.01, CI 3.83–4.21).[284,285] The HF mortality rate among Maori was more than twice as high as that of non-Maori (RR 2.36, CI 1.76–3.17).[284,285] The reasons behind these inequalities are multifactorial including socio-economic deprivation, cultural beliefs in health and differences in adherence to guideline recommendation treatment.[286,287] Among the 54 Maori patients who received these devices, 19 (35.2%) died during the follow-up period. HF was the cause of death in 26.3% of these patients. This suggests that more effective methods of optimising HF therapy in Maori patients are required but the effective strategies to achieve this remain uncertain. Asians have lower incidence of HF and this was reflected by the low number of device implantations.[288]

Overall the peri-operative risk is low for these devices but the longer-term complications of these devices cannot be ignored. A recent meta-analysis reported a complication rate of 9.1% in 6433 patients with ICD implantation over 16-months.[66] Similarly, the National Cardiovascular Data Registry (NCDR) ICD registry reported 6.1 (CI, 6.0 to 6.2) ICD-related complications per 100 patient-years that required reoperation or hospitalisation.[128] Our results suggest that whilst the implant rates are low, patients who had the devices implanted had slightly higher but acceptable rate of complications comparable to international published reports. Our success rate of LV lead implantation at first procedure was 89.7% compared to 97% in the REsynchronization reVErses Remodeling in Systolic Left vEntricular Dysfunction (REVERSE) trial, 94% in the Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) study and 98.4% in Multicenter Automatic Defibrillator Implantation Trial with

Cardiac Resynchronization Therapy (MADIT-CRT) trial.[86,87,177] However, these centres are centres with high volumes. Given the limited resources and low volume implant rate, the acute peri-operative complication rates are similar to published data and only 3.4% patients did not get CRT-D devices because of failed LV lead placement.

With the increasing number of complex device implantations, infection becomes a major challenge to face. Rates of device-related infection between 0.5 and 5.1% have been reported in retrospective and prospective studies with current estimated risk close to 1%.[211,289] Our infection rate (1.4%) was similar to those published.

Data is lacking regarding the management of patients with ICD who subsequently develop indications for CRT. Clinical predictors of upgrade during the main RAFT study included NYHA class III versus II and a wider QRS duration.[87] This was similar to the reasons of upgrade in our cohort. The rate of CRT upgrade varies widely among studies. In a retrospective single centre study, the upgrade rates from ICD to CRT-D at 1, 3, and 5 years were 0.03%, 2.4%, and 5.1%, respectively.[290] Only 5 (1.9%) of our patients were upgraded from ICD to CRT-D. This could be explained by the small number of implants. In the European Cardiac Resynchronization Therapy Survey, there were no significant differences in clinical outcomes or complication rates between upgrades and de novo procedures.[291] Our patients were successfully upgraded at the initial attempt and there were no acute complications. It is also striking that the incidence hospitalisation for both ventricular arrhythmias and HF was significantly lower in the CRT-D group suggesting that where appropriate this should be the device of choice.

Limitations

There are several limitations in our study. This is a retrospective study where all the patients were retrospectively recruited but prospectively followed-up. The published 2010 New Zealand guidelines have stricter recommendations for ICD and CRT-D in patients with HF

compared to the International guidelines. There is the potential that a sizable group of HF patients not being referred therefore, missing out on appropriate device support. Confounders and selection bias should therefore be kept in mind when interpreting the results of our study. Our study does not represent the entire New Zealand. The 4 DHBs in Northern Region serve 38% of the total New Zealand population with estimated 1.76 million people in this region.[292] The implant rate and the practice may differ in other implant hospitals in the country.

The latest available cause of mortality data from the MoH was only up until 2013 due to delays related to ongoing coronial enquires. For those with no cause of death data available after year 2013, we reviewed clinical records to determine the cause of death. There were 8 patients who died outside the hospital where no formal record of mortality cause was available. This potentially could impact on the accuracy of the sub-analysis of HF and ventricular arrhythmia mortalities. The main strength of our study was the long duration of follow-up. The mean follow-up was 3.64 ±2.17 years, with 73.3% patients having 5-years of follow-up. We managed to capture all deaths rather than just death in the hospital and all the hospitalisation events in detail for these patients.

The New Zealand Cardiac Implanted Device Registry (ANZACS-QI 15) has recently been developed to collect information on all cardiac device implantations in New Zealand, which will aid quality improvement initiatives and to allow subsequent examination of equity of access to therapy, outcomes and complications in a "real-world" view. The first description of data on new pacemaker implants from this Registry has been recently published.[274] We believe our study adds to the ANZACS-QI 15 data, giving a more detailed picture of current New Zealand practice with primary prevention ICD/CRT-D use in selected HF patients.

Conclusion

Based on our observational study, effective ICD/CRT-D in appropriately selected HF patients resulted in a very low incidence of arrhythmic death. The incidence of hospitalisation for both

ventricular arrhythmias and HF was significantly lower in the CRT-D group suggesting that where appropriate this should be the device of choice for HF patients. Significant challenges remain in order to improve access to device therapy amongst these patients given the limited funding available in New Zealand.

Appendix A

International Classification of Diseases diagnosis 10 (ICD-10) codes used for data extraction

Heart failure:

I110

I130

I132

I500

I501

I509

Ventricular arrhythmias:

I460

I461

I469

I470

I472

I490

5.4 UTILISATION OF CARDIAC RESYNCHRONISATION THERAPY IN PATIENTS WITH HEART FAILURE IN THE NORTERN REGION OF NEW ZEALAND

Preface

CRT is an important adjunctive therapy developed to treat patients with systolic HF who have LBBB and wide (>120ms) QRS complex and are optimally medically managed. There is paucity of data on CRT implantation and outcomes in the local context of New Zealand HF populations.

The aim of the research presented in this chapter was:

- To describe the trends in the use of CRT in the Northern Region of New Zealand and their outcomes

The research study demonstrated a difference between the use of CRT-D and CRT-P in this region. Additionally, no difference noted in the mortality in those who received either CRT-D or CRT-P. This information has important impact on management approach. CRT-P appears to be more useful in selected HF patients for medical economics especially in the current economic era with limited resources and funding.

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Contribution of Candidate:

Khang-Li Looi was involved in the data collection and analysis, as well as in developing arguments and writing of the manuscript for publication.

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Abstract

Background: Cardiac resynchronisation therapy (CRT) has been shown to improve morbidity and mortality for heart failure (HF) patients. Little is known about the trends in CRT use and outcomes of these patients in New Zealand.

Method: Mortality, hospitalisation events and complications in HF patients in the Northern Region of New Zealand implanted with CRT devices from Jan-2007 to June-2015 were reviewed.

Results: Two-hundred patients underwent CRT implantation during the study period. There was a gradual increase in CRT-D implantation (n=157) but the number remained static for CRT-P (n=43). Patients who received CRT-P were older (mean age 65.9±14.0 vs. 61.5±10.2 years, $p<0.0007$) but had a higher left ventricular ejection fraction (LVEF) (33.7±10.5% vs. 24.7±6.1, $p<0.0001$) than those undergoing CRT-D implant procedures.

During a median follow-up of 4 (2.8) years, 29 (14.5%) patients (14.7% in CRT-D vs.13.9% in CRT-P, $p=0.91$) had died. HF was the cause of death in 73.9% of the patients. There was no difference in all-cause mortality between patients with CRT-D and CRT-P.

Conclusions: Despite the proven benefits of CRT in selected HF patients, there continued to be under-utilisation of these devices in HF patients in the Northern Region. Reasons for under-utilisation of these devices need further exploration. These data should be useful for benchmarking individual patient management and national practice against wider experience in the country.

Introduction

Heart failure (HF) is a major health burden in many developed countries. The prevalence of HF is estimated at 1–2 % in the western world, and the incidence approaches 5–10 per 1,000 persons per year.[7] In New Zealand, approximately 5,500 patients are hospitalised due to decompensated HF annually.[19]

Cardiac resynchronisation therapy (CRT) has been shown in multiple studies to improve symptoms, quality of life and survival in HF patients who remain symptomatic despite optimal medical therapy, who have left ventricular ejection fraction (LVEF) $\leqslant$35% and left bundle branch block (LBBB) with QRS width $\geqslant$120 ms.[80-84] Despite recommendations, there remain many barriers and challenges to implanting CRT in patients with HF patients who meet guideline criteria. The 2006-2007 US National ICD Registry data showed that 32.2% of patients eligible for implantable cardioverter-defibrillator (ICD) also met criteria for CRT.[293] Of those eligible, only 4/5 received a CRT-capable device. The largest published series of CRT procedures in New Zealand had only 139 patients during the period between 2000 and April 2011.[273]

Little is known about the CRT use and outcomes of these patients in New Zealand. Our study aimed to examine the trends of CRT use in eligible HF patients living in the Northern Region of New Zealand and their outcomes.

Method

This was an observational study documenting the use of CRT in HF patients in the Northern Region of New Zealand. New Zealand has a population of 4.43 million. The Northern Region of New Zealand is defined as the 4 northernmost District Health Board (DHB) areas that consist of the Auckland DHB (ADHB), Counties Manukau DHB (CMDHB), Northland DHB (NDHB), and Waitemata DHB (WDHB). The 4 DHBs in the Northern Region serve 38% of the total

New Zealand population.[292] Patients residing in the catchment areas of the 4 DHB were included over the study period from 1st January 2007 to 1st June 2015. All de novo transvenous CRT-pacemaker (CRT-P) and CRT-defibrillator (CRT-D) implants, all upgrades of pacemakers to CRT-P or CRT-D, upgrades of ICD to CRT-D and epicardial lead placement for CRT-P or CRT-D capable devices were included. Procedures involving solely pulse generator replacement were excluded. The indications for CRT-D and CRT-P were based on the published 2010 New Zealand guidelines (**Table 17**).[271] All referrals for CRT were discussed by the Northern Region implanting electrophysiologists regarding suitability and appropriateness of CRT support. To illustrate the number of potential candidates needed to be reviewed for CRT-support, the number of unique patients hospitalised with HF in each year from year 2007-2015 in the Northern region were reviewed using the data of Ministry of Health (MoH) and National Minimum Datasets (NMDS) inpatient hospitalisation data.

Data pertaining to the procedure and the post-procedure period were obtained via review of clinical records held on electronic Clinical Record Information System (CRIS). Data collected via notes review included patient demographic data, procedure-related data, acute (within 24 hours of implant), early (>24 hours to 2 weeks after implant) and late (⩾2-weeks after device implantation) complications.

Hospitalisation events were identified using the administrative data of MoH and NMDS inpatient hospitalisation data via National Health Index (NHI) number linkage up to December 2015. The NHI number is a unique identifier that is assigned to every person who uses health and disability support services in New Zealand. HF hospitalisation was defined using the International Classification of Diseases diagnosis 10 (ICD-10) codes (I110, I130, I132, I500, I501 and I509).

Mortality data was collected using New Zealand mortality collection and NMDS. These include all registered deaths not just in-hospital deaths. The cause of death data was available

up until the end of 2013. For those with no cause of death data from NMDS, adjudicated review of clinical records was performed to further determine the cause of death.

Ethics approval of the study was obtained from the Central Health and Disability Ethics Committee (Ethics ref: 15/CEN/58/AM02).

Table 17: New Zealand Primary Implantable Cardioverter Defibrillator Implantation and Cardiac Resynchronisation Therapy Guidelines

Recommendations for primary ICD implantation in New Zealand: • Patients with ICM at least 1 month after acute MI or a NICM present for at least 3 months. • EF ≤30% measured ≥3 months after optimal heart failure treatment. • NYHA class II or III • On maximal heart failure medications, including ACE-inhibitors or angiotensin receptor blockers, beta-blockers and spironolactone as tolerated for at least 3 and preferably 6 months • No clinical symptoms or findings that would make them a candidate for a revascularisation procedure • At least 3 months remote from any revascularisation procedure • No associated disease with a likelihood of survival <18 months • Age ≤75 years
Recommendations for Cardiac Resynchronisation Therapy in New Zealand: • EF ≤35% after ≥6 weeks of optimal heart failure treatment, with QRS duration is >149 ms or is 120–149 ms with 2 additional criteria for dyssynchrony (aortic pre-ejection delay >140 ms, interventricular mechanical delay >40 ms or delayed activation of the posterolateral left ventricular wall) • NYHA Class III • No major cardiovascular event in the prior 6 weeks and be in sinus rhythm • No major comorbidity reducing survival <18 months or seriously impairing quality of life

Abbreviations:
ACE: angiotensin converting enzyme; EF: ejection fraction; ICD: implantable cardioverter defibrillator; ICM: ischaemic cardiomyopathy; MI: myocardial infarction; NICM: Non-ischaemic cardiomyopathy; NYHA: New York Heart Association

Statistical analysis

Baseline characteristics were summarised as either mean with standard deviation (SD), median with interquartile range (IQR) or frequency with percentage depending on the nature of the data. Comparisons between CRT-P and CRT-D were conducted using either the Wilcoxon rank-sum test, the Chi-Squared test or the two-sample Z test. Survival rates over time were depicted in Kaplan-Meier curves and the differences between survival distributions were evaluated with the log-rank test. Statistical analyses were performed using the statistical package SAS version 9.3 (SAS Institute, Cary, NC). All p-values resulted from two-sided tests and a p-value of <0.05 was considered statistically significant.

Results

A total of 200 patients had a CRT device (157 CRT-D and 43 CRT-P) implanted during the study period. The majority of patients were male (76%) and of European descent (79.5%). Mean age of patients was 62.4±11.2 and median age was 64.4(12.8) years, respectively. The median duration of follow-up was 4 [2.8-9] years. Patients were more likely to have non-ischaemic cardiomyopathy (NICM) (49.5%). Ischaemic cardiomyopathy (ICM) (22.5%) and pacemaker-induced cardiomyopathy (19.5%) were the other common aetiologies for underlying cardiomyopathy.

Among the 157 CRT-D patients, 116 (73.9%) patients received these devices as primary prevention for sudden cardiac death (SCD). Five patients had epicardial lead placement at initial procedure because of known difficult anatomy (i.e. upgrades with occluded venous access and extraction was not considered appropriate or declined). A left ventricular lead was successfully placed transvenously via the coronary sinus (CS) in 136 patients (89.5%) at the initial procedure. Eight required a second procedure with 3 unsuccessful CS-lead implantations needing epicardial lead placement. Two patients underwent a redo-procedure using an

epicardial lead because of adverse coronary sinus anatomy, and/or unintended stimulation of the left phrenic nerve during transvenous CS-lead placement; in total ten patients had epicardial lead placement for CRT-D devices. Only 6 patients did not receive CRT-D because of failed left ventricular lead placement. Twenty-three (14.7%) patients were upgraded from pacemakers to CRT-D and 18 (11.5%) were upgraded from ICDs to CRT-D.

In the CRT-P group, left ventricular lead placement was successful at initial implant in 41 patients (95.3%) and 1 required a second procedure which failed and required epicardial lead placement. Thirty-two (74.4%) were upgrades from pacemakers to CRT-P. One patient did not receive the intended CRT-P device because of failed left ventricular lead placement.

Context of Northern Region in CRT implantation

In the Northern Region, the number of individuals admitted with a diagnosis of HF was increasing year by year (**Figure 15**). In a Swedish Heart Failure Registry, QRS prolongation with LBBB morphology $\geqslant$ 120 ms was present in 31% of patients with HF.[78] If ~30% of patients each year with HF have underlying LBBB and systolic dysfunction, then the number of patients to be considered for CRT-support in the Northern Region should also increase proportionally. However, throughout the study period, the number of CRT implanted remained low (**Figure 16**). There were differences in CRT-D and CRT-P utilisation (**Figure 16**). The percentage of CRT-D utilisation gradually increased from 2007 to mid-2015. However, the utilisation of CRT-P remained static during these times.

Shown in **Table 18** are the baseline characteristics of patients who received CRT-P and CRT-D. In general, patients receiving CRT-P were older, more likely to have pacemaker-induced cardiomyopathy, have more severe HF symptoms (NYHA class III) but better LVEF, higher prevalence of permanent atrial fibrillation (AF) and previous history of atrio-ventricular (AV) nodal ablation, and have smaller body habitus than those who received CRT-D.

Figure 15: Number of unique heart failure patients, potential cardiac resynchronisation therapy (CRT) candidates and number of patients who received CRT-device support in Northern Region of New Zealand: Year 2007-2015

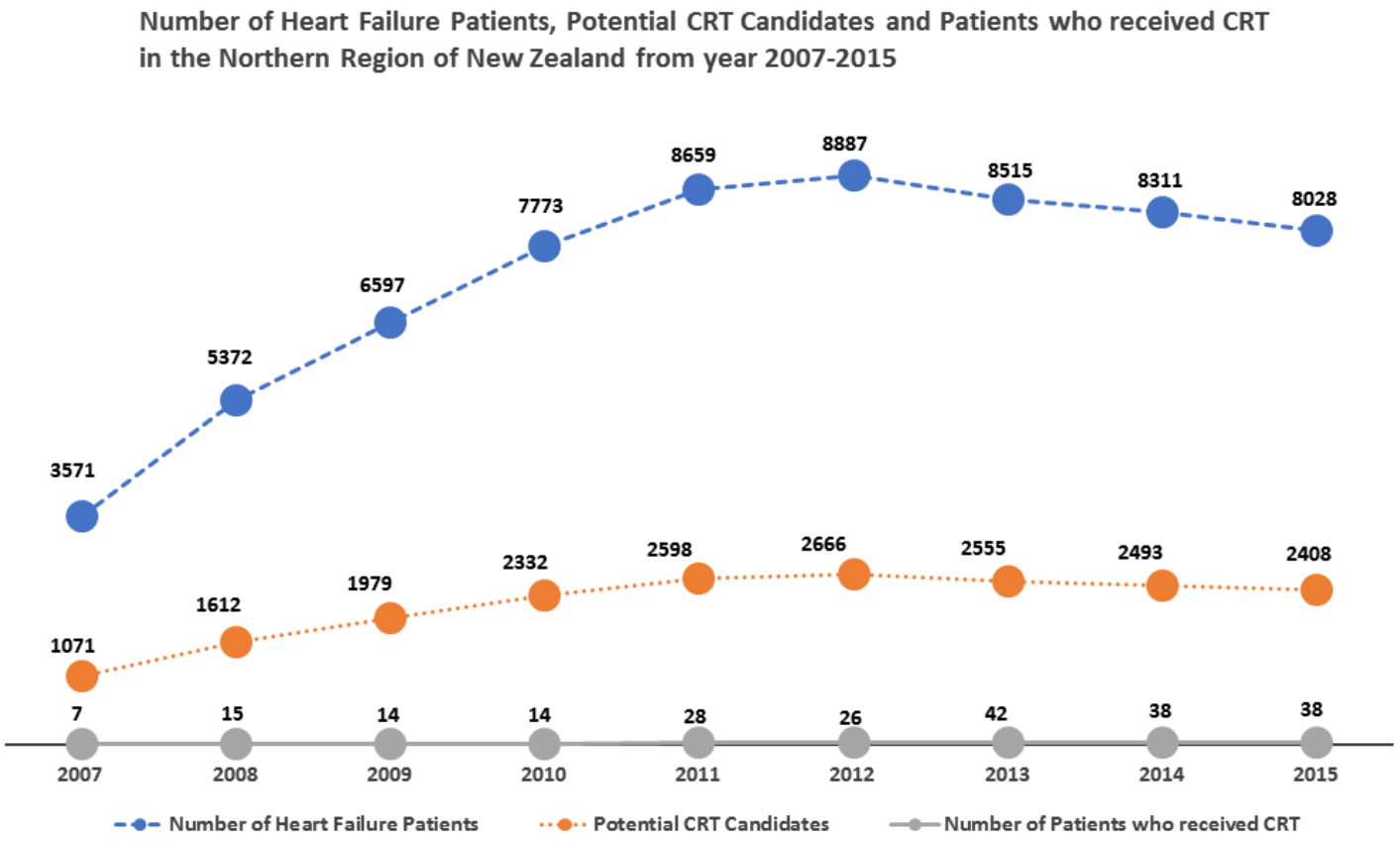
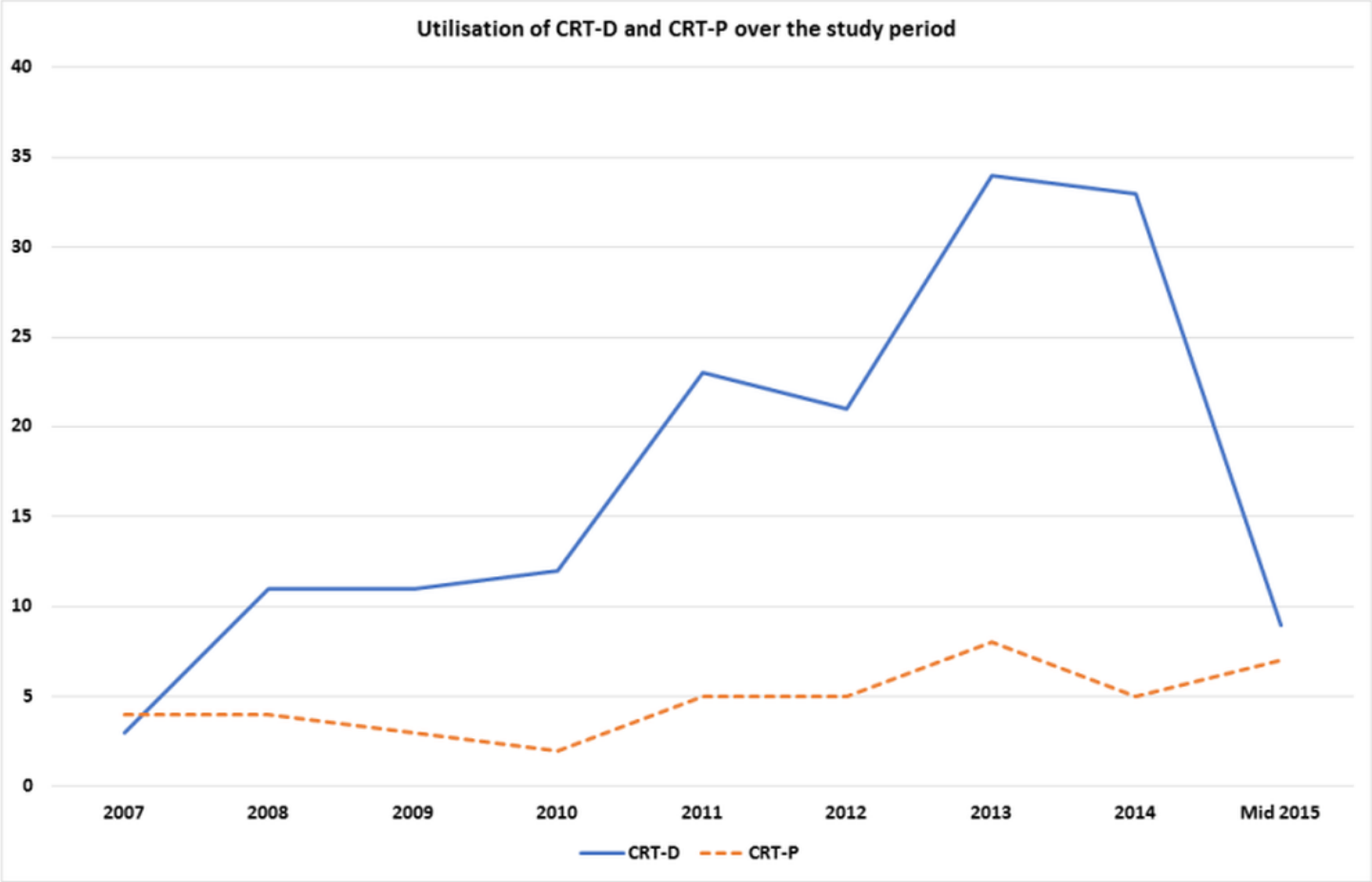


Figure 16: Number of CRT-P and CRT-D devices implanted during the study period



Abbreviations:
*CRT-D: cardiac resynchronisation therapy-defibrillator, CRT-P: cardiac resynchronisation therapy-pacemaker. *The number of cases implanted in Jan 2015 to mid-2015 have been annualised*

Table 18: Baseline characteristics of patients who received CRT-P and CRT-D

	CRT-D (n=157)	CRT-P (n=43)	P value
Mean Age (years ±SD)	61.5±10.2	65.9±14.0	0.0007
Median Age (IQR)	63.4 (57.3)	69.7 (60.4)	
Gender			
Male (%)	123 (78.3)	29 (67.4)	0.14
Female (%)	34 (21.7)	14 (32.6)	
Ethnicity (%)			
New Zealand European/Other	121 (77.1)	38 (88.3)	0.35
Maori	9 (5.7)	2 (4.7)	
Pacific Island	19 (12.1)	1 (2.3)	
Asian	7 (4.5)	2 (4.7)	
Underlying Aetiology (%)			
Non-ischaemic cardiomyopathy	93 (59.2)	6 (14)	<0.0001
Ischaemic cardiomyopathy	40 (25.5)	4 (9.3)	0.02
Pacemaker-induced cardiomyopathy	10 (6.4)	29 (67.4)	<0.0001
Valvular heart disease	4 (2.6)	3 (7)	0.16
Mean LVEF (% ± SD)	24.7 ± 6.1	33.7 ± 10.5	<0.0001
NYHA Class (%)			

I	18 (11.5)	6 (14)	0.03
II	75 (47.8)	12 (27.9)	
III	64 (40.8)	24 (55.8)	
IV	0	1 (2.3)	
Median Height (meter) (IQR)	1.74 (1.67)	1.72 (1.67)	0.91
Median Weight (kg) (IQR)	86.3 (74.1)	81.5 (75)	0.02
Median BMI (m/kg2) (IQR)	28.3(25.9)	26.5 (24.8)	0.01
Atrial Arrhythmias (%)			
Permanent AF	16 (10.2)	15 (34.9)	<0.0001
Paroxysmal AF	20 (12.7)	3 (7)	0.29
AV node Ablation	3 (1.9)	11 (25.6)	<0.0001
Diabetes Mellitus (%)	41 (26.3)	3 (7.1)	0.008
Hypertension (%)	44 (28.2)	12 (28.6)	0.96
QRS morphology (%)			
IVCD	1 (0.6)	1 (2.3)	<0.0001
LBBB	131 (83.4)	12 (27.9)	
Paced	23 (14.7)	29 (67.4)	
QRS duration (ms)			
Mean (± SD)	175.1±24.6	177.3±33.0	0.36

Estimated glomerular filtration rate (eGFR)			
Median (IQR)	60 (51)	60 (50)	0.33

Abbreviations:
AF: atrial fibrillation; AV: atrio-ventricular; BMI: body mass index; CRT-P: cardiac resynchronisation therapy-pacemaker; CRTD: cardiac resynchronisation therapy-defibrillator; IQR: interquartile range; IVCD: intraventricular conduction delay; LVEF: left ventricular ejection fraction; LBBB: left bundle branch block; NYHA: New York Heart Association

Complications

There was a total of 26 complications between the groups (12.7% in CRT-D group vs. 13.9% in CRT-P group, p=0.83) (**Table 19**). During the first 24-hours after device implantation, there were 11 perioperative complications (5.7% in CRT-D vs. 4.7% CRT-P, p=0.78). There was no difference in the occurrence of early and late complications (**Table 19**).

Mortality

During the follow-up of up to 10.2 years (median of 4 (2.8) years), 29 (14.5%) patients (14.7% in CRT-D vs.13.9% in CRT-P, p=0.91) had died. Of these deaths, 23 were classified as cardiovascular death, 3 deaths were due to malignancy and 2 from other non-cardiac causes (p=0.91). One was classified as unspecified cause

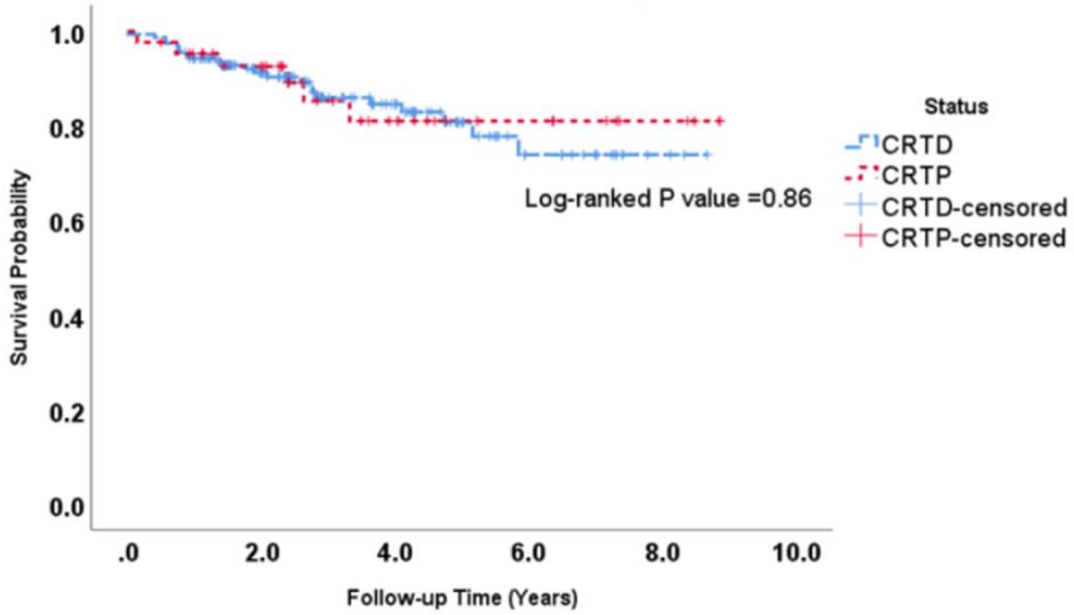
Of the 23 cardiovascular deaths, 17 (73.9%) were due to HF and 6 (26.1%) deaths were attributable to myocardial infarction (MI), or cerebrovascular accidents. No sudden arrhythmic death was reported. There was no difference in all-cause mortality observed over time (**Figure 17**).

Table 19: Complications among CRT-D and CRT-P Patients

	CRTD (n = 157)	CRTP (n = 43)	P Value
Acute Perioperative Complications	9 (5.7%)	2 (4.7%)	0.78
Lead displacement/remanipulation	7 (4.5%)	1 (2.3%)	0.53
Coronary sinus dissection	1 (0.6%)	1 (2.3%)	0.97
Cardiac Tamponade needing intervention	1 (0.6%)	0	-
Early Complications	**2 (1.3%)**	-	-
Lead displacement/remanipulation	2 (1.3%)	0	-
Late Complications	9 (5.7%)	4 (9.3%)	0.4
Lead issues needing intervention	7 (4.5%)	3 (6.9%)	0.5
Device/pocket issues requiring intervention	1 (0.6%)	0	-
Device pocket infection needing extraction	1 (0.6%)	1 (2.3%)	0.97

Abbreviations:
CRT-D: cardiac resynchronisation therapy-defibrillator, CRT-P: cardiac resynchronisation therapy-pacemaker

Figure 17: Kaplan-Meier survival curve of all-cause mortality in CRT-D and CRT-P patients



Number At Risk					
Year	0	2	4	6	8
CRT-D	156	106	28	17	2
CRT-P	42	32	15	8	3

All-cause and Heart Failure Hospitalisations

During follow-up, there were 566 all-cause hospitalisations in 139 patients. These include 114 (20.1%) HF admissions. The median duration from implant to first HF hospitalisation were 2.86 (9.23) months. The median length of stay was 4 (2) days. For CRT-D and CRT-P patients, the median duration to first HF hospitalisation after implant was similar (2.9 [0.53] vs. 2.7 [1.3] months, respectively).

Device Therapy

Among the 157 CRT-D patients, 34 (21.7%) had device therapy (anti-tachycardia pacing [ATP] with or without shocks). Twenty-three (19.8%) of these occurred in those with a primary prophylactic device and 11 (26.8%) in patients with secondary prevention devices (p=0.35). Overall 6.4% (10) of the patients had inappropriate shocks, most commonly because of AF (60%) or supraventricular tachycardia (SVT) (30%).

Discussion

This study describes the trends of CRT therapy use for eligible HF patients in New Zealand. We have observed a gradual increase in CRT-D implantation across the study period, with an increase in the proportion of patients receiving these devices for primary prevention of SCD and management of HF. However, CRT-P devices still accounted for <25% of the total CRT devices implanted over the study period. Despite the increasing evidence supporting CRT use in appropriate HF patients and a rapidly growing HF population, there are still a large number of eligible patients not receiving this therapy. In the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF) Study, a total of 1373 patients were eligible for CRT devices based on guideline criteria but only 533 (38.8%) received CRT devices, with 84.1% of these treated with CRT-D.[294] In the Swedish Heart Failure Registry (SwedeHF), 3094 patients (24%) of 12807 patients met the indication for CRT

but did not receive the device and only 841 (7%) had CRT.[295] The trends of CRT implantation in the United States from the Nationwide Inpatient Sample (NIS) database showed that the total number of CRT implants increased significantly between year 2002 and 2006 but has not shown a significant increase since 2006.[296] The majority of the devices implanted were CRT-D (86%) with CRT-P constituting the minority, with a progressive decrease in use from 28.8% in 2002 to 15.2% in 2010.[296] By contrast, other European countries are still implanting a significant number of CRT-P: 39% in France, 44% in Sweden, 46% in Belgium in 2013.[297] The regional differences in implant rates most likely reflect the differences in health care system and the reimbursement situations.

Martin et al. published the largest series of CRT procedures in New Zealand with only 139 patients between year 2000 and April 2011 in the Auckland region.[273] Since then, there has been a steady increase in the number of implant of these devices as shown in our study with the majority of the devices implanted being CRT-D. The number of CRT-P implanted remained static throughout the study. Affordability and capacity are of concern in this region. Despite the increasing number of HF patients year-by-year, only a small proportion of patients received these devices (**Figure 15** and **Figure 16**). For example, in the 2014 year, 8311 patients with HF were admitted within the region. Assuming that approximately 30% would potentially meet criteria for consideration of CRT support, there is a clear evidence of under referral for and implantation of such devices (**Figure 15**).

There are numerous potential reasons for this including: (1) concerns regarding affordability and capacity, (2) lack of familiarity with the indications for CRT, under-appreciation of the potential benefits of an upgrade to CRT from an existing ICD or pacemaker, and (3) physicians misconceptions about the procedural risks and device complications, which may discourage referrals for implantation.[298] Identification of eligible patients for possible CRT implantation is important. It may seem to be a relatively straightforward to identify the inclusion and

exclusion criteria as outlined in peer-reviewed guidelines, but in clinical practice recognition of appropriate patients and utilisation rate of CRT are far from satisfactory. Findings from several large registries have suggested that underutilisation of CRT in potentially appropriate patients exists.[249,294,299] Utilisation of CRT devices varies widely among contemporary outpatient HF practices, ranging from 38.8% of eligible patients receiving CRT-P to 84.1% of eligible patients receiving CRT-D.[294] Considering current workforce, funding constraints and the conservative approach taken, the published 2010 New Zealand guidelines (**Table 17**) have more restrictive recommendations for CRT. Given the funding issues, all referrals required discussion by the Northern Region implanting electrophysiologists regarding suitability and appropriateness before undergoing implantation.

CRT is limited to HF patients who meet specific clinical criteria (low LVEF and wide QRS duration on ECG). Assessment of LVEF is a criteria common to ICD and CRT referrals but McHale et al. showed that restricted access to investigations such as echocardiography are considered a significant barrier to referral.[280] Regional differences in echocardiography services were described in New Zealand in 2005 using the Survey of Clinical Echocardiography Around New Zealand (SCANZ).[300] In the Recent 2013 SCANZ Workforce Survey, Buckley et al demonstrated that regional disparity in public echocardiography in New Zealand still exists with unequal geographic distribution of echo services.[301] The reasons are likely multifactorial and contributed to by DHB demographic differences in age, ethnicity, and socioeconomic deprivation status as well as the size and demographics of the cardiac sonographer workforce.[301] In our study, echocardiographic assessments and cardiac MRI were the most commonly used measures, with all patients requiring LVEF to be quantified prior to discussion regarding clinical care with device support. LVEF is one of the most commonly reported measures of left ventricular systolic function. LVEF can be determined using several invasive and non-invasive imaging modalities, either subjectively by visual estimation or

objectively by quantitative methods.[302] Currently, there is no universally accepted 'gold standard' for measuring LVEF. Each method has limitations and potential for error.[302] Many factors should be taken into account when deciding which method is the most appropriate for an individual patient. The different ways to assess LVEF is beyond the scope of the current study because our study aimed to review the utilisation and outcomes of CRT patients in the Northern Region of New Zealand.

In our study, 29 (14.5%) patients (14.7% in CRT-D vs.13.9% in CRT-P, p=0.91) had died at the end of follow-up. The total mortality was relatively low compared to the published Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial (15%) and the CArdiac REsynchronization-Heart Failure (CARE-HF) trial (20%).[83,84] One explanation is the younger population in our study. The mean age of our patients was 62.4 years vs. 67 years in both COMPANION and CARE-HF.[83,84] Even though our CRT-P patients was older compared to the CRT-D patients, they were still relatively younger (mean age of 64.9 years) when compared to CARE-HF where only the impact of CRT-P was assessed.[83] This is likely due to the more conservative New Zealand guidelines for ICD and CRT-D in patients with HF compared to the International guidelines.[276] Another potential factor contributing to the lower mortality relates to the majority of the cohort have NICM or pacemaker-induced cardiomyopathy. Patients with NICM are known to respond better to CRT than those with ICM. Data from recent clinical trials showed that patients with ICM and NICM gained similar clinical benefit from CRT when compared with medical treatment, but NICM patients had greater reverse remodelling compared with ICM patients.[217,303,304] In The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchroniszation Therapy (MADIT-CRT), the magnitude of the echocardiographic effects of CRT-D with reverse remodelling effects was shown to be significantly higher among NICM patients.[97]

Thirty-nine (19.5%) of our patients had underlying pacemaker-induced cardiomyopathy. Pacemaker-induced cardiomyopathy may be more common than previously reported. Yu et al. found a 9% incidence of pacemaker-induced cardiomyopathy and Zhang et al. reported new-onset HF symptoms in 26% of patients with frequent right ventricular (RV) pacing over 7.8 years follow-up.[305,306] In a retrospective study by Khurshid et al, 19.5% developed pacemaker-induced cardiomyopathy with a decrease in mean LVEF from 62.1% to 36.2% over a mean follow-up period of 3.3 years.[307] In the Mode Selection (MOST) Trial, RV pacing >40% increased risk for HF hospitalisation and incidence of AF compared to values below 40%.[308] We defined pacemaker-induced cardiomyopathy based on the preserved/normal LVEF and absence of HF symptoms at the time of initial pacemaker implantation and the progressive deterioration of HF symptoms and deterioration of LVEF years after chronic RV pacing without any other plausible alternate explanation. Eleven of the 29 patients with pacemaker-induced cardiomyopathy underwent AV nodal ablation therefore rendering them pacemaker-dependent. The remainder have had at least 98% RV pacing with deteriorating LVEF and HF symptoms over time. According to recent guidelines, upgrade from conventional pacemaker or ICD to CRT is a class 1 indication in HF patients with LVEF <35% and a high percentage of RV pacing who remain between NYHA class III and ambulatory class IV despite adequate medical treatment.[85] An upgrade to CRT can potentially prevent the adverse remodelling associated with chronic RV pacing. Response to CRT further decreases the risk for ventricular arrhythmias, SCD, and all-cause mortality which could account for the lower mortality in our study patients.

Changes in the way in which HF patients are managed (including advances in medical therapy, treatment of comorbid disease and risk factors for the development of HF, and the recognition of the value of HF disease management programmes) throughout the study period could also explain the lower mortality in our study.[1] All of our CRT-P patients met indications for primary

prevention ICD implantation based on international guidelines but not the New Zealand guidelines.[271,276] An ICD was not implanted in this group of patients with a poorer baseline status and higher LVEF compared with those who received CRT-D. However, the number of deaths observed was similar and there was no survival difference between the two groups. No sudden arrhythmic death was reported in either group. This could be explained by the small sample size of both CRT-D and CRT-P and potential selection bias of candidates due to the more conservative recommendations of the New Zealand guidelines.

During the longer follow-up period in our study, 27.6% deaths were a result of progressive HF. This suggests that despite a more conservative approach, there was no survival penalty for those undergoing CRT-P rather than CRT-D support in our study. The mode of death in the COMPANION trial was most commonly pump failure (44.4%) even though both CRT-D and CRT-P modestly reduced mortality.[96] The CARE-HF trial confirmed that progressive HF deaths remained the leading cause of death in HF populations.[83] Current international guidelines give the same level of recommendation for CRT-P and CRT-D use.[85,309] No clear preference is given to any treatment modality compared with the other. Prescription of these costly and complex devices should be preferentially for patients in need of secondary prevention or for the purpose of primary prevention in younger patients without major comorbidities.

Despite the low implant numbers, our peri-operative and late complication rates are comparable to published data.[128,310] There is cumulative evidence that implanting CRT-D devices is associated with a higher perioperative and postoperative risk of major complications compared with CRT-P. Romeyer-Bouchard et al. reported an increased risk of infection with CRT-D devices compared with CRT-P.[211,310] Another Danish study showed that the incremental risk of perioperative or 6-months postoperative complications was 1.5 (0.9–2.3), (p=0.11) for CRT-P and 2.6 (1.9–3.4), (p<0.001) for CRT-D compared with conventional pacemakers.[310]

However, in our study there was no differences in peri-operative and late complication rates between the two groups. This may be explained by the small number of CRT-P included in the study, and therefore no conclusive differences in complications could be drawn.

Limitations

Our study is a retrospective study with prospective follow-up. The sample size of CRT-P was very small compared with CRT-D. Device prescription was not randomised, therefore patients with poorer functional status and limited expected survival were implanted preferentially with CRT-P compared to CRT-D.

There were more NICM and pacemaker-induced cardiomyopathy patients compared to ICM patients in our study. The published 2010 New Zealand guidelines have stricter recommendations for ICD and CRT-D in patients with HF compared to the International guidelines. Considering only a small proportion of HF patients in the Northern Region have been selected for CRT-support, it is likely that a sizable group of HF patients are not being referred therefore, missing out on appropriate device support. Confounder and selection bias should be kept in mind when interpreting the results of our study.

Our study does not represent the entire New Zealand. The 4 DHBs in Northern Region serve 38% of the total New Zealand population.[292] The implant numbers and the practice will be different from other implanting centres in the country.

The main strength of our study was long duration of follow-up (total duration of 10.2 years), accepting the limitation of a small cohort size. Uniquely we were able to classify the mode of death in 99.5% patients and able to capture all deaths rather than just in-hospital death. Only 1 patient had an unspecified cause of death in the community. We were also able to capture all the hospitalisation events in detail for patients. Furthermore, our study measured the outcomes including mortality and hospitalisations after implant, which is important when making decisions about the appropriate device choice for individual HF management.

Conclusion

There has been a steady increase in CRT implantation over time in the Northern Region of New Zealand. While the optimal per population implantation rate is speculative, this data suggests that there is a significant unmet clinical need for CRT implantation in the Northern Region. The reasons for low implantation of CRT devices require further examination.

Additional analysis: Cardiac Resynchronisation Therapy in heart failure patients with chronic kidney disease

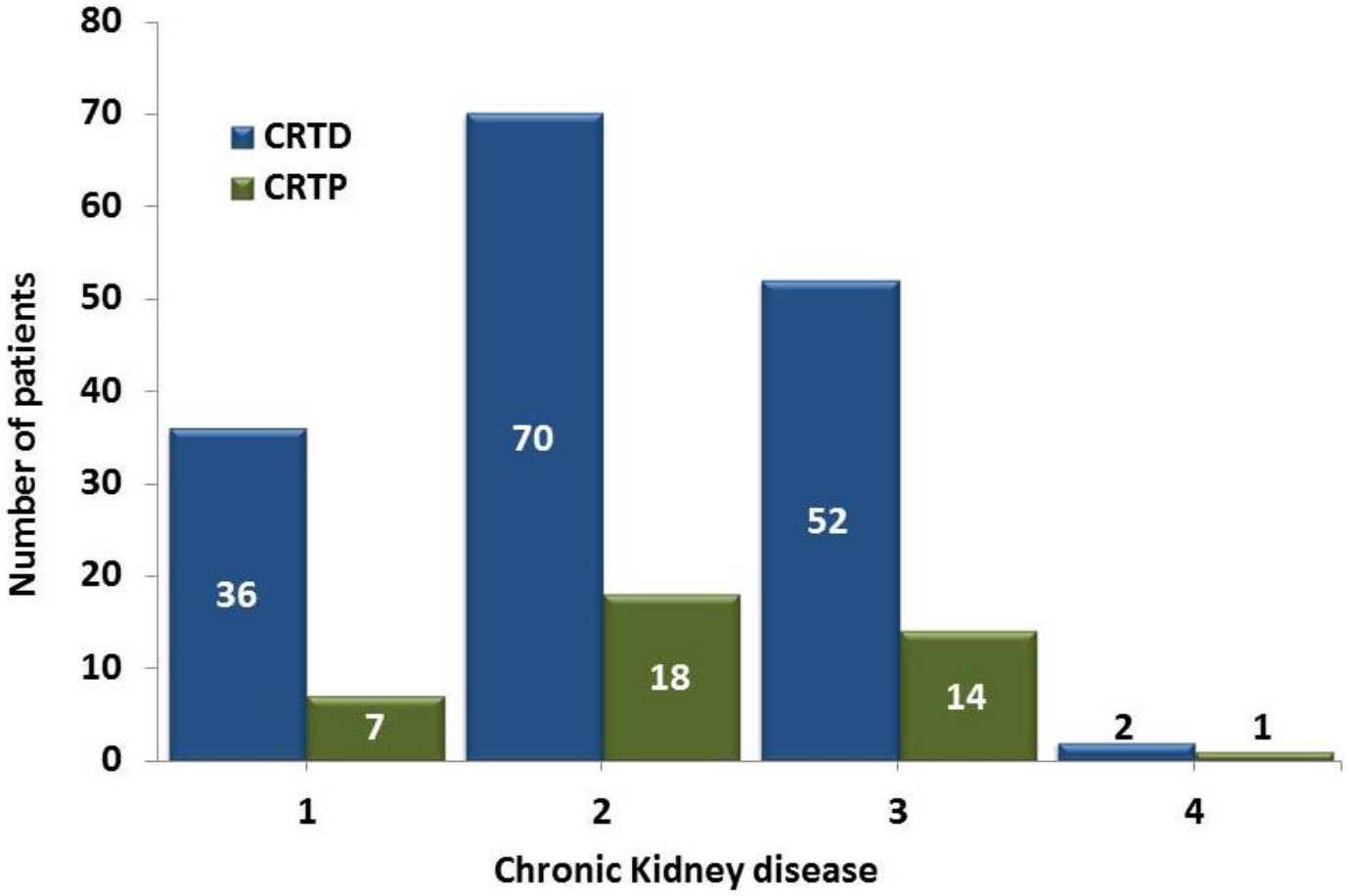
Patients with both HF and chronic kidney disease (CKD) have increased risk of mortality and morbidity. CRT has been shown in multiple studies to improve HF symptoms, quality of life (QoL) and improve survival. However, the majority of the studies supporting the use of CRT have limited data on HF patients with CKD.

We examined the trends in CRT use and outcomes in HF patients with CKD. All the HF patients in the Northern Region of New Zealand who were implanted with CRT devices from Jan 2007 to May 2015 were included. This includes all de-novo CRT (CRT-P and CRT-D) implants, upgrades and epicardial lead implants. All-cause mortality and procedure-related complications were compared in HF patients with different stages of CKD.

A total of 200 patients had a CRT device implanted during the study period. Majority of the patients [89(44%)] were in CKD stage 2 (mean eGFR 71.2±9.1mL/min/1.73m2) **(Figure 18** and **Table 20)**.

No patients were on renal replacement therapies (CKD stage 5) in the study.

Figure 18: The distribution of CRT-D and CRT-P in different stages of CKD



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

Table 20: Baseline characteristics of patients with heart failure and CKD who received CRT devices

	CKD 1 (n=43)	CKD 2 (n=88)	CKD 3 (n=66)	CKD 4 (n=3)	P value
Mean Age (years)	55.5 (13.5)	62.6 (10.3)	66.8 (7.1)	67.2 (11.4)	<0.0001
Gender					0.0918
Female	6 (14%)	22 (25%)	19 (29%)	2 (67%)	
Male	37 (86%)	67 (75%)	47 (71%)	1 (33%)	
Ethnicity					0.3782
NZ European/Other European	36 (84%)	67 (75%)	54 (82%)	2 (67%)	
Maori	1 (2%)	8 (9%)	3 (5%)	0	
Pacific Islander	2 (5%)	11 (12%)	5 (8%)	1 (33%)	
Asian	3 (7%)	3 (3%)	4 (6%)	0	
Mean LVEF	25.6 (7.2)	26.4 (7.7)	28 (8.9)	28.3 (2.9)	0.4768
Mean eGFR	>90	71.2 (9.1)	48.3 (7.9)	28.7 (0.6)	<0.0001
Diabetes Mellitus	6 (14%)	23 (26%)	13 (20%)	2 (67%)	0.1111
Hypertension	10 (23%)	19 (21%)	23 (35%)	2 (67%)	0.0856
NYHA Class					0.1134
I	11 (26%)	9 (10%)	4 (6%)	0	
II	17 (40%)	39 (44%)	28 (42%)	2 (67%)	
III	15 (35%)	41 (46%)	33 (50%)	1 (33%)	
IV	0	0	1 (2%)	0	

Abbreviations:
CKD: chronic kidney disease; CRT: cardiac resynchronisation therapy; eGFR: estimated glomerular filtration rate; LVEF; left ventricular ejection fraction; NYHA: New York Heart Association

Acute procedural complications occurred more frequently in CRT patients with CKD stage 3 and 4 (7.7% and 33%, respectively, p=0.0291) but there were no differences in the late complications between the CKD groups (p=0.1679) (**Table 21**).

The total follow-up duration was 10.2 years with a mean follow-up duration was 4.51±2.26 years (median 4 [2.82 - 5.86] years). There was no difference in mortality rates between CKD groups were noted (P=0.5807) (**Figure 19**).

In "real-world" clinical practice, HF patients with severe CKD (stage 5) were excluded from receiving CRT devices. Our study showed that HF patients with CKD stage 3 and 4 have higher rates of acute procedural complications. Additional studies are needed to further evaluate the role of CRT on morbidity and mortality in such patients. A National registry is crucial to collecting the data, complications and outcomes to aid quality improvement initiatives and to allow examination of equity of access to these devices.

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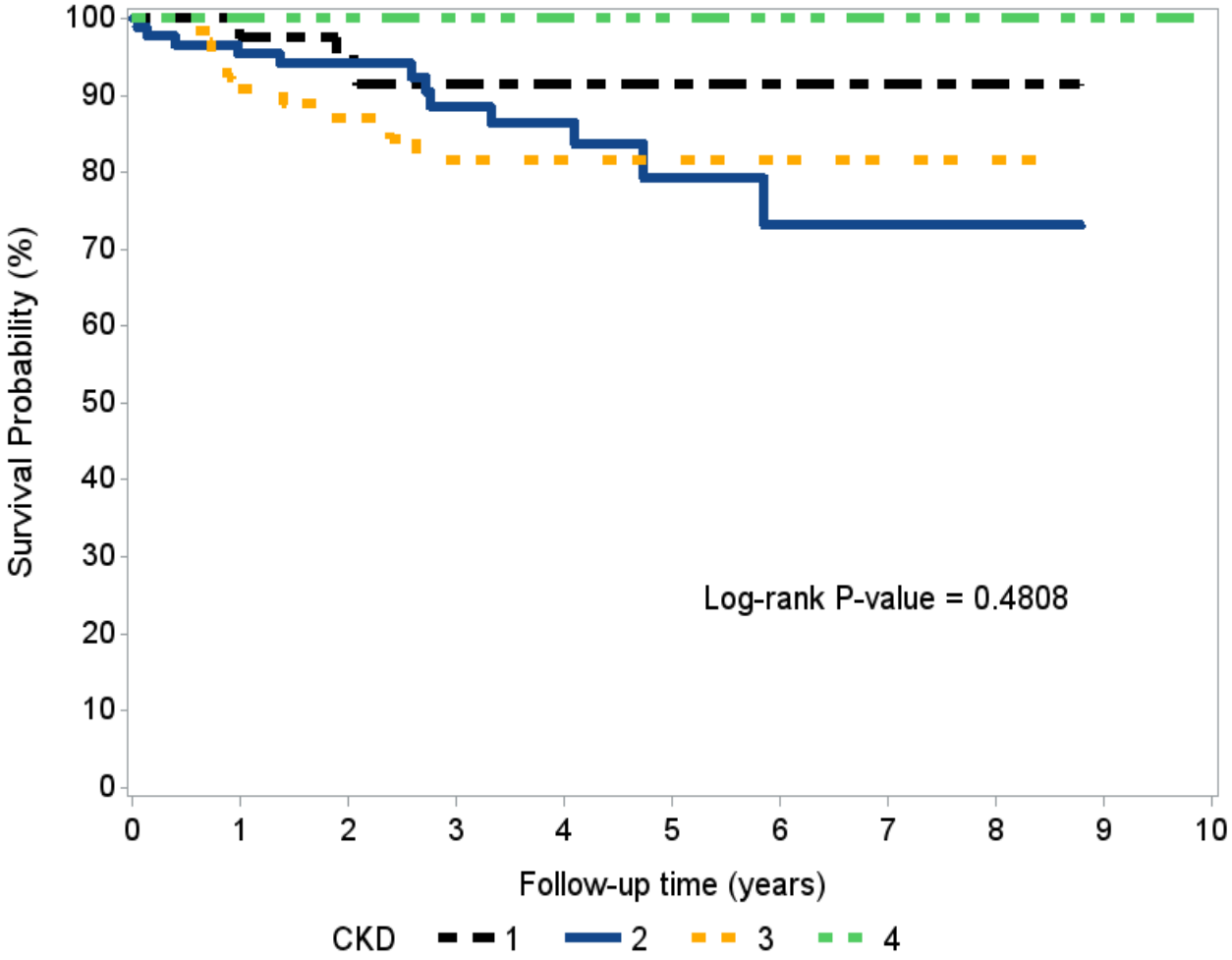
Table 21: Acute complications vs late complications between the CKD groups

Complications	CKD 1 (n=43)	CKD 2 (n=88)	CKD 3 (n=66)	CKD 4 (n=3)	P Value
Acute (≤ 24 hours)	0	2 (2%)	5 (7%)	1 (33%)	0.0291
Late (≥ 24 hours)	5 (12%)	7 (8%)	3 (4%)	1 (33%)	0.1679

Abbreviations:
CKD: chronic kidney disease

Figure 19: Kaplan Meier survival curve of CRT patients with different stages of CKD



Abbreviations:
CKD: chronic kidney disease; CRT: cardiac resynchronisation therapy

5.5 GENDER DIFFERENCES IN THE USE OF PRIMARY PREVENTION ICDs IN NEW ZEALAND HEART FAILURE PATIENTS

Preface

Epidemiological and clinical registry data suggest that women account for approximately one half of the patients hospitalised for HF.[110-112] Previous studies have shown that women treated for HF are more likely than men to have preserved systolic function and significantly less likely to be prescribed guideline-recommended evidence-based medications, and when these are prescribed for women, they tend to be prescribed at suboptimal doses.[111,113,114] The reasons behind the discrepancy in management of HF in men and women remain unclear.

Clinical trials of ICDs have demonstrated the overall survival benefits of primary prevention ICDs.[60-63,67] The recommendations of ICDs have not differed for men and women according to current guidelines.[64] However, many of the clinical trials of ICDs were underpowered to assess the impact of ICDs for women. Only small numbers of women were enrolled into and received ICDs in these trials: <20 each in MUSTT and MADIT trials and only 185 in SCD-HeFT.[61,63,115] Similarly, women remain significantly under-represented in CRT trials despite multiple studies demonstrating a significant mortality benefit with CRT in eligible HF patients.[83,84,86,87]

The aim of the research presented in this chapter was:

- To investigate gender differences in the use of primary prevention ICD in HF patients from the Northern Region of New Zealand.

The research study shows that despite the higher perioperative complications in women who received primary prevention ICDs, there was no significant mortality difference compared to men. This study highlights the importance of ongoing gender-specific analysis in medical device clinical studies to further improve the application of available evidence on ICDs in appropriate eligible women with HF.

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Contribution of Candidate:

Khang-Li Looi was involved in the data collection and analysis, as well as in developing arguments and writing of the manuscript for publication.

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Abstract

Objective

Women have been under-represented in randomised clinical trials for primary prevention implantable cardioverter-defibrillators (ICDs) and there are concerns about the efficacy of devices between the genders. Our study aimed to investigate gender differences in the use of primary prevention ICD in heart failure patients from the Northern Region of New Zealand.

Method

Heart failure patients with systolic dysfunction who received primary prevention ICD/cardiac resynchronisation therapy-defibrillator (CRT-D) in the Northern Region New Zealand from 1st Jan-2007 to 1st June-2015 were included. Complications, mortality and hospitalisation events were reviewed.

Results

Of the 385 heart failure patients implanted with ICD/CRT-D, women comprised of 15.1% (n=58) and no change in utilisation of these devices was observed over the study period among women. Women were more likely to have non-ischaemic cardiomyopathy and have higher perioperative complications (8.6% vs. 2.5%, p=0.02) with non-significant higher trend towards increased lead displacement (5.2% vs. 1.8%, p=0.12). Women appeared to have lower all-cause (10.3% vs. 18.7%, p=0.12), cardiovascular (5.2% vs. 11.9%, p=0.13) and heart failure mortalities (3.5% vs. 7.9%, p=0.22) but was not statistically significant. There were no gender differences in all-cause (70.7% vs. 67%, p=0.58) or heart failure readmissions (19% vs. 25%, p=0.32).

Conclusion

Perioperative complications were significantly more common in women referred for ICD/CRT-D. Although there has been a significant increase in ICD implantation rates, gender

differences in the use of these devices still exist in New Zealand, in keeping with the demographics of ischaemic heart disease and systolic dysfunction between the genders.

Introduction

Clinical trials in the use of implantable cardioverter defibrillators (ICDs) and cardiac resynchronisation therapy (CRT) have demonstrated overall survival benefits in selected patients with heart failure (HF).[62,63,67,83,84] ICDs reduce the risk of sudden cardiac death (SCD), whereas the mortality benefit of CRT is related, in part, to favourable left ventricular reverse remodelling with attenuation of both HF death as well as SCD.

The role of primary prevention ICD in women with HF has not been well established. Many of the clinical trials of ICDs were underpowered to assess risks and benefits of ICDs in women. Traditionally women have been under-represented in trials of HF and ICD therapy with only small numbers of women being enrolled.[61,63,115] According to current international guidelines, recommendations for primary prevention ICD/CRT-D are not different for men and women with HF and impaired left ventricular function. A meta-analysis of the 5 primary prevention trials (Multicenter Unsustained Tachycardia Trial [MUSTT], Multicenter Automatic Defibrillator Implantation Trial [MADIT II], The Defibrillator in Acute Myocardial Infarction Trial [DINAMIT], Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation [DEFINITE] and Sudden Death in Heart Failure [SCD-HeFT]) showed that men, but not women derived a survival benefit from ICD as compared to anti-arrhythmic drugs.[224] However, a recent primary prevention trial in patients with HF confirmed equal survival advantage in both men (hazard ratio [HR] 0.76, 95% confidence interval [CI], 0.67-0.87, $p<0.001$) and women (HR 0.78, 95% CI, 0.66-0.92, $p=0.003$).[311] These findings support the use of primary prevention ICD in eligible patients regardless of gender.

Despite women accounting for 50% of HF admissions, eligible women were less likely to receive an ICD compared to men (40% lower odds).[312] In New Zealand, a gender difference in

ICD implantation was documented by Larsen et al. during the period of 2000-2007.[265] The study showed the majority (71%) of the primary prevention ICDs being implanted were in men.[265] Currently there is no data on the use of primary prevention ICD for women with HF in New Zealand. Our study aimed to examine the gender differences in the use of primary prevention ICDs in HF patients in the Northern Region of New Zealand.

Method

This was an observational study that included HF patients who received primary prevention ICD/CRT-D in the Northern Region of New Zealand. The Northern Region of New Zealand is defined as the 4-northernmost District Health Boards (DHBs) areas and consists of Auckland DHB, Counties Manukau DHB, Northland DHB, and Waitemata DHB. The 4 DHBs in the Northern Region serve 38% of the total New Zealand population with an estimated 1.76 million people in this region.[292] The study period was from January 2007 to 1st June 2015. We included patients undergoing all de novo ICD and CRT-D implants, all pacemakers upgrades to ICD and CRT-D and epicardial lead placement with CRT-D. Procedures involving solely ICD and CRT-D pulse generator replacement were excluded.

Patient demographic data, procedure-related data, acute (within 24 hours of implant), early (>24-hours to 2 weeks from implant) and late (≥2-weeks after device implantation) complications were obtained via review of pacing database and clinical records held on electronic Clinical Record Information System (CRIS).

Mortality data was collected using New Zealand mortality collection and National Minimum Datasets (NMDS) inpatient hospitalisation data. These include all registered deaths rather than just deaths in the hospital. The cause of death data was available up until the end of 2013. For those with no cause of death data from NMDS, review of clinical records was performed to further determine the cause of death.

Hospitalisation events were identified using the administrative data of the Ministry of Health (MoH) and NMDS inpatient hospitalisation data via National Health Index (NHI) linkage up to December 2015. The NHI number is a unique identifier that is assigned to every person who uses health and disability support services in New Zealand. HF hospitalisation was defined using the International Classification of Diseases diagnosis 10 (ICD-10) codes (I110, I130, I132, I500, I501 and I509).

Ethics approval for the study was obtained from the Central Health and Disability Ethics Committee (Ethics ref: 15/CEN/58/AM02).

Statistical analysis

Baseline demographics were summarised as means with 1 standard deviation (SD) or frequencies with percentage (%). Comparisons of baseline characteristics between genders were conducted with either the Wilcoxon rank-sum test, the Chi-Squared test or the two-sample Z test. Plots to depict the implantation frequency of ICD and CRTD among men and women over the course of the study were constructed. Kaplan-Meier survival curves were generated to depict the distribution of cardiovascular and heart failure mortalities over time. The difference of the survival distributions between men and women were evaluated with the log-rank test.

The difference in complication rates, device therapy treatment rates and mortality rates between genders were assessed with the Chi-Squared test or the two-sample Z test. Readmission rates between genders were compared with the two-sample Z test. Logistic regression was used to determine predictors of all-cause mortality and heart failure mortality after adjusting for baseline characteristics.

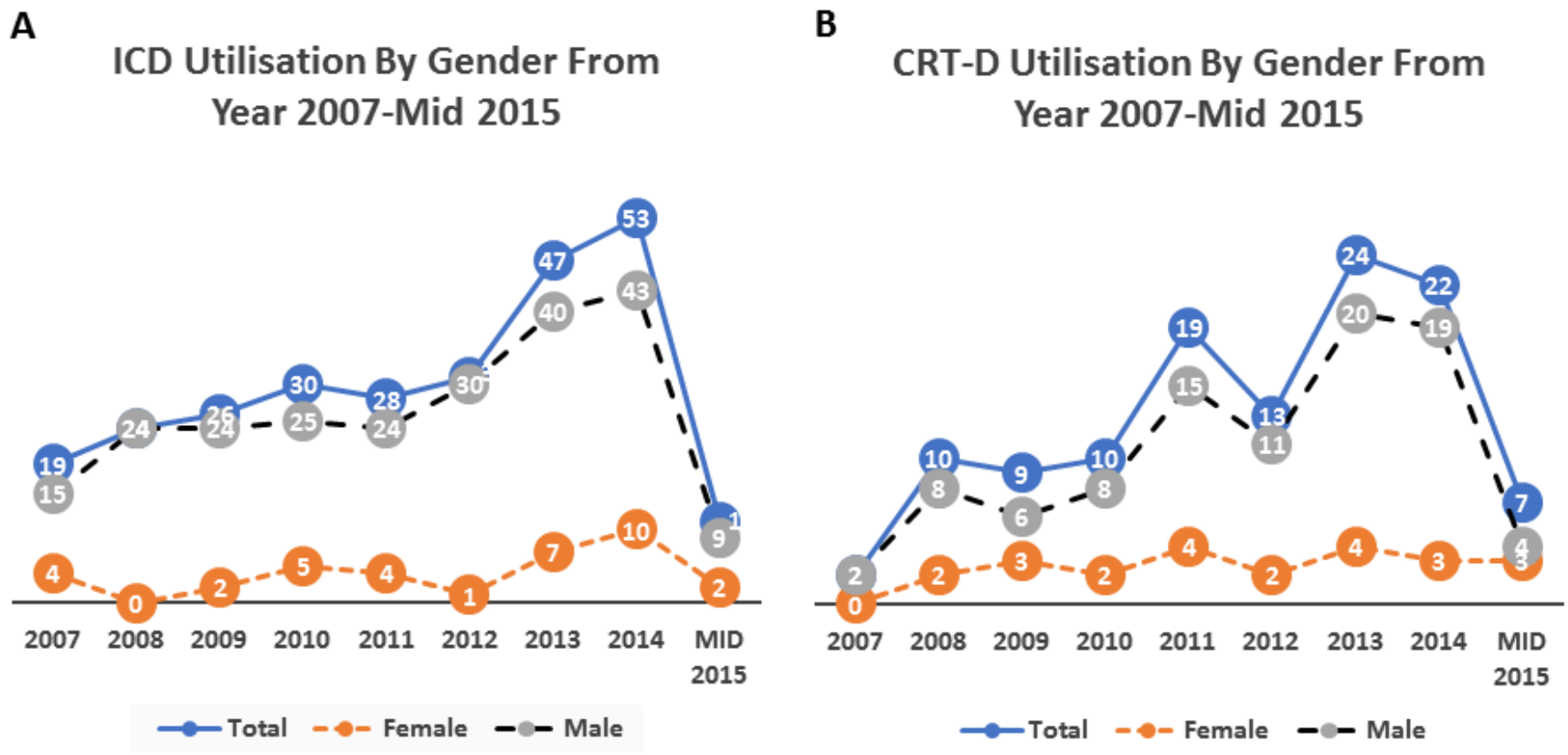
Statistical analyses were performed using the statistical package SAS version 9.3 (SAS Institute, Cary, NC). All p-values resulted from two-sided tests and a p-value of <0.05 was considered statistically significant.

Results

From January 2007-June 2015, a total of 385 HF patients underwent 404 procedures. Women comprised 15.1% (n=58) of the study cohort. Throughout the study period, there were differences in ICD/CRT-D utilisation in men and women. In men, there was a steady increase in ICD/CRT-D utilisation but this trend of increase was not seen in women (**Figure 20**).

Differences in baseline characteristics were summarised in **Table 22**. Women were more likely to have non-ischaemic cardiomyopathy (NICM) and cardiac sarcoidosis than men. In addition, women had a higher prevalence of left bundle branch block (LBBB) (43.1% vs. 32.4%) but were less likely to have chronic atrial fibrillation (AF). No significant differences were found in age, mean left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) functional classes or other co-morbidities.

Figure 20: Utilisation of ICD/CRT-D in men and women over the study period



Panel A: Overall ICD utilisation in men and women over the study period

Panel B: Overall CRT-D utilisation in men and women over the study period

Table 22: Baseline characteristics of women and men with primary prevention ICD

	Women (n=58)	**Men (n=327)**	**p**
Mean Age (years ±SD)	58.2±12.3	59.2±11.3	0.68
Ethnicity (%)			
New Zealand European	40 (69.0)	197 (60.2)	
Maori	11 (18.9)	43 (13.2)	
Pacific Island	4 (6.9)	40 (12.2)	0.19
Asian	3 (5.2)	41 (12.6)	
Unspecified	0	6 (1.8)	
Height (meters)	1.63±0.07	1.75±0.07	<0.001
Weight (kg)	79.3±17.9	88.7±17.3	0.0012
BMI (m/kg^2)	29.9±6.3	28.9±5.3	0.29
DHBs (%)			
Auckland DHB	16 (27.6)	73 (22.3)	
Counties Manukau DHB	16 (27.6)	92 (28.1)	0.82
Northland DHB	4 (6.9)	29 (8.9)	
Waitemata DHB	22 (37.9)	133 (40.7)	
Underlying Aetiology			
Ischaemic cardiomyopathy	9 (15.5)	149 (45.6)	<0.0001
Non-ischaemic cardiomyopathy	37 (63.8)	155 (47.4)	0.0213
Valvular heart disease	2 (3.5)	5 (1.5)	0.3134
Cardiac Sarcoidosis	4 (6.9)	1 (0.3)	<0.0001
Others	4 (6.9)	17 (5.2)	0.6
Type of Devices			
ICD	35 (60.3)	234 (71.6)	0.08

Single chamber ICD	29 (50.0)	176 (53.8)	
CRT-D	23 (39.7)	93 (28.4)	
NYHA Class			
I	11 (19)	93 (28.4)	
II	35 (60.3)	169 (51.7)	0.31
III	12 (20.7)	65 (19.9)	
Mean LVEF (%)	24.2±5.0	24.4±5.4	0.48
Atrial Arrhythmias			
Paroxysmal AF	6 (10.3)	32 (9.8)	0.89
Chronic AF	3 (5.2)	65 (19.9)	0.0068
AV node Ablation	1 (1.7)	1 (0.3)	0.28
Diabetes Mellitus	12 (20.7)	72 (22.1)	0.81
Hypertension	15 (25.9)	94 (28.8)	0.64
QRS morphologic type			
RBBB	1 (1.7)	27 (8.3)	0.07
LBBB	25 (43.1)	106 (32.4)	
IVCD	4 (6.9)	19 (5.8)	
Paced	4 (6.9)	9 (2.8)	
Mean QRS duration (msec)	140.2±35	137.2±35.4	0.68
Estimated glomerular filtration rate(eGFR)			
Mean	60±15.2	63.4±14.9	0.13

Abbreviations:

AF: atrial fibrillation; BMI: body mass index; CRT-D: cardiac resynchronisation therapy-defibrillator; DHB: District Health Board; NYHA: ICD: implantable cardioverter defibrillator; IVCD: intraventricular conduction delay; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; RBBB: right bundle branch block; New York Heart Association

Complications

During the 24-hours immediately after device implantation, acute perioperative complications were more common in women compared with men (8.6% vs. 2.1%, p=0.008) (**Figure 21)**. In particular, women had a non-significant higher trend of lead displacement (5.2% vs. 1.8%, p=0.12) and cardiac tamponade requiring interventions (0.18% vs. 0) when compared with men. No significant differences were observed in early and late complications between men and women **(Figure 21**).

Device therapy

Overall 19.7% of patients received anti-tachycardia pacing (ATP) and 17.1% had appropriate ICD shocks for ventricular tachyarrhythmias. There was no gender difference in the need for appropriate ATP (13.8% in women vs.20.8%, p=0.22) or shocks (12.1% in women vs. 18%, p=0.27). There was no gender difference in the time to first ATP (3.6±2.6 years vs. 3.61±2.3 years, p=0.89) or time to first appropriate ICD shocks (3.7±2.6 years vs. 3.6±2.2 years, p=0.77). At the end of the follow-up, 9.1% of patients had received inappropriate shocks but no gender difference was noted (8.6% vs. 9.2%, p=0.89).

Mortality

The total duration of follow-up was 10.2 years with a mean duration of 3.64 ±2.17 years. At the end of the follow-up, a total of 67 (17.4%) patients had died: 61 (18.7%) men and 6 (10.3%) women (p=0.12). Women appeared to have lower cardiovascular mortality (5.2% vs. 11.9%, p=0.13) and HF mortality (3.5% vs. 7.9%, p=0.22) compared to men but was not statistically significant. There were only 2 sudden arrhythmic deaths and both were men. **Figure 22** and **Figure 23** showed the Kaplan-Meier survival curve for cardiovascular and HF mortalities in women and men.

Figure 21: Acute, early and late complications by gender

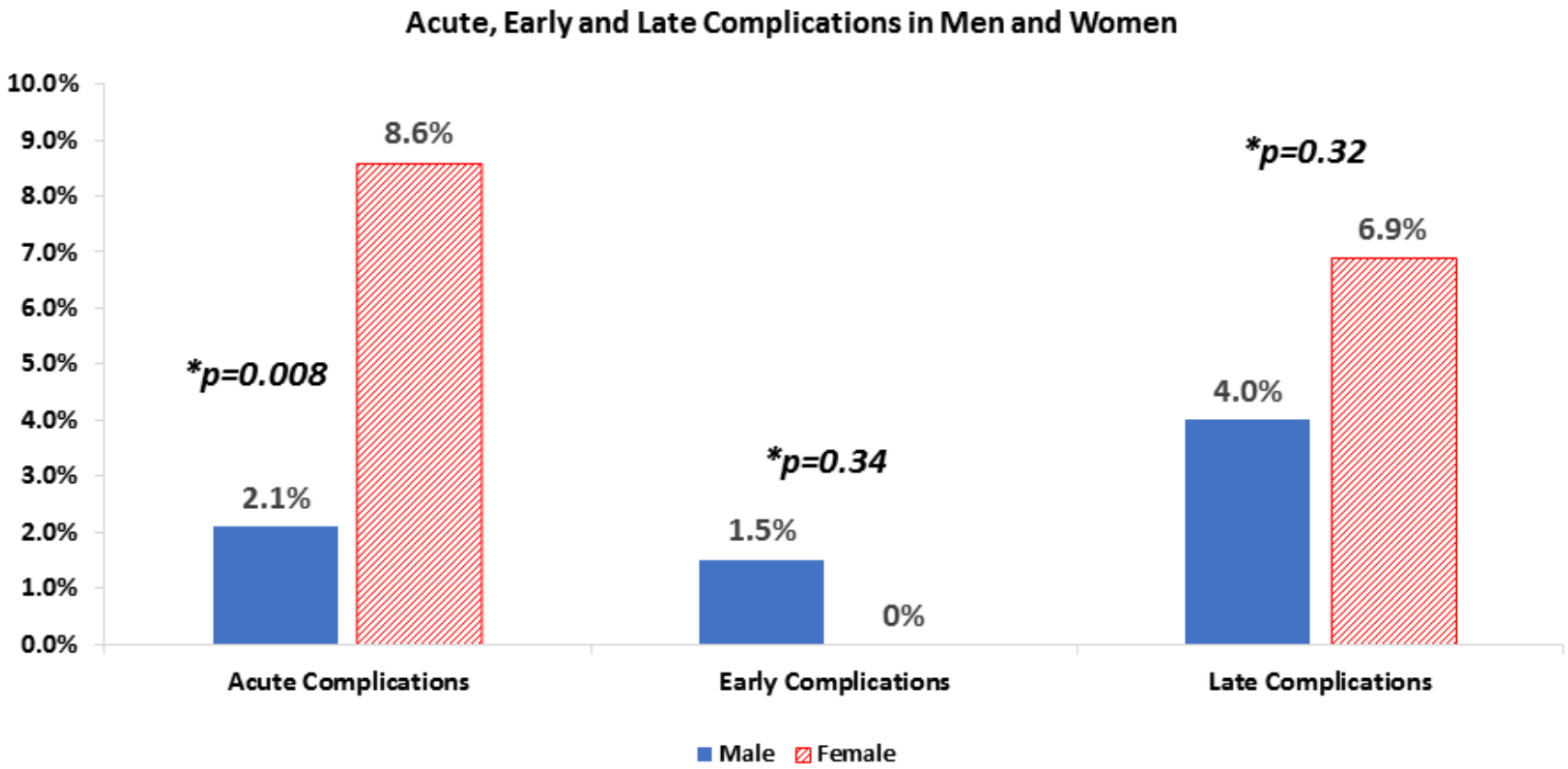


Figure 22: Kaplan-Meier survival curve for cardiovascular mortality

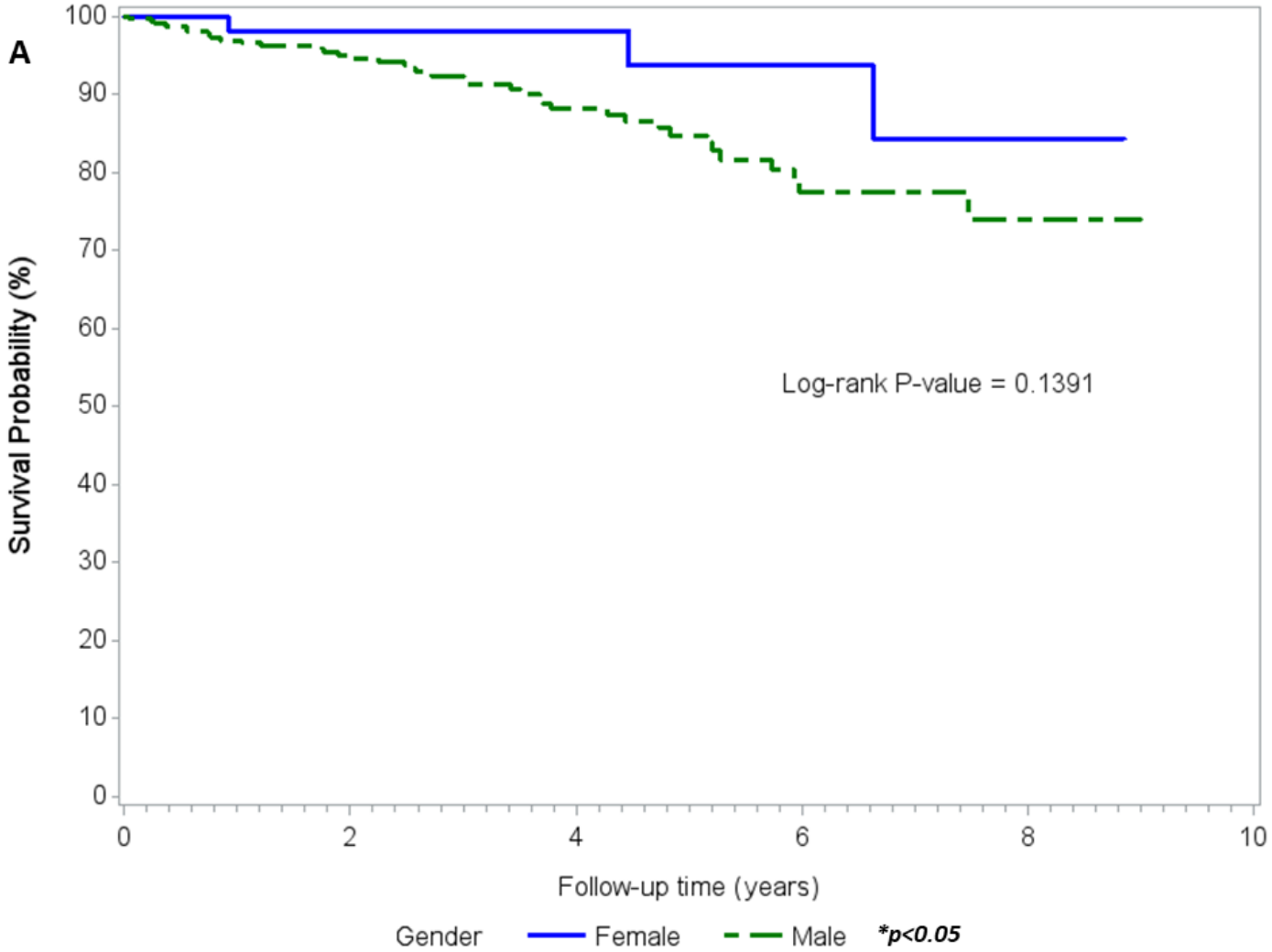
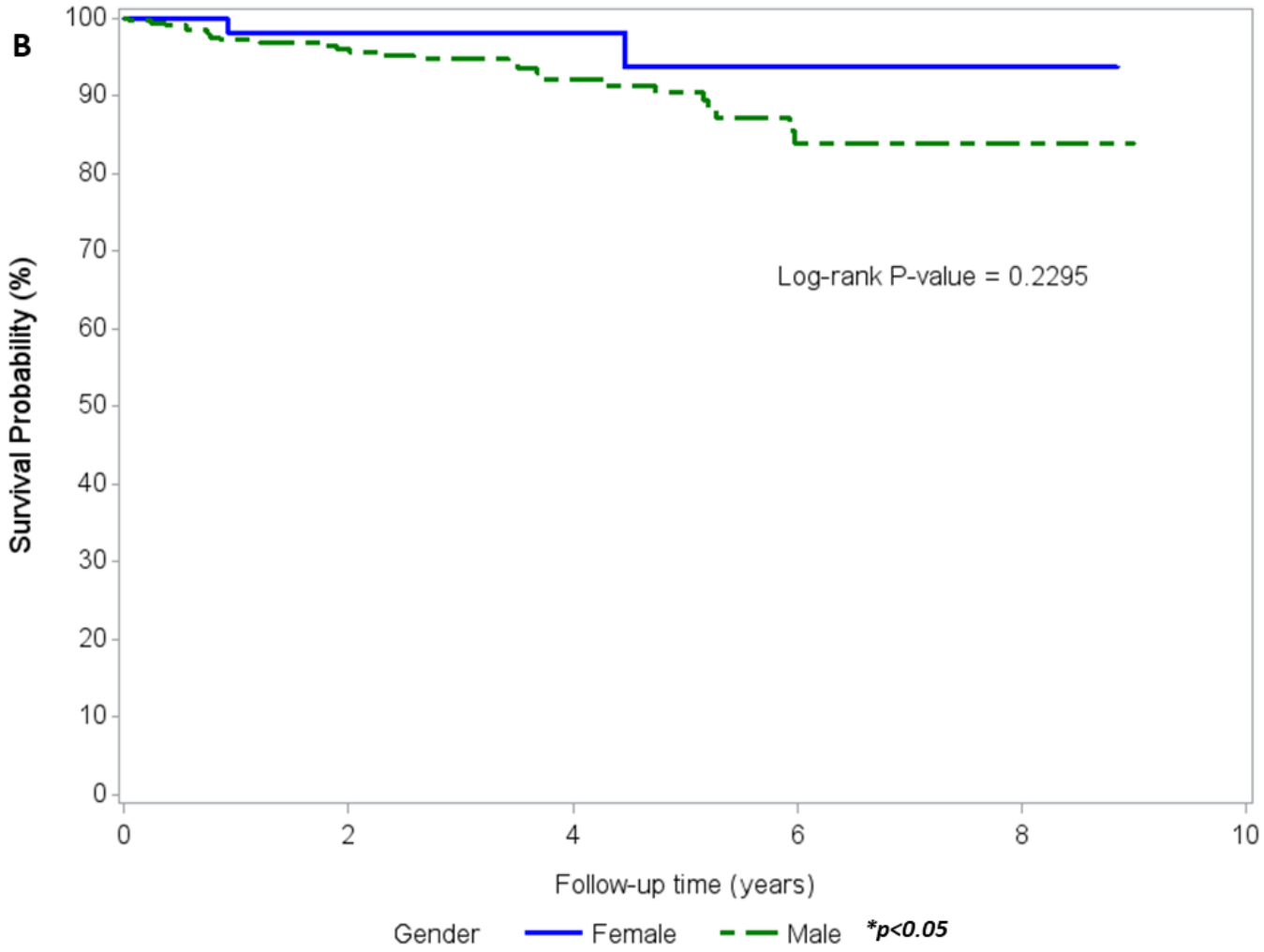


Figure 23: Kaplan Meier survival curve for heart failure mortality



After adjusting for baseline differences including gender, low LVEF (odds ratio [OR] 0.94, 95% confidence interval [CI] 0.892 - 0.99, p=0.02) was the only predictor of all-cause mortality whereas CRT-D use was associated with improved all-cause survival (OR 0.419, 95% CI 0.183 - 0.962, p=0.04). No predictors were of statistically significance in HF mortality.

All-Cause and Heart Failure Readmissions

During follow-up, there were 1194 all-cause hospital readmissions in 260 patients which include 275 (23%) HF admissions. All-cause readmissions occurred in 70.7% of women compared with 67% of men (p=0.58). HF admissions occurred in 19% of women compared with 25% of men (p=0.32).

Discussion

We examined the gender differences in the use of primary prevention ICD/CRT-D in real-world HF population in the Northern Region of New Zealand. The main findings are: (1) Women comprised only 15.1% of those who received primary prevention ICD/CRT-D. (2) In women undergoing implantation, there was a higher prevalence of NICM, LBBB with broader complex width and a lower prevalence of AF. (3) Women have overall higher periprocedural complication rates but similar early and late complication rates. (4) No gender differences were noted in rates of appropriate and inappropriate ICD shocks. (5) No gender differences were noted in all-cause and HF rehospitalisation rates and mortality.

Epidemiological and clinical studies have suggested gender-related differences in the delivery of guideline-recommended HF treatments.[111,313] In the Get With the Guidelines-Heart Failure (GWTG-HF) programme, a significant increase in ICD use was observed over time in patients with history of HF and LVEF ≤35% but gender differences persisted.[314] A study by Hernandez et al. showed that while 44% of eligible men with HF and LVEF ≤30% received ICD, only 28% of eligible women received ICD therapy.[315] New Zealand, traditionally has had lower implant

rates/million population for ICD.[265] Taking into account affordability and capacity constraints, the published 2010 New Zealand guidelines are relatively conservative (**Table 17**) and this may result in low referral rates.[271]

In our study, the percentage of ICD/CRT-D utilisation in men gradually increased from year 2007 to mid-2015 but this is not seen in women and a gender discrepancy remained in the use of these complex devices (**Figure 20**). The original trials of ICD/CRT-D showed the benefit derived from ICD is greater in patients with ICM which is more common in males and occurs at a younger age.[61-63] Women are more likely to have HF with preserved systolic function and present at a later age.[114] Similarly, we have observed women with different clinical profiles compared to men (**Table 22**) which may account for the lower ICD/CRT-D implant rates in women. The mean age of women who received these devices were younger because of our more restrictive recommendations, otherwise they shared similar baseline characteristics to other published data.[127,271,316]

MacFadden et al reported a 50% higher occurrence of any major or minor complications in women at 45-day follow-up.[316] Similarly, recent findings from the National Cardiovascular Data Registry (NCDR) demonstrated a higher risk of cardiac perforation and pneumothorax in women.[127] In our current study, women had higher perioperative complication rates than men, but there were no gender differences in the longer-term device-related complications. This differs from the previously described increased risk of complications in women in general. This may be explained by the small number of women included in the study and therefore no conclusive evidence of gender differences in late complications could be drawn.

Some studies have shown that women receiving primary prevention ICDs have a lower risk of death and appropriate ICD shocks than men. In a large multicentre French registry, women who had ICD implantation for primary prevention had a significantly lower likelihood of receiving appropriate ICD therapies (17.4% vs. 23%, $p<0.001$) but had similar mortality

compared with men (hazard ratio [HR]=0.87, 95% CI 0.66-1.15, p=0.324).[317] There was no gender difference observed with inappropriate shocks (6.7% vs 6.7&, OR 1.0, 95% CI 0.74-1.35, p=0.997).[317] Similarly, Seegers et al. showed that women received 50% less appropriate ICD shocks than men (3.6% vs. 6.3% per year, p=0.002) though both groups have similar mortality (p=0.08).[318] In a recent systematic review and meta-analysis, women were found to have a lower incidence of first appropriate ICD shocks and death than men but a similar risk of receiving inappropriate ICD shocks.[319] Contrary to the published studies, our study showed that there was no gender difference in the appropriate and inappropriate ICD shocks. There appeared to be a trend towards lower all-cause, cardiovascular and HF mortalities in women but it was not statistically significant. This may be explained by the small number of women and our results would be consistent with the literature with lower mortalities observed in women.

There has been increasing interest in the optimisation of ICD programming to prevent inappropriate and appropriate but unnecessary device therapy. Prior to 2013, our ICD programming was not standardised and were often comprised of manufacturer defaults which were tailored to each patient by depending on history, results of defibrillation threshold (DFT) testing and the electrophysiologists' preferences. Three different trials demonstrated recently that a longer number of intervals to detect ventricular fibrillation (NID) and a high rate cut off reduce ICD therapies in primary prevention patients.[320-322] Subsequent to these publications, we have moved to a programming strategy of longer NID in line with the published expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing.[323]

HF is a chronic, long-term health condition, but improved survival has brought with it significant financial burdens on our healthcare system. In New Zealand, approximately 5,500 patients are hospitalised with decompensated HF each year.[19] Poor outcomes are common after

hospitalisation for HF, with 1-year readmission rates >50% and 1-year mortality >30%.[324] Findings from the NCDR showed that women had higher HF readmission rates than did men (14% vs 10%, p<0.001).[127] Even all-cause readmissions within 6 months were higher in women than in men and these differences persisted after adjusting for baseline differences (OR 1.22, 95% CI 1.16-1.28, p<0.001).[127] However, in our study there was no gender differences in all-cause hospitalisation rates including HF hospitalisation rates. It is possible that the small number of women included in our study could not account for differences. It is also possible that higher CRT use in women in our population (39.7%), potentially contributed to the comparable HF hospitalisation rates. A recent meta-analysis revealed that women derived greater benefit from CRT than men.[121] However, additional studies with a larger number of women are needed to determine if there are other unmeasured confounders which might contribute to gender differences and outcomes in our population.

Limitations

Firstly, our study lacks the denominator describing women with HF who were eligible but not implanted to demonstrate a real disparity in the use of these complex devices. Secondly, our study is limited by the small number sample size of women included which in itself may not be powered enough to detect differences in the outcome. Thirdly, our study was a non-randomised observational study from 4 DHBs, therefore our result may not apply to other centres in New Zealand. However, given the paucity of data of these devices in New Zealand, our study represents the real-world data on the use of these devices in HF women and their outcomes.

Conclusion

In our study, the incidence of early complications was higher in women referred for primary prevention ICD/CRT-D. Women also presented with a different clinical profile from men and

account for a minority of ICD/CRT-D recipients. The differences in disease pattern and LV impairment between the genders may have contributed to our results. Although these results should not preclude eligible women from receiving these devices, a broader perspective on outcomes such as cost and quality of life is needed to inform decisions around primary ICD implantation in women with HF.

Chapter 6 QUALITY OF LIFE ASSESSMENT IN HEART FAILURE PATIENTS WITH DEVICE THERAPY

6.1 QUALITY OF LIFE IN HEART FAILURE PATIENTS

HF is a chronic disease. As HF progresses, there are increasingly frequent hospitalisations and considerable morbidity. HF affects quality of life (QoL) more profoundly than many other chronic diseases.[325] Although most HF patients seem to cope relatively well, the impact of HF on their lives can be profound. Symptom burden, the disabling consequences of HF and the medical regimen (including side-effects from medications) impact the daily life of HF patients and contribute to decrease in QoL.[326] HF is a complex syndrome and it contributes to severe physical, social and functional impairment as well as increasing psychological distress to patients.

Sleep disturbance is common; almost 60% of HF patients report sleep problems which relates to poor QoL.[327,328] Pain is also being reported to be common in HF patients. The prevalence is estimated to be between 23% and 75% of HF patients.[329,330] Pain can have significant effect on almost all aspects of life. It can influence the ability to maintain adequate self-management. Pain is one of the most compelling reasons for seeking medical attention and can be a precipitant for hospital readmission.[329]

Depression is common among HF patients. The reported prevalence of depression in HF patients varies between 9 and 60%.[326,331] A meta-analysis by Rutledge et al. reported an overall estimated depression prevalence rate of 21.6%.[332] This indicated that HF patients experience clinically significant depression at a rate similar to the 15% to 20% levels cited for patients with coronary artery disease and at 2 to 3 times the rate of the general population.[333-335]

Several factors are related to symptoms of depression in HF patients. Development of depression in HF patients is associated with living alone, the financial burden associated with medical cost of treatment, alcohol abuse and poor self-related health.[336] Younger age at diagnosis, advanced NYHA functional class, sleep deprivation and negative attitudes towards loss of autonomy are other factors associated with depression in HF patients.[337,338]

HF patients with depression have a substantially worse prognosis.[332] In recent reviews, the mortality results were reinforced by equally large differences in hospital readmission and health care use by depressed versus non-depressed HF patients.[339,340]Several biological mechanisms are common in HF and depression. HF and depression are both associated with sympathetic activation and elevated proinflammatory cytokines.[341-343] These additive effects of inflammation likely adversely affect the heart in patients with HF.[344,345] At the very least, treatment of depression could potentially improve outcomes in the patients. However, to date there is a paucity of data on the effectiveness of interventions to treat depression in HF patients.[326,332]

HF is a progressive disease. As in the natural course of HF, patients show a decline in QoL over time as the disease progresses. It is very important to integrate all available health services to deliver a multidisciplinary care to patients with HF. Pharmacological treatment such as beta-blockers, Angiotensin Converting Enzyme Inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) have proven to improve symptoms and QoL as well as reducing hospitalisation and decreased mortality rates.[1] CRT devices have shown to positively influence symptoms and improve QoL.[269]

An analysis from CARE-HF reported that CRT improved long-term QoL and survival in HF patients.[346] QoL was assessed at baseline, 90-days, 18-months and at the end of the study using disease-specific Minnesota Living with Heart Failure Questionnaire (MLWHFQ) as well as the European Quality of Life-5-Dimensions (EQ-5D). At baseline, HF patients had a substantially lower mean EQ-5D score than a representative age-matched general population (0.60 vs. 0.78).[346] At 3 months after randomisation, patients who received CRT improved their mean EQ-5D score (mean difference 0.08, $p<0.0001$). Compared to those assigned to medical therapy alone, CRT patients had a mean reduction in MLWHFQ score of 10.6 points ($p<0.001$) at 3 months and this improvement was maintained throughout the study.[346] This confirms that

CRT in addition to pharmacologic therapy in appropriate HF patients improves symptoms and QoL that persist for several years.

Kloch Badelek et al recently assessed the impact of CRT on the physical ability and QoL on 60 CRT patients with advanced HF (NYHA class II or IV).[347] At 3 months, there was overall improvement in HF symptoms by one NYHA class reduction in 66.6% patients, and by two NYHA class reductions in 15.8% patients ($p<0.05$). At the end of the study, there was an increase in the walking distance during the 6-minute walk test (6-MWT) in 2/3 of the patients ($p<0.001$) and there was increased in QOL after 3 months of CRT as characterised by lower baseline values of the Psychological General Well-Being Index (PGWB) index.[347] This shows that application of CRT in the management of advanced HF patients could still lead to a reduction in the symptoms of disease and improvement in the physical ability and QoL.

6.2 IMPACT OF CARDIAC RESYNCHRONISATION THERAPY ON BURDEN OF HOSPITALISATIONS AND SURVIVAL

Preface

HF is still a major challenge for health care. Not only is HF associated with a high use of resources and healthcare cost, but prevalence of HF is increasing due to better management of HF and to the aging of the population.[4] Moreover, the outcome of HF is grim. Mortality rate is high and hospitalisations are frequent in HF patients and associated with worse outcomes. The majority of studies that analysed HF outcomes have focused on HF hospitalisations. However, all-cause hospitalisations can affect up to 23–58% of HF patients at 1-year follow-up.[348,349] Non-cardiovascular hospitalisations are also associated with increased risk of subsequent mortality similar to cardiovascular hospitalisations.[350]

A systematic review published by McAlister et al. concluded that appropriate use of CRT has the potential to reduce all-cause mortality by 22% (95% CI, 9–33%) and hospitalisations by 37% (95% CI, 7–57%) as well as improve the QoL (weighted mean reduction in MLWHFQ, 8.0 points; 95% CI, 5.6–10.4), and functional status (improvements of $\geqslant$1 NYHA class were observed in 59% of CRT patients).[351] "Days alive and Out of Hospital" (DAOH) is another new approach to measure QoL in HF patients.[352] It captures the number and duration of all hospitalisations as well as mortality, therefore has the potential to add statistical power to detecting treatment differences. It also gives greater weight to the impact of survival.

The aim of the research presented in this chapter was:

- To describe the burden of hospitalisations, using the DAOH in HF patients implanted with CRT devices in the Northern Region of New Zealand.
- To determine whether DAOH differs by type of CRT devices, aetiology of HF, gender or ethnicities

The research study shows that patients implanted in 'real world' clinical practice with a CRT device have a relatively favourable outcome with less total hospitalisation, less total hospital days and increase in DAOH.

The manuscript has been submitted to BMJ Open in November 2018 and first published on May 27, 2019. BMJ Open is an online, open access journal, dedicated to publishing medical research from all disciplines and therapeutic areas. Its current impact factor is 2.413.

Contribution of Candidate:

Khang-Li Looi was involved in the data collection and analysis, as well as in developing arguments and writing of the manuscript for publication.

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Abstract

Objective

Cardiac resynchronisation therapy (CRT) devices have been shown to improve heart failure (HF) symptoms, survival and improve quality of life (QoL). We evaluated the overall impact of CRT on recurrent hospitalisations and survival in real-world patients with HF.

Design

Retrospective observational study

Setting

Northern Region of New Zealand

Participants

Patients with HF who underwent CRT device implantation in between 2008–2014 were followed-up for 1-year

Interventions

CRT

Primary and Secondary Outcomes Measured

Survival, all-cause hospitalisations, length of stay, from which days alive and out of hospital (DAOH) were calculated.

Results

177 patients were included, of whom 8 died (4.5%) within 1 year of follow up. Pre-CRT implantation, 83% of all patients had been hospitalised for a total 248 hospitalisation events. Following CRT, 47 patients (27%) were readmitted to hospital within 1 year (total of 98 admissions; $p<0.01$ compared with pre-device implant). Length of hospital stay was significantly shorter than in the year prior to CRT implantation at a median of 4 (interquartile range [IQR] 2-6) vs. 7 (IQR 3.5-10.5) days ($p=0.03$). An increase in the median number of DAOH was observed from 362 (IQR 355-364) to 365 (IQR 364-365) ($p<0.01$) after CRT

implant. The improvement in DAOH was seen regardless of gender and type of CRT devices. Greater DAOH was also seen in those with non-ischaemic cardiomyopathy (NICM) and Caucasians.

Conclusion

After CRT implant, HF patients have greater DAOH with reduction of total hospitalisation and fewer hospital days. These results support CRT devices use as a treatment option for appropriate HF patients. DAOH represents an easily measured, patient-centred endpoint that may reflect effectiveness of interventions in future CRT studies.

Introduction

Heart failure (HF) is a chronic and progressive condition. HF affects quality of life (QoL) more profoundly than many other chronic diseases.[325] Symptom burden, the disabling consequences of HF and the medication regimen (including side-effects) all impact on the daily life of HF patients and contribute to impaired QoL.[326] As the disease progresses, HF patients show a decline in QoL with increasingly frequent hospitalisations.

Cardiac resynchronisation therapy (CRT) devices have been shown to positively influence symptoms and improve QoL in selective group of patients with HF with LBBB.[269] An analysis from the Cardiac Resynchronization–Heart Failure (CARE-HF) trial showed that CRT improved long-term QoL and survival in HF patients.[346] At baseline, HF patients had a substantially lower mean European Quality of Life-5-Dimensions (EQ-5D) score than a representative age-matched general population (0.60 vs. 0.78).[346] Three months after randomisation, patients who received CRT had significant improvement in mean EQ-5D score (mean difference 0.08, $p<0.0001$) compared to those assigned to medical therapy alone. CRT patients had a mean reduction in Minnesota Living with Heart Failure Questionnaire (MLHFQ) score of 10.6 points ($p<0.001$) at 3 months and this improvement was maintained throughout

the study.[346] These data support that CRT, in addition to medical therapy, in appropriate patients with HF improves symptoms and QoL that persist for several years .

Objective

The aim of our study was to describe the burden of hospitalisations, using the "Days alive and out of hospital" (DAOH) in HF patients implanted with CRT devices in the Northern Region of New Zealand.[352] We also aimed to determine whether DAOH differs by type of CRT devices, aetiology of HF, gender or ethnicities.

Study Design and Population

This is a retrospective observational study. The study cohort consisted of consecutive patients implanted with CRT-capable devices between January 2008 to end of year 2014 in the Northern Region of New Zealand. All patients undergoing implantation of de novo CRT-pacemaker (CRT-P) and CRT-defibrillator (CRT-D), all upgrades from pacemakers to CRT-P or CRT-D, upgrades of implantable cardioverter-defibrillators (ICD) to CRT-D using transvenous or epicardial LV lead placement were included. The Northern Region of New Zealand is defined as the 4 northernmost District Health Board (DHB) areas. Patients undergoing CRT implantation who resided in the Auckland (ADHB), Counties Manukau (CMDHB), Northland (NDHB), or Waitemata (WDHB) DHBs were included. The 4 DHBs in Northern Region serve 38% of the total New Zealand population with estimated 1.76 million people in this region.[292] New Zealand has a government-funded health system with universal coverage for all New Zealand residents that includes both acute and elective secondary and tertiary services. Currently there is no health insurance coverage for CRTs in New Zealand. All CRT implantation and follow up is provided for by the public sector. The indications for CRT-D and CRT-P were based on the published 2010 New Zealand guidelines (**Table 17**).[271] All referrals for CRT were discussed by the Northern Region implanting electrophysiologists regarding suitability and appropriateness of CRT support.

Patient and Public Involvement

This study is based on existing health system data with no direct patient and public involvement.

Study Design and Data Collection

Every New Zealander has a National Health Index (NHI) number, a unique identifier that is assigned to each person who uses health and disability support services in New Zealand. Hospitalisation data for all patients was assessed using the administrative data of Ministry of Health (MoH) and National Minimum Datasets [NMDS] inpatient hospitalisation data via NHI linkage up to end of year 2015. All-cause mortality data was collected using New Zealand mortality collection and NMDS.

Hospitalisation data for all patients were assessed for a full year prior to implantation (CRT-D or CRT-P) and after implantation or till death at the end of follow-up. An admission was defined as a presentation to hospital requiring an overnight stay. Same day admissions were excluded to prevent influencing per admission length of stay. The total hospital days were calculated by adding the durations of each individual hospital admission to obtain days in hospital.

DAOH were calculated for each patient as follows[352]: the total follow-up time was determined as number of days from device implant date until the date of the final patient examination (if alive) or end of follow-up date i.e. 1-year for the whole study cohort to ensure complete data ascertainment. The number of DAOH at 1-year were calculated using mortality and hospitalisation data from the date of implantation (to account for in-hospital mortality). Hence, DAOH is the difference between total follow up time (i.e.1-year) and total time in hospital with number of days dead, where days dead refers to the number of days from death to the end of the assigned follow up period (i.e. 1-year) i.e. DAOH = total follow up time i.e.1-year – (total time in hospital + days dead)

For example; if a patient died during their index implant hospitalisation, they were assigned 0 DAOH (**Figure 24-1A**) If a patient was admitted for 5 days but then was not re-hospitalised and survived to the end of the ascertainment period (for instance 1-year i.e. 365 days) they were assigned 360 DAOH (**Figure 24-1B**). If a patient was admitted for 5 days, then re-hospitalised for 3 days 90 days later then subsequently died at 110 days after their index hospitalisation they were assigned 102 DAOH (**Figure 24-1C**).

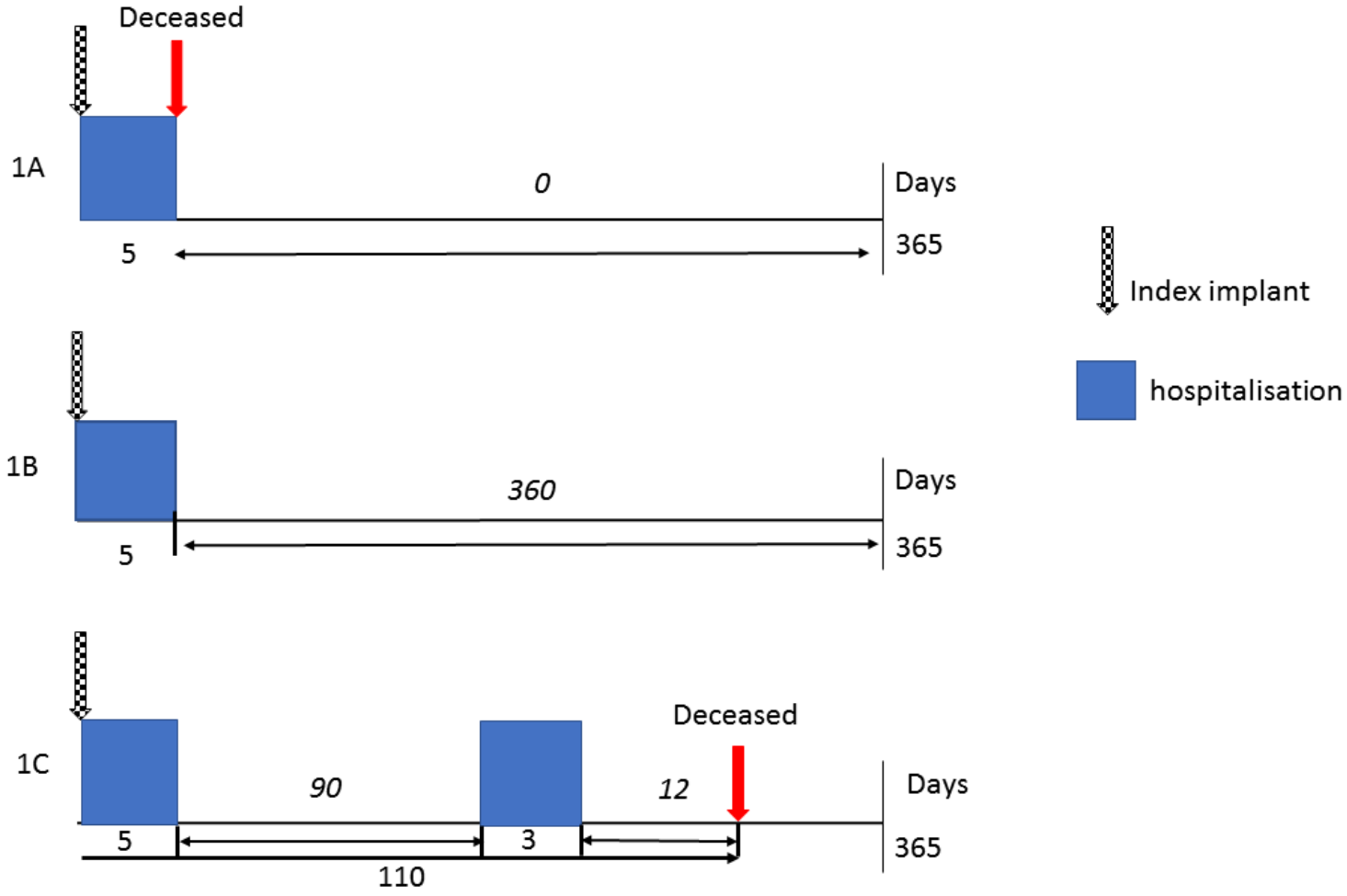
Ethics Statement

The study was approved by the Central Health and Disability Ethics Committee (Ethics ref: 15/CEN/58/AM02).

Statistical analysis

All calculations were performed using SPSS V.25.0 (IBM Software, USA). Baseline characteristics were summarised either as mean and standard deviation (SD) (age and QRS duration), median and interquartile range (IQR) or frequency with percentage depending on the nature of the data. Comparison of continuous data was performed using the two-sample T test. Length of hospital stay, DAOH and % DAOH were expressed as median and interquartile range (IQR) and compared using the Wilcoxon rank-sum test and Mann-Whitney test. A multivariate linear regression model was used to evaluate association between DAOH and baseline patient characteristics. A two-sided p value <0.05 was considered statistically significant.

Figure 24: Examples of calculation of Days Alive and Out of Hospital (DAOH)



Results

From year 2008-2014, 177 patients were implanted with either CRT-D or CRT-P devices. Baseline characteristics of patients were shown in **Table 23:** three quarters of the patients were male and 81% Caucasians. CRT-D was the most common device implanted (82%). Patients were more likely to have non-ischaemic cardiomyopathy (NICM) (51%) with a mean left ventricular ejection fraction (LVEF) of 26 ± 8%. Twenty-six patients had permanent atrial fibrillation (AF) in whom 13 had had atrio-ventricular (AV) nodal ablation. Shown in **Table 24** are the baseline characteristics of patients who received CRT-P and CRT-D. In general, patients receiving CRT-P were older, more likely to be female Caucasians, have pacemaker-induced cardiomyopathy but better LVEF, higher prevalence of permanent AF and previous history of AV nodal ablation, and have smaller body habitus than those who received CRT-D. Follow up data were available for all patients, and 8 patients (4.5%) died within one year (3 were from HF-deaths and 5 from cardiovascular deaths attributable to myocardial infarction (MI), or cerebrovascular accidents).

Hospitalisations

Pre-CRT implantation, there were 248 hospitalisation events among 147 (83.1%) patients. This resulted in total of 1126 hospital days with a median length of hospital day of 7(3.5-10.5). After excluding implant admission (i.e. all contiguous admissions pre-and post-implant date and included inter-hospital transfers and periods of rehabilitation after implant prior to first discharge home), the number of total admissions post-CRT implant decreased to 98 episodes in 47 (26.6%) patients after first discharge within the first-year follow-up ($p<0.01$). Total hospital days had decreased from 1126 to 605 with a relative 46% reduction in total bed days. Length of hospital day was also significantly shorter than in the year prior to CRT implantation at a median of 4(2-6) ($p<0.01$).

Table 23: Baseline characteristics of patients implanted with Cardiac Resynchronisation Therapy (CRT)

	N=177
Median Age (years) (IQR)	64.4 (57.5 – 70.6)
Gender	
Male (%)	135 (76.3)
Female (%)	42 (23.7)
Ethnicity (%)	
NZ European/Other European	143 (80.8)
Maori	10 (5.6)
Pacific Island	17 (9.6)
Asian	7 (4)
Type of Device	
CRT-P	32 (18.1)
CRT-D	145 (81.9)
Aetiology	
Ischaemic cardiomyopathy	40 (22.6)
Non-ischaemic cardiomyopathy	90 (50.8)
Pacing-induced cardiomyopathy	32 (18.1)
Valvular heart disease	6 (3.4)
Complex congenital heart disease	2 (1.1)
Cardiac sarcoidosis	4 (2.3)
Other causes	3 (1.7)
Mean LVEF (% ± SD)	26.4 ± 7.9
NYHA Functional Class I/11/III	18 (10%)/79 (45%)/80 (45%)
Median Height (meter) (IQR)	1.74 (1.67-1.78)

Median Weight (kg) (IQR)	85.1 (75.8-96.8)
Median BMI (m/kg2) (IQR)	28.3 (25.5-32.2)
Permanent AF (%)	26 (15)
Paroxysmal AF (%)	20 (11.3)
AV node Ablation (%)	13 (7.4)
Diabetes Mellitus (%)	42 (23.7)
Hypertension (%)	47 (26.6)
QRS Morphology (%)	
LBBB	135 (76.3)
Paced	42 (23.7)
Mean QRS duration (msec)	176.3 ± 25.2
Median eGFR (ml/min/1.73m^2)	66 (54.5-85.5)
Stages of Chronic Kidney Disease n (%)	
1	37 (20.9)
2	84 (47.5)
3	54 (30.5)
4	2 (1.1)

Abbreviations:
AF: atrial fibrillation; BMI: body mass index; CRT-D: cardiac resynchronisation therapy with defibrillator; CRT-P: cardiac resynchronisation therapy with pacemaker; eGFR: estimated glomerular filtration rate; IVCD: intraventricular conduction delay; LVEF: left ventricular ejection fraction; LBBB: left bundle branch block; NYHA: New York Heart Association

Table 24: Baseline characteristics of patients implanted with CRT-D and CRT-P

	CRT-D (n=145)	CRT-P (n=32)	P value
Median Age (years [IQR])	63.4(56.8-69.2)	69.3(60.3-73.9)	0.004
Gender			
Male (%)	115(79.3)	20(62.5)	0.04
Female (%)	30(20.7)	12(37.5)	0.04
Ethnicity (%)			
NZ European/Other European	113(77.9)	30(93.8)	0.04
Maori	8(5.5)	2(6.3)	0.87
Pacific Island	17(11.7)	-	-
Asian	7(4.8)	-	-
Aetiology (%)			
Ischaemic cardiomyopathy	37(25.5)	3(9.4)	0.05
Non-ischaemic cardiomyopathy	88(60.7)	2(6.3)	<0.01
Pacing-induced cardiomyopathy	9(6.2)	23(71.9)	<0.01
Valvular heart disease	3(2.1)	3(9.4)	0.04
Complex congenital heart disease	2(1.4)	-	-
Cardiac sarcoidosis	4(2.8)	-	-
Other causes	2(1.4)	1(3.1)	0.49
Mean LVEF (% ± SD)	24.6±6.0	34.6±10.3	<0.01
NYHA Functional Class I/11/III (%)	16(11)/68(46.9)/61(42.1)	2(6.3)/11(34.4)/19(59.4)	0.42/0.19/0.08

Median Height (meter) (IQR)	1.74(1.67-1.78)	1.74(1.66-1.79)	0.95
Median Weight (kg) (IQR)	87(74.6-98.1)	81.9(76.8-85.7)	0.03
Median BMI (m/kg2) (IQR)	28.6(25.9-32.7)	26.6(24.9-30.2)	0.05
Permanent AF (%)	18(12.4)	12(37.5)	<0.01
Paroxysmal AF (%)	14(9.7)	2(6.3)	0.32
AV node Ablation (%)	3(2.1)	10(31.3)	<0.01
Diabetes Mellitus (%)	35(24.1)	2(6.3)	0.03
Hypertension (%)	38(26.2)	9(28.1)	0.83
QRS Morphology (%)			
LBBB	126(86.9)	9(28.1)	<0.001
Paced	19(13.1)	23(71.9)	<0.01
Mean QRS duration (msec)	175±23.6	182.3±31.4	0.08
Median eGFR (ml/min/1.73m2)	68(55.5-87.5)	65(50.3-73.8)	0.13
Stages of Chronic Kidney Disease n (%)			
1	31(21.4)	6(18.8)	0.74
2	70(48.3)	14(43.8)	0.64
3	43(29.7)	11(34.4)	0.60
4	1(0.7)	1(3.1)	0.24

Abbreviations:
AF: atrial fibrillation; BMI: body mass index; CRT-D: cardiac resynchronisation therapy with defibrillator; CRT-P: cardiac resynchronisation therapy with pacemaker; eGFR: estimated glomerular filtration rate; IVCD: intraventricular conduction delay; LVEF: left ventricular ejection fraction; LBBB: left bundle branch block; NYHA: New York Heart Association

Days Alive and Out of Hospital Prior and After Device Implantation

Table 25 showed the DAOH of the whole study cohort and according to gender, ethnicity, aetiology of HF and type of devices. An increase in the median number of DAOH was observed from 362 (355-364) to 365 (364-365) ($p<0.01$) after CRT implant. Post implant, the patients had significantly more time out of hospital than they did in the year prior to implant. This increase in DAOH was seen for both men and women, Caucasians, patients with NICM and both patients with CRT-D and CRT-P. For Māori patients, CRT implant was associated with reduction in total patients' admissions and length of hospital stay but not DAOH (**Table 25**).

Table 25: Hospital admissions pre- and post CRT implantation at 1-year according to gender, ethnicity, aetiology of heart failure and type of devices

Characteristics	1-year Prior to Implant	1-year Post Implant	P value
Total Cohort (n = 177)			
Total Hospital Admissions	248	98	<0.01
Total Patients' Admitted	147	47	<0.01
Total Hospital Days	1126	605	<0.01
Length of Hospital Stay (median [IQR] days)	7(3.5-10.5)	4(2-6)	0.03
DAOH (median[IQR])	362(355-364)	365(364-365)	<0.01
DAOD (mean ± SD)	358.6±8.4	354.7±44.8	0.24
Number of Deaths (%)	0	8 (4.5)	N/A
Gender			
Male (n = 135)			
Total Hospital Admissions	193	78	<0.01
Total Patients' Admitted	113	39	<0.01
Total Hospital Days	889	396	<0.01
Length of Hospital Stay Days (median [IQR] days)	5(2.5-7.5)	4(2-6)	0.69
DAOH (median [IQR])	362(355-364)	365(363-365)	<0.01
DAOH (mean ± SD)	358.4±8.6	354.5±45.7	0.15
Number of Deaths (%)	0	6(4.4)	N/A
Female (n = 42)			

Total Hospital Admissions	55	20	<0.01
Total Patients' Admissions	34	8	<0.01
Total Hospital Days	237	209	<0.01
Length of Hospital Stay (median [IQR] days)	3.5(2-5)	7.5(4-11)	0.14
DAOH (median [IQR])	363(354.8-364)	365(365-365)	<0.01
DAOH (mean ± SD)	359.4±7.8	355.5±42.4	0.39
Number of Deaths (%)	0	2(4.8)	N/A
Ethnicity			
NZ European/Other European (n = 143)			
Total Hospital Admissions	189	69	<0.01
Total Patients' Admitted	118	35	<0.01
Total Hospital Days	813	389	<0.01
Length of Hospital Stay (median [IQR] days)	3.5(2-9)	3(1.5-4.5)	0.28
DAOH (median [IQR])	363(357-364)	365(364-365)	<0.01
DAOH (mean ± SD)	359.3±8.2	357.1±40.2	0.50
Number of Deaths (%)	0	5(3.5)	N/A
Maori (n = 10)			
Total Hospital Admissions	21	12	0.26
Total Patients' Admitted	10	4	<0.01
Total Hospital Days	128	76	0.35
Length of Hospital Stay (median [IQR] days)	14.5(7-21)	10(5-15)	0.02
DAOH (median [IQR])	350(347.5-356)	365(346-365)	0.39

DAOH (mean ± SD)	352.2±6.1	335.2±74.1	0.48
Number of Deaths (%)	0	1(10)	N/A
Aetiology of Heart Failure			
ICM (n=40)			
Total Hospital Admissions	61	35	0.01
Total Patients' Admitted	35	13	<0.01
Total Hospital Days	298	297	0.99
Length of Hospital Stay (median [IQR] days)	6(3-9)	7(3.5-10.5)	0.22
DAOH (median [IQR])	361(354.3-364)	365(360.8-365)	0.21
DAOH (mean ± SD)	357.6±9.7	337.1±69.7	0.06
Number of Deaths (%)	0	5(12.5)	N/A
NICM (n = 90)			
Total Hospital Admissions	116	51	<0.01
Total Patients' Admitted	70	27	<0.01
Total Hospital Days	487	212	<0.01
Length of Hospital Stay (median [IQR] days)	4.5(2-7)	3(1.5-4.5)	0.93
DAOH (median [IQR])	363(356.8-364)	365(361.8-364)	<0.01
DAOH (mean ± SD)	359.6±7.5	356.3±40.3	0.44
Number of Deaths (%)	0	2(2.2)	N/A
Type of Devices			
CRT-D (n = 145)			
Total Hospital Admissions	200	92	<0.01

Total Patients' Admitted	118	43	<0.01
Total Hospital Days	919	589	0.05
Length of Hospital Stay (median [IQR] days)	5(2.5-7.5)	4(2-6)	0.84
DAOH (median [IQR])	363(355-364)	365(363-365)	<0.01
DAOH (mean ± SD)	358.7±8.5	350.9±49.6	0.06
Number of Deaths (%)	0	8(5.5)	N/A
CRT-P (n = 32)			
Total Hospital Admissions	48	6	<0.01
Total Patients' Admitted	29	4	<0.01
Total Hospital Days	207	16	<0.01
Length of Hospital Stay (median [IQR] days)	4(2-6)	4(2-6)	0.63
DAOH (median [IQR])	362(355-364)	365(365-365)	<0.01
DAOH (mean ± SD)	358.5±8.4	362±3.9	0.02
Number of Deaths (%)	0	0	N/A

Abbreviations:
CRT-D: cardiac resynchronisation therapy with defibrillator; CRT-P: cardiac resynchronisation therapy with pacemaker; DAOH: days alive and out of hospital; ICM: ischaemic cardiomyopathy; IQR: interquartile range; NICM: non-ischaemic cardiomyopathy; SD: standard deviation

Influences of Gender

At the time of implant, median age between men and women was similar (64.4(57.2-70.8) vs. 64.9(59.2-69.7) years, p=0.89). There were more CRT-P devices implanted in women (28.6% vs. 14.8%, p=0.04). There was no difference in total hospital admissions, total hospital days, length of hospital days and DAOH between gender prior to implant (**Table 26**). Post implant, women had lower total hospital days (209 vs. 396, p=0.04) compared to men. However, the length of hospital day was longer in women compared to men (7.5(4-11) vs. 4(2-6), p=0.03). There were no gender differences observed in DAOH.

Influences of Type of Devices

CRT-D devices were the most common devices implanted in our study cohort (81.9%).

CRT-D patients have more admissions prior to implant (118 vs. 29, p<0.01) and thirty-eight (26.2%) of these patients had either survived a cardiac arrest or had had occurrence of symptomatic ventricular arrhythmias (**Table 26**). At 1-year follow-up, CRT-D patients continued to have more total hospital admissions (92 vs. 6, p<0.01), total hospital days (589 vs. 16, p=0.01) and shorter DAOH (p=0.04) compared to CRT-P patients. There were more deaths at follow-up in CRT-D group (8 vs. 0, p<0.01).

Influence of Aetiology of Heart Failure

Among the cohort of patients, half (50.8%) had underlying NICM and 22.6% had ICM. Patients with ICM were older (median age 66.1[59.1-71.3] vs. 62.8[56.3-69.7], p=0.09) but this was not statistically significant. Six patients with ICM died within 1-year compared to 2 with NICM (15% and 2% respectively; p<0.01). At 1-year follow-up, NICM patients had less total hospital days (212 vs. 297, p<0.01) compared to those with ICM but there was no difference between total hospital admissions, total patients' admissions, length of hospital day and DAOH (**Table 26**).

Influences of Ethnicity

The majority of the patients were Caucasians (80.8%). Maori patients consisted of only a minority of CRT device recipients (5.6%). Prior to implant, Maori patients have longer length of hospital stay (14.5(7-21) vs. 3.5 (2-9) days, $p<0.01$) and shorter DAOH (350 (347.5-356) vs. 363(357-364), $p<0.01$) compared to Caucasians (**Table 26**).

At 1-year follow-up, there was no difference between the groups in terms of total hospital admissions ($p=0.06$), total patients' admissions ($p=0.15$), total hospital days ($p=0.11$), length of hospital stay ($p=0.22$) and DAOH ($p=0.23$) between the two groups (**Table 26**).

Table 27 showed the results of multivariable linear regression that accounted for 20% of the variance in the difference between the DAOH prior and post CRT implant (adjusted $R2=0.14$, $F(17,159)=2.35$, $p=0.030$). A significant increase in DAOH was associated with higher QRS duration at implant among NYHA Class 1 patients ($p=0.0065$). Similarly, a significant reduction in DAOH was found for history of AF and ICM ($p=0.0091$).

Table 26: Comparison of hospital admissions and DAOH pre- and post CRT implantation between gender, ethnicity, aetiology of heart failure and type of devices

	Male(n=135)	Female(n=42)	P value
Median Age (IQR)	64.4 (57.2-70.8)	64.9 (59.2-69.7)	0.89
Type of devices (%)			0.04
CRT-P	20 (14.8)	12 (28.6)	
CRT-D	115 (85.2)	30 (71.4)	
Total Hospital Admissions Prior	193	55	0.4
Total Patients' Admissions Prior	113	34	0.42
Total Hospital Days Prior	889	237	0.66
Length of Hospital Days Prior (median [IQR])	5 (2.5-7.5)	3.5 (2-5)	0.53
DAOH prior (median [IQR])	362 (355-364)	363 (354.8-364)	0.52
DAOH prior (mean±SD)	358.4±8.6	359.4±7.8	0.67
Total Hospital Admissions Post	78	20	0.78
Total Patients Admissions Post	39	8	<0.01
Total Hospital Days Post	396	209	0.04
Length of Hospital Days Post (median [IQR])	4 (2-6)	7.5 (4-11)	0.03
DAOH after implant (median [IQR])	365 (363-365)	365 (365-365)	0.22
DAOH after implant (mean±SD)	354.5±45.7	355.5±42.4	0.89
Number of Deaths at 1-year follow-up (%)	6 (4.4)	2 (4.8)	0.86
	NZ European/Other European (n=143)	**Maori (n=10)**	**P value**
Median Age (IQR)	65.5 (58.7-71.2)	59.9 (55.2-66.2)	0.17
Type of devices (%)			0.88
CRT-P	30 (21)	2 (20)	
CRT-D	113 (79)	8 (80)	
Total Hospital Admissions Prior	189	21	0.79
Total Patients' Admissions Prior	118	10	<0.01

Total Hospital Days Prior	813	128	0.68
Length of Hospital Days Prior (median [IQR])	3.5(2-9)	14.5 (7-21)	<0.01
DAOH prior (median [IQR])	363 (357-364)	350 (347.5-356)	<0.01
DAOH prior (mean±SD)	359.3±8.2	352.2±6.1	0.68
Total Hospital Admissions Post	69	12	0.06
Total Patients Admissions Post	35	4	0.15
Total Hospital Days Post	389	76	0.11
Length of Hospital Days Post (median [IQR])	3 (1.5-4.5)	10 (5-15)	0.22
DAOH after implant (median [IQR])	365 (364-365)	365 (346-365)	0.23
DAOH after implant (mean±SD)	357.1±40.2	335.2±74.1	0.01
Number of Deaths at 1-year follow-up (%)	5 (3.5)	1 (10)	0.18
	ICM (N=40)	**NICM (N=90)**	**P value**
Median Age (IQR)	66.1 (59.1-71.3)	62.8 (56.3-69.7)	0.09
Type of devices (%)			0.04
CRT-P	3 (7.5)	2 (2.2)	
CRT-D	37 (92.5)	88 (97.8)	
Total Hospital Admissions Prior	61	116	0.73
Total Patients' Admissions Prior	35	70	<0.01
Total Hospital Days Prior	298	487	0.41
Length of Hospital Days Prior (median [IQR])	6 (3-9)	4.5 (2-7)	0.09
DAOH prior (median [IQR])	361 (354.3-364)	363 (356.8-364)	0.09
DAOH prior (mean±SD)	357.6±9.7	359.6±7.5	0.09
Total Hospital Admissions Post	35	51	0.07
Total Patients Admissions Post	13	27	0.58
Total Hospital Days Post	297	212	<0.01
Length of Hospital Days Post (median [IQR])	7 (3.5-10.5)	3 (1.5-4.5)	0.55
DAOH after implant (median [IQR])	365 (360.8-365)	365 (361.8-364)	0.58
DAOH after implant (mean±SD)	337.1±69.7	356.3±40.3	0.58
Number of Deaths at 1-year follow-up (%)	5 (12.5)	2 (2.2)	<0.01
	CRT-D (N=145)	**CRT-P (N=32)**	**P value**

Median Age (IQR)	63.4 (56.8-69.2)	69.3 (60.3-73.9)	0.04
Total Hospital Admissions Prior	200	48	0.99
Total Patients' Admissions Prior	118	29	<0.01
Total Hospital Days Prior	919	207	0.82
Length of Hospital Days Prior (median [IQR])	5 (2.5-7.5)	4(2-6)	0.47
DAOH prior (median [IQR])	363 (355-364)	362 (355-364)	0.47
DAOH prior (mean±SD)	358.7±8.5	358.5±8.4	0.47
Total Hospital Admissions Post	92	6	<0.01
Total Patients Admissions Post	43	4	<0.01
Total Hospital Days Post	589	16	0.01
Length of Hospital Days Post (median [IQR])	4 (2-6)	4(2-6)	0.06
DAOH after implant (median [IQR])	365 (363-365)	365 (365-365)	0.04
DAOH after implant (mean±SD)	350.9±49.6	362±3.9	0.01
Number of Deaths at 1-year follow-up (%)	8 (5.5)	0	<0.01

Abbreviations:
CRT-D: cardiac resynchronisation therapy with defibrillator; CRT-P: cardiac resynchronisation therapy with pacemaker; DAOH: days alive and out of hospital; ICM: ischaemic cardiomyopathy; IQR: interquartile range; NICM: non-ischaemic cardiomyopathy; SD: standard deviation

Table 27: Results of a multiple regression analysis predicting difference between the days alive and out-of-hospital (DAOH) prior and post CRT implant

Variables	β	SE	*p*
Age at implant	-0.01	0.34	0.97
NZ European (reference non-European)	-9.99	9.46	0.29
Maori (reference non-Maori)	10.1	15.3	0.56
Gender	2.03	8.08	0.80
LVEF at implant	0.07	0.46	0.87
eGFR at implant	-0.32	0.20	0.11
QRS Duration at implant	0.14	0.15	0.35
ICM	-3.76	12.3	0.76
NICM	2.34	10.34	0.82
Type of Devices	10.55	11.96	0.38
Primary Prevention	-11.54	8.32	0.17
NYHA Class I (reference class II)	144.89	60.97	0.01
NYHA Class III (reference class II)	4.91	6.93	0.45
History of AF	-3.38	8.81	0.70
History of AV node ablation	-5.87	13.68	0.67
History of AF*ICM	-43.46	16.46	<0.01
NYHA Class I*QRS Duration at Implant	0.99	0.36	<0.01

Abbreviations:
AF: atrial fibrillation; β: standardised coefficients Beta; BMI: body mass index; CRT-D: cardiac resynchronisation therapy with defibrillator; CRT-P: cardiac resynchronisation therapy with pacemaker; eGFR: estimated glomerular filtration rate; ICM; ischaemic cardiomyopathy; LVEF: left ventricular ejection fraction; NICM: non-ischaemic cardiomyopathy; NYHA: New York Heart Association; SE: coefficient standard errors

Discussion

We report here the burden of hospitalisations in a real-world cohort of patients with HF receiving CRT therapy. Prior to device implantation the patients in our study had frequent hospitalisations. During 1-year post-CRT implantation, hospitalisations were reduced by two-thirds, length of hospital stay decreased and total bed days were virtually halved. Mortality rates were low and overall there was a significant increase in DAOH.

Health-related QoL in HF patients is an important outcome as it reflects the impact of HF on individual's daily lives.[353] New York Heart Association (NYHA) classification has been used traditionally to assess functional status in HF patients. Although simple, it is subject to inter-observer variability, captures only a limited range of health status and is applied from a physician's perspective instead of the patient's.[354] The MLHFQ is a commonly used standard assessment instrument in clinical practice.[355,356] However, the MLHFQ does have limitations that include lack of responsiveness to clinical change and sensitivity when differentiating across different levels of HF symptom burden and objective measures of the functional capacity of the heart compared to NYHA and LVEF.[357] The Kansas City Cardiomyopathy Questionnaire (KCCQ) is another self-administered, 23-item questionnaire that quantifies physical limitation, symptoms (frequency, severity and recent change over time), QoL, social interference and self-efficacy. KCQQ has been validated in stable and decompensated HF patients and its sensitivity was substantially greater than that of the MLHFQ and the 36-Item Short Form Health Survey (SF-36) questionnaires.[358] The KCCQ score also provides significant incremental predictive ability over NYHA for HF outcomes.[359]

Recurrent hospitalisations can adversely impact on QoL but assessing numbers or rates of admissions alone does not consider the overall burden of disease. DAOH could be used to measure QoL in HF patients.[352] It captures the number and duration of all hospitalisations as well as mortality, provides a readily comprehensible summary of treatment difference and

therefore has the potential to add statistical power to detecting treatment differences.[352] It also gives greater weight to the impact of survival: for example, if a patient has a short hospitalisation in week 1 because of worsening HF symptoms but survives and is not hospitalised for the remainder of their follow-up, they will have a greater DAOH. A recent study by Boriani et al. reported the long-term "real world" outcomes in HF patient with ICDs and CRT-Ds devices using mortality, hospitalisations and DAOH.[360] In this study, comorbidities were one of the key determinants of the DAOH. By reporting DAOH, this study has made it possible to assess the global burden of hospitalisation during follow-up, and enable us to summarise the absolute treatment effect of ICDs and CRT-Ds on mortality and morbidity.[360]

Assessing outcomes beyond survival is becoming increasingly important in an era where indications for CRT devices are expanding. DAOH puts emphasis on deaths occurring early in follow-up and captures the duration of all hospitalisations. In our study, patients implanted with CRT actually spent fewer days in hospital, with a reduction in total hospital bed-days over 1-year period (605 vs. 1126 days, $p<0.01$). Therefore CRT, using these measures of impact, has the potential not only for significant patient benefit but also reducing hospital costs as a result of the reduction of total hospitalisation and hospital bed-days with a greater DAOH i.e. patients spent more time out of hospital alive.

We have shown that CRT implantation is associated with increase in DAOH regardless of gender and type of devices, consistent with previous studies that women derived similar benefits from CRT as men and CRT with or without ICD have major impact on morbidity and mortality.[83-85] In our study, patients with NICM have less total hospitalisations, shorter length of hospital days and increased DAOH. NICM is a known predictor of better response to CRT, thus our findings are consistent with published data.[98,99] In our study, there was no difference in total hospital days and length of stay post CRT implant in patients with ICM despite the

reduction in hospitalisations. This could be explained by the fact that patients with ICM had more comorbidities (older, more cardiac arrest and lower LVEF). Patients with ICM have more vascular risk factors and therefore have high probabilities of staying in hospital for other interventions. This could also affect the total hospital days and length of stay. They also have more CRTD devices implanted. Despite improvement in DAOH after implant, CRT-D patients still had more total hospital admissions, total hospital days and shorter DAOH compared to those with CRT-P. About 26% of these ICM patients with CRT-D had had suffered a cardiac arrest or symptomatic ventricular arrhythmias. There is also cumulative evidence that implanting CRT-D devices is associated with a higher perioperative and postoperative risk of major complications compared with CRT-P.[211,310] Almost 2/3 of CRT-P patients have pacemaker-induced cardiomyopathy. An upgrade to CRT can potentially prevent the reverse remodelling associated with chronic right ventricular pacing. Response to CRT further decreases the risk for ventricular arrhythmias, sudden cardiac death, and all-cause mortality. All these factors likely account for the differences in DAOH between the two groups.

For Maori patients with HF, CRT implant was associated with reduction in total patients' admissions and length of hospital stay but not DAOH (**Table 25**). Compared to the Caucasian patients, the median length of hospital stay was longer and the median DAOH ($p<0.01$) was shorter prior to CRT implant. Post CRT implant, these were not statistically significant. Maori patients in generally are disproportionately represented in adverse health outcomes with higher rates of admission and mortality from HF when compared with the non-Maori population.[286] However, the number of Maori patients with CRT in our study was small. Additional studies with a larger number of Maori patients are needed to determine if there are other unmeasured confounders that might contribute to ethnicity differences and outcomes in our population. Taking socio-economic factors into account in future studies, not only ethnicity, would also allow to clarify the reasons of such differences noted.

Two pairs of clinical variables were found with significant interactions: 1) NYHA Class 1 symptoms and QRS duration at implant and 2) History of AF and ICM. A significant increase in DAOH was associated with higher QRS duration at implant among NYHA Class 1patients. NYHA Class I patients have minimal HF symptoms, therefore the chance of hospitalisation will be much reduced. QRS duration has been used as an enrolment criterion in multiple CRT clinical trials. Response to CRT seems to increase as the QRS duration becomes longer, with greatest benefit in QRS duration ≥150ms. In the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) study, CRT-D was better than optimal HF therapy at all QRS durations, although the effect was greater with increasing QRS duration.[84] CRT-P benefited those with QRS duration ≥150ms.[84] In the CARE-HF (Cardiac Resynchronization-Heart Failure) study, CRT therapy was better than pharmacological therapy alone at all QRS durations, although the benefit was greater in those with a QRS duration ≥160ms.[83] Similarly, in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) the benefit of CRT-D compared with an ICD alone was confined to those with QRS duration ≥150ms.[86]

The multivariable analyses for prediction of DAOH demonstrated that history of AF and the presence of ICM was associated with lower DAOH. In our study, there was no difference in DAOH post CRT implant in patients with ICM despite the reduction in hospitalisations as these patients have more comorbidities with high probabilities of staying in hospital for other interventions. The benefits of CRT appear to be attenuated in patients with AF. They exhibit loss of AV synchronicity, a higher risk for insufficient CRT delivery because of uncontrolled ventricular rates, inappropriate ICD shocks, inadequate symptomatic improvement, repeated hospitalisation and increased mortality.[361,362] Furthermore, in patients with AF, phases of effective biventricular capture alternate with phases of competing AF rhythm, which causes spontaneous, fusion or pseudofusion beats.[104] Such beats render the pacing counters

inaccurate for assessing true biventricular capture beats. The combination of these 2 variables would result in lower DAOH.

HF adversely affects QoL in HF patients and results in significant morbidity and mortality.[363] CRT has been shown in multiple studies to improve symptoms, QoL and survival in HF patients who remain symptomatic despite optimal medical therapy, and who have LVEF ⩽35% and left bundle branch block (LBBB) with QRS width ⩾120 ms.[82-84] Although the mortality was low post CRT implant in our study, it was still 4.5% at 1-year. CRT is an expensive therapy. Given the limited resources in New Zealand and the high upfront costs of CRT devices, identifying appropriate HF patients most likely to benefit from a CRT device is essential.

Limitations

This was a single-centre, retrospective observational study with relatively low sample size. We have recently published trends of CRT therapy use for eligible HF patients in New Zealand and the data suggests that there is a significant unmet clinical need for CRT implantation in the Northern Region.[364] Affordability and capacity are of concern in this region. Considering current workforce, funding constraints and the conservative approach taken, the published 2010 New Zealand guidelines (**Table 17**) have more restrictive recommendations for CRT. This could all result in the low sample size. Our data do not provide specific information on the type of hospitalisation (HF-related vs non-HF-related) prior and post CRT implantation and on the different aspects of non-hospital HF management such as outpatient HF clinics or the use of pharmacotherapy after discharge.

Our study has not included comparison between CRT-responders vs. non-responders. There are a significant number of current issues that exist when assessing CRT response. Firstly, the CRT response definition is highly dependent on the criteria used to define the response.[365] The response rates tend to be higher when clinical measures, such as subjective measurements i.e.

NYHA class, are used but are much lower when remodelling or outcome measurements are used.[366] There is no consensus on the optimal timeline to assess response in clinical trials that involved CRT. Secondly, response criteria may vary greatly among investigators in different trials. Thirdly, multiple different factors between individual patients can affect the CRT response. In addition, it is unknown which CRT response definition i.e. improvement in clinical symptoms or LV reverse modelling will result in overall improved survival.

Another limitation is the short follow-up period used in our study (1-year). Borioni et al. reported in a study on ICD and CRT-D implantations with a follow-up of minimum 3 years and maximum 8 years has suggested that studies with even longer follow-up could beneficially use DAOH and themselves advocate the calculation of DAOH "from administrative databases with full coverage of long follow-up periods". Although the results of some studies indicate gradual improvement in the QoL up to two years after CRT, others have reported high fluctuations (improvement and deterioration over the course of several months) in the first year after CRT.[87,367] Huynh et al. reported the results of 382 HF patients (61% male, median age 75 years) from the MARATHON study in Australia that compare predictors of 30-day readmission or death with those of an alternative outcome in HF, DAOH within 12 months of discharge, which incorporates mortality and all hospitalisations into a single measure.[368] The study showed that median DAOH within 12 months was 350 days (IQR 302, 363). The final predictive model of DAOH included NYHA classification ($r=–0.29$, $p<0.001$), LV volume index ($r=–0.27$, $p<0.001$), LA volume index ($r=–0.26$, $p<0.001$), presence of CKD ($r=–0.22$, $p=0.007$), cognitive function using MoCA score ($r=0.21$, $p<0.001$) and presence of life-threatening arrhythmia ($r=–0.16$, $p=0.002$) and this model of DAOH was more predictive than the risk score of 30-day readmission or death.[368] Therefore, DAOH provides a valuable tool to estimate longevity and QoL in HF even the follow-up duration was short. In our study, patients implanted in 'real world' clinical practice with CRT device have a relatively favourable

improvement within a year of the implant. It is also difficult to compare patients before and after CRT implant as most of our patients would be hospitalised with their index event leading to causing HF in the year prior to the implantation. The main strength of our study was the ability to assess the global burden of hospitalisation during follow-up, combining data with DAOH summarising the overall impact of CRT on HF mortality and morbidity.

Conclusion

HF patients implanted with CRT have greater DAOH within 1-year follow-up. The use of DAOH provides an alternative method for measuring the overall positive impact of CRT on HF mortality and morbidity. This technique may have more utility in assessing treatment impact generally compared to crude mortality or other measures of morbidity or change in function and warrants further testing in larger HF and CRT patient cohorts.

6.3 OUTCOMES OF HEART FAILURE PATIENTS AFTER PRIMARY PREVENTION ICD UNIT GENERATOR REPLACEMENT

Preface

Under current guidelines, ICDs are implanted for primary prevention of SCD, mainly in those with ICM or NICM with LVEF ≤35%, NYHA functional class II/III, on optimal medical therapy with good life expectancy and no identifiable reversible causes of low LVEF.[276] However, the current guidelines do not distinguish between patients receiving initial devices and those undergoing elective unit generator replacement. A debate continues on how to approach patients implanted in primary prevention ICDs referred for elective replacement due to battery depletion.

After the initial ICD implantation, the clinical characteristics of patients may change. HF is a chronic disease and can progressively deteriorate, resulting in poor long-term prognosis. The number of HF patients approaching the end of their life with an active ICD or CRT-D is on the rise. ICDs improve prognosis by treating life-threatening ventricular arrhythmia, but do not modify the disease progression. At the end-of-life, ICDs frequently deliver multiple shocks, which is a matter of anxiety and poor QoL for both patients and carers.

The New Zealand Cardiac Implanted Device Registry has recently been developed on the All New Zealand Acute Coronary Syndrome – Quality Improvement (ANZACS-QI) platform.[274] Data on ICD implant is still pending. There is lack of data on outcomes of HF patients after ICD replacement at time of battery depletion in New Zealand.

The aim of the research presented in this chapter was:

- To determine clinical characteristics of HF patients with primary prevention ICD/CRTS who underwent unit generator replacement in the Northern Region of New Zealand.

- To describe the outcomes of HF patients in the Northern Region of New Zealand implanted with primary prevention ICD/CRTS who underwent unit generator replacement.

The research study shows that these patients developed significant co-morbidities during follow-up and there were high procedural complication rates. There were no predictors for those at lower risk of needing ICD therapy identified. These data may support discussion with ICD patients about life expectancy and accumulated comorbidity as this will allow each patient to choose in advance what interventions they wish to receive as part of end-of life care.

The manuscript was submitted as Original Research in Heart Asia and has been accepted for publication in December 2018. Heart Asia aims to convey the best cardiology research and practice from the developing regions of the world, with the Asia Pacific being a region of particular focus to an international audience.

Contribution of Candidate:

Khang-Li Looi was involved in the data collection and analysis, as well as in developing arguments and writing of the manuscript for publication.

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Abstract

Objective

Data describing outcomes after implantable cardiovert-defibrillator (ICDs) unit generator replacement in heart failure (HF) patients with primary prevention devices are limited.

Method

Data on HF patients who underwent primary prevention ICD/cardiac resynchronisation therapy-defibrillator (CRT-D) implantation from 2007 until mid-2015 who subsequently received unit generator replacement were analysed. Outcomes assessed were mortality, appropriate ICD therapy and shock, and procedural complications.

Results

61 patients of 385 HF patients with primary prevention ICD/CRT-D undergoing unit generator replacement were identified. Follow-up period was 1.8 ± 1.5 years after replacement. 43 (70.5%) patients had not received prior appropriate ICD therapy prior to unit replacement. The cumulative risks of appropriate ICD therapy at 1-, 3-, and 5- years after unit replacement in those without prior ICD therapy were 0%, 6.2% and 50% compared to 6.2%, 59.8% and 86.6%, respectively (p=0.005) in those with prior ICD therapies. No predictive factors associated with appropriate ICD therapy after replacement could be identified. 41 (32.8%) patients no longer met guideline indications at the time of unit replacement but risks of subsequent appropriate ICD interventions were not different compared to those who continued to meet primary prevention ICD indications. The 5-year mortality risk after unit replacement was 18.4% and there were high procedural complication rates (9.8%).

Conclusion

No predictive marker successfully stratified patients no longer needing ICD support prospectively. Finding such a marker is important in decision-making about device

replacement particularly given the concerns about the complication rates. These factors should be considered at the time of ICD unit replacement.

Introduction

Implantable cardioverter - defibrillators (ICDs) and cardiac resynchronisation therapy defibrillators (CRT-Ds) are standard treatments for the prevention of sudden cardiac death (SCD) in selected heart failure (HF) patients.[369] Despite advances in technology, the majority of ICD or CRT-D patients outlive their device and have to undergo 1 or more unit generator replacement.[370] Registry data has shown that only 1/4 of primary prevention patients will experience appropriate ICD therapy during the initial generator service life (or lifespan).[229,371] This means that approximately 75% of patients have not required ICD therapy by the time of unit replacement.

The risk/benefit ratio of ICDs varies over time and should be re-evaluated at the time of replacement. Whether these patients require device replacement is still a matter of debate. There are many gaps in the current knowledge related to optimal ICD replacement strategy. A comprehensive assessment of the overall benefits and implications of ongoing ICD therapy should be undertaken based on a patient's needs and preferences. Shared decision making needs to take place allowing valid informed consent prior to the implantation process.

The New Zealand Cardiac Implanted Device Registry has recently been developed on the All New Zealand Acute Coronary Syndrome – Quality Improvement (ANZACS-QI) platform.[274] The first description of data on new pacemaker implants from this Registry has been recently published.[274] Data on ICD implants is still pending. The aim of our study was to determine the clinical characteristics and outcomes of HF patients in the Northern Region of New Zealand implanted with primary prevention ICD/CRT-Ds who underwent unit generator replacement.

Method

This was a retrospective observational study. The study protocol was approved by the Central Health and Disability Ethics Committee (Ethics ref: 15/CEN/58/AM02).

The Northern Region of New Zealand is defined as the 4-northernmost District Health Boards (DHBs) areas and consists of Auckland DHB, Counties Manukau DHB, Northland DHB, and Waitemata DHB. The 4 DHBs in the Northern Region serve 38% of the total New Zealand population with an estimated 1.76 million people in this region.[292] We have previously reported the long-term outcomes of 385 HF patients in the Northern Region of New Zealand with primary prevention ICD/CRT-D implanted between 2007 to mid-2015.[372] This group of patients was followed-up to end of year-2017 until they reached elective replacement of the generator due to battery depletion.

Data collection included patient characteristics, type of device implanted, left ventricular ejection fraction (LVEF), renal function using estimated glomerular filtration rate (eGFR) and the presence comorbidities at baseline and at the time of generator replacement. Echocardiographic assessments were used to assess LVEF prior to ICD generator change. Comorbidities of interest included neoplastic disease, atrial fibrillation (AF), and history of transient ischaemic attack (TIA)/stroke. Pertinent medication use (beta-blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), and antiarrhythmic drugs) at baseline and at the time of generator replacement was reviewed. Data were also collected from device interrogation records, which included delivery of appropriate therapies (shock or antitachycardia pacing (ATP) for ventricular arrhythmia) and inappropriate therapies (shock or ATP for non-ventricular arrhythmia event). Programming the new ICD unit generator was based on the published expert consensus statement on optimal ICD programming and testing.[323]

Statistical analysis

Baseline characteristics were summarised as either mean ± standard deviation (SD) or frequency with percentage depending on the nature of the data. The paired sample T-test was used for comparison of continuous variables and the $\chi 2$ was used for comparing frequencies between the groups where appropriate. Survival rates over time were depicted in Kaplan-Meier curves, and the differences between survival distributions were evaluated with the log-rank test. Multivariable logistic regression analysis was performed to identify potential clinical predictors of appropriate ICD therapy and death after generator replacement.

Statistical analyses were performed using SPSS V.25.0 (IBM Software, USA). All statistical tests were two-sided. P values <0.05 were considered statistically significant.

Results

From year 2007-mid 2015, 385 HF patients were implanted with primary prevention ICD or CRT-D. The mean follow-up was 7.7 ± 2.2 years after the initial implantation. At the end of follow-up, 95 (24.7%) patients had died and 20 (5.2%) patients had been lost to follow-up as they had moved out of the Northern Region. During the follow-up, fifteen (3.9%) patients had had their ICD/CRT-D devices deactivated: 10 deactivated the devices prior to their deaths and the remaining 5 patients had had their device deactivated as part of their advanced care planning (ACP). Fifteen (3.9%) patients had their devices removed during orthotopic cardiac transplant. Two patients with no pacing indications had devices extracted due to sepsis and declined further reimplantation. One patient died prior to the scheduled generator replacement and two patients with no pacing indications decided against replacement after comprehensive medical evaluation and discussion.

Only 61 patients underwent unit generator replacement during the follow-up period. The majority were male (n=50, 81.9%) and of European descent (n=39, 63.9%). These patients

were more likely to have non-ischaemic cardiomyopathy (NICM) (n=38, 62.3%). ICD was the most common device replaced (n=39, 63.9%), and the majority of the ICDs were single-chamber devices (56.4%). CRT-D comprised of 36.1% device replaced. The mean time between the initial implantation and generator replacement was 5.83±2.0 years. The mean longevity was 5.8 ± 1.9 years for single-chamber devices, 6.1± 1.4 years for dual-chamber devices, 5.7± 0.4 years for subcutaneous ICD (S-ICD) and 5.5 ±1.6 years for CRT-D devices (p=0.24).

Table 28 showed the baseline characteristics of patients at the time of the initial implantation and at the time of generator replacement. At the time of generator replacement, patients had a significantly higher LVEF (31.2±11. vs. 24.8±5.2, p<0.01), higher prevalence of diabetes mellitus (p=0.04) and lower mean eGFR (p=0.02) but no other significant differences were found. One patient downgraded from CRT-D to CRT-P at the time of replacement as there was significant improvement in LVEF. One patient with no previous ICD therapy downgraded from dual chamber ICD to pacemaker at time of generator replacement as part of ACP. For 21 (34.4%) patients receiving generator replacement, an upgrade/lead addition was also performed.

Indications and predictors of continued ICD use at Unit Generator Replacement

Forty-one (67.2%) patients fulfilled the guideline criteria based on LVEF for continued ICD use at unit generator replacement (**Figure 25**).

Among the 8 ICD patients who did not meet the guideline criteria, 50% had received appropriate ICD therapy in the intervening years despite improvement in LVEF at time of generator replacement. For those with CRT-D, 45.4% fulfilled the guideline criteria for replacement. The other 54.5% had demonstrated improvement in LVEF to ≥40% and only 1 patient had received appropriate ICD therapy prior to generator replacement.

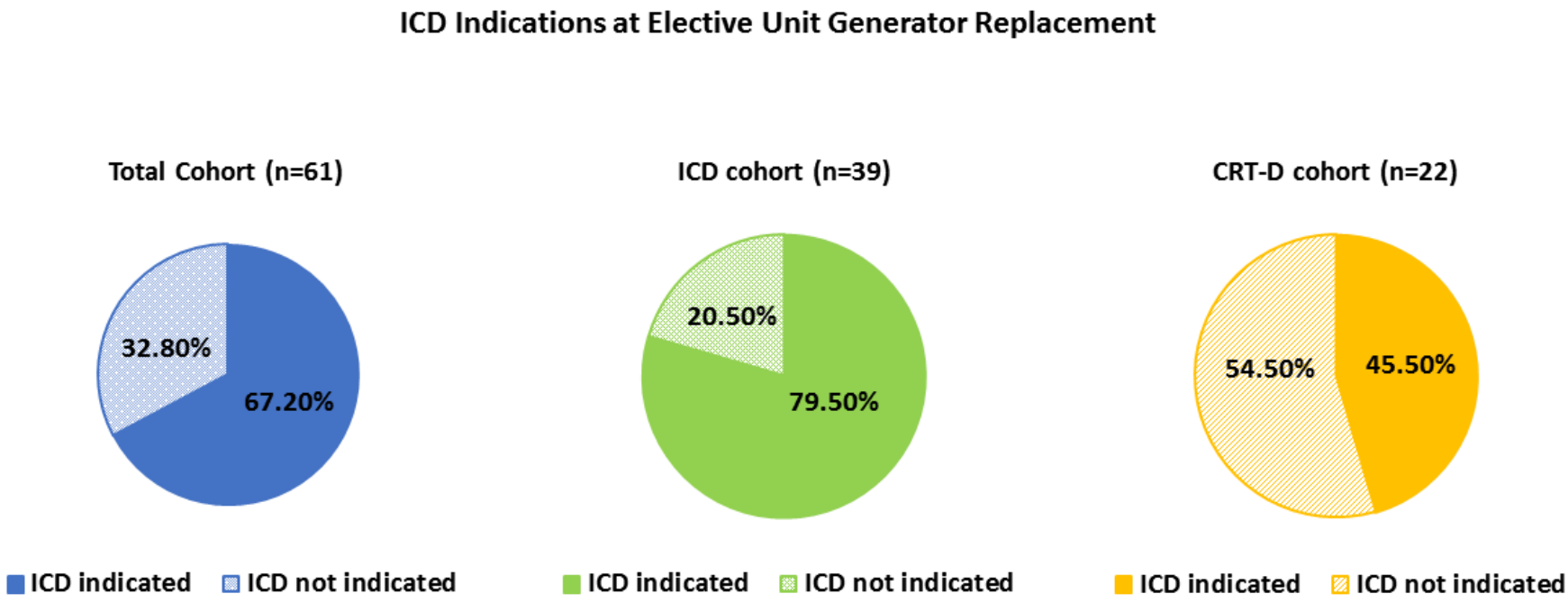
Table 28: Characteristics of patients at initial ICD/CRT-D implantation and at the time of ICD/CRT-D replacement

	Initial Implantation (n=61)	**Generator Replacement (n=61)**	**P Value**
Mean Age	58.2±11.4	64.1±12.1	<0.01
Median Age	60.3 (15.8)	65.9 (18.7)	
Mean LVEF (%)	24.8±5.2	31.2±11.6	<0.01
Type of devices			N/A
ICD			
Single chamber	22	22	
Dual chamber	9	9	
Subcutaneous IC (S-ICD)	4	4	
CRT-D	26	26	
NYHA Heart Failure Class (%)			
Class I	16 (26.2)	23 (37.7)	0.08
Class II	32 (52.5)	33 (54.1)	
Class III	13 (21.3)	4 (6.6)	
Class IV	0	1 (16)	
Mean eGFR (ml/min/1.73m$^{2)}$	70.3±16.7	65.3±19.2	0.02
History of Atrial fibrillation (%)	15 (24.6)	23 (37.7)	1.0

History of TIA/stroke (%)	4 (6.6)	6 (9.8)	0.53
Neoplastic disease (%)	0	1 (1.6)	0.32
Diabetes Mellitus (%)	12 (19.7)	16 (26.2)	0.04
Hypertension (%)	14 (22.9)	16 (26.2)	0.42
Medications use			
Diuretics (%)	39 (63.9)	37 (60.7)	0.57
ACE inhibitor or ARB (%)	58 (95.1)	55 (90.2)	0.26
Beta-blocker (%)	53 (86.9)	55 (90.2)	0.48
Antiarrhythmic drugs			
Sotalol (%)	7 (11.5)	2 (3.3)	0.16
Amiodarone (%)	8 (13.1)	13 (21.3)	0.17

Abbreviations:
ACE: angiotensin converting enzyme; ARB: angiotensin receptor blockers; eGFR: estimated glomerular filtration rate; ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction; TIA: transient ischaemic attack

Figure 25: ICD indications at elective unit generator replacement



Abbreviations:
CRT-D: cardiac resynchronisation therapy with defibrillator; ICD: implantable cardioverter-defibrillator

Characteristics of patients who continued to meet criteria for an ICD at the time of replacement versus those who no longer met criteria are compared in **Table 29**. No differences in terms of mean age and ethnicity were noted in the two groups. However, there were significantly higher LVEF, more females, more patients with CRT-D use and with NICM as well as higher use of ACE inhibitors/ARBs and beta-blockers in those who did not meet guideline criteria.

Incidence and Predictors of Appropriate ICD therapy After Unit Generator Replacement

Among the 61 patients who underwent generator replacement, 18 (29.5%) had received prior appropriate ICD therapy. Baseline characteristics of those with or without prior appropriate ICD therapy are shown in **Table 30**. Those with prior ICD therapy were more likely to be male and more often treated with diuretics and amiodarone at time of generator replacement.

The mean follow-up was 1.8 ± 1.5 years after generator replacement. During follow-up, 13 (21.3%) of the 61 patients received appropriate ICD therapy (ATP and/or ICD shocks) after unit replacement. The mean time from unit replacement to appropriate ICD therapies was 0.9±0.9 years. As expected, the occurrence of appropriate ICD therapy after ICD generator replacement was considerably higher for patients who met the guideline criteria for ICD (**Table 29**) and those with prior ICD therapies (**Table 30**). The cumulative risks of appropriate ICD interventions 1-, 3-, and 5- years after generator replacement in those with prior ICD therapy were 6.2%, 59.8% and 86.6% and in those without prior ICD therapies 0%, 6.2% and 50%, respectively, log-rank p=0.005 (**Figure 26**). No predictive factors for lower need of ICD therapy could be identified in either groups.

For the 20 patients who underwent ICD device replacement (despite no longer meeting accepted indications for primary prevention ICD therapy), 10% received appropriate ICD therapies compared to 26.8% who continued to meet primary prevention ICD indications ($p<0.01$). The cumulative risks of appropriate ICD interventions after 1-, 3-, and 5- years after generator replacement in those who no longer met indications were 0%, 25% and 62.5% and

in those who continued to meet primary prevention ICD indications were 3%, 28.4% and 85.9% respectively, log-rank p=0.23 (**Figure 27**).

Table 29: Characteristics of patients who met or did not meet criteria for primary prevention ICD at the time of Unit Generator Replacement

	Met Guideline Criteria (n=41)	Did Not Meet Guideline Criteria (n=20)	P value
Gender (%)			
Male	36 (87.8)	14 (70)	0.02
Female	5 (12.2)	6 (30)	
Type of Device (%)			
ICD	31 (75.6)	8 (40)	0.04
CRT-D	10 (24.4)	12 (60)	
Cardiomyopathy (%)			
ICM	17 (41.5)	2 (10)	<0.01
NICM	21 (51.2)	17 (85)	
Other causes	3 (7.3)	1 (5)	
Mean LVEF (%)	24.7±5.4	44.5±9.2	0.01
Mean eGFR (ml/min/1.73m^2)	62.6±17.6	67.6±21.5	0.19
Hypertension (%)	12 (29.3)	4 (20)	0.11

Diabetes Mellitus (%)	12 (29.3)	4 (20)	0.11
Atrial Fibrillation (%)	16 (39)	8 (40)	0.89
History of Stroke/TIA (%)	5 (12.2)	1 (5)	0.07
Medications Use At Generator Replacement			
ACE inhibitor or ARB (%)	35 (85.3)	20 (100)	<0.01
Beta-blocker (%)	35 (85.3)	20 (100)	<0.01
Anti-arrhythmic Drugs			
Amiodarone (%)	9 (21.9)	4 (20)	0.44
ICD therapy prior to generator replacement (%)	13(31.7)	5(25)	0.27
ICD therapy after generator replacement (%)	11(26.8)	2(10)	<0.05

Abbreviations:
ACE: angiotensin converting enzyme; ARB: angiotensin receptor blockers; CRT-D: cardiac resynchronisation therapy with defibrillator; eGFR: estimated glomerular filtration rate; ICD: implantable cardioverter defibrillator; ICM: ischaemic cardiomyopathy; LVEF: left ventricular ejection fraction; NICM: non-ischaemic cardiomyopathy; TIA: transient ischaemic attack

Table 30: Baseline clinical and demographic characteristics of patients with and without prior ICD therapy

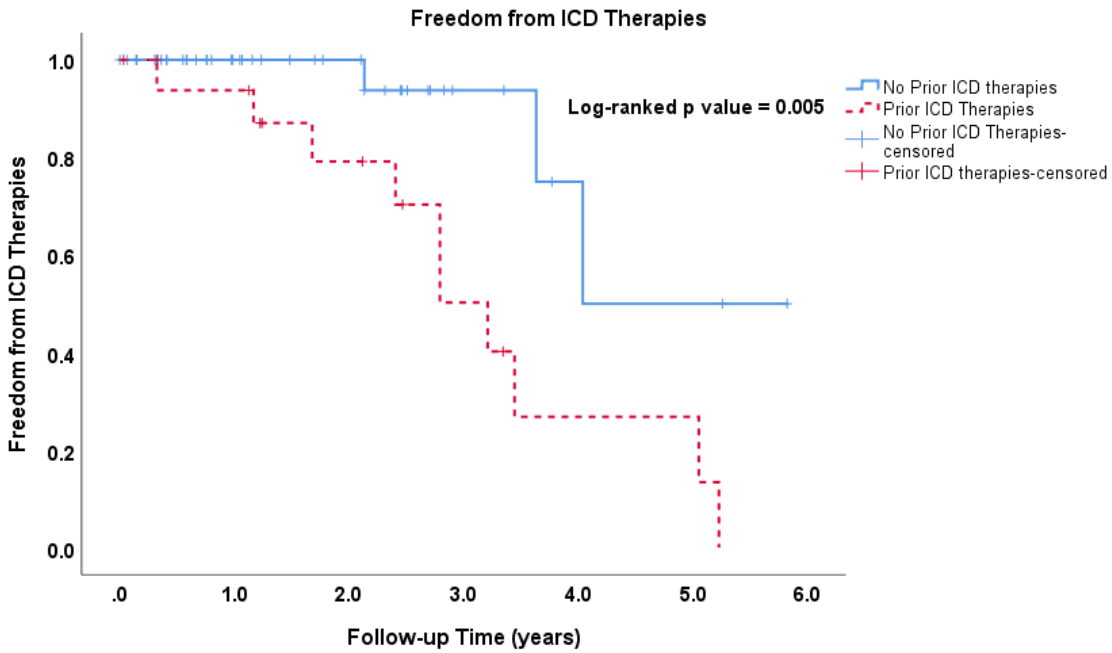
Characteristic	Patients with prior ICD therapy (n=18)	Patients without prior ICD therapy (n=43)	p Value
Mean age at implantation	59.9 ± 9.3	57.5 ± 12.1	0.42
Mean age at replacement	66.1 ±9.5	63.2 ± 13	0.29
Gender (%)			
Male	17 (94.4)	33 (76.7)	<0.01
Female	1 (5.6)	10 (23.3)	
Type of Device (%)			
ICD	13 (72.2)	26 (60.5)	0.05
CRT-D	5 (27.8)	17 (39.5)	
Cardiomyopathy (%)			
ICM	7 (38.9)	12 (27.9)	0.81
NICM	11 (61.1)	27 (62.8)	
Other causes	0	4 (9.3)	
Mean LVEF at Implant (%)	25.6 ± 5.8	24.6 ± 5.0	0.39

Mean LVEF at replacement (%)	27.6 ± 8.3	32 ± 11.9	0.13
Mean eGFR at Implant	61.8 ± 9.1	62.1 ± 14.2	0.12
Mean eGFR at Replacement	58.8 ± 18.2	66.4 ± 19.3	0.19
Medications At Initial Implant			
Diuretics (%)	15 (83.3)	22 (51.2)	<0.01
ACE inhibitor/ARB (%)	18 (100)	38 (88.4)	0.02
β-Blocker (%)	14 (77.8)	37 (86)	0.01
Amiodarone (%)	3 (16.7)	5 (11.6)	0.29
Medications At Replacement			
Diuretics (%)	13 (72.2)	24 (55.8)	<0.01
ACE inhibitor/ARB (%)	17 (94.4)	38 (88.4)	0.14
B-blockers (%)	15 (83.3)	40 (93)	0.03
Sotalol (%)	1 (5.6)	1 (2.3)	0.32
Amiodarone (%)	9 (50)	4 (9.3)	<0.01
ICD Therapy After Replacement (%)	10 (55.6)	3 (7)	<0.01

ATP	10	3	<0.01
ICD Shocks	7	1	<0.01
Inappropriate ICD Therapy After Replacement (%)	0	1 (2.3)	0.19
Number of Death After Replacement (%)	1 (5.6)	4 (9.3)	0.33

Abbreviations:
ACE: angiotensin converting enzyme; ARB: angiotensin receptor blockers; CRT-D: cardiac resynchronisation therapy with defibrillator; eGFR: estimated glomerular filtration rate; ICD: implantable cardioverter defibrillator; ICM: ischaemic cardiomyopathy; LVEF: left ventricular ejection fraction; NICM: non-ischaemic cardiomyopathy

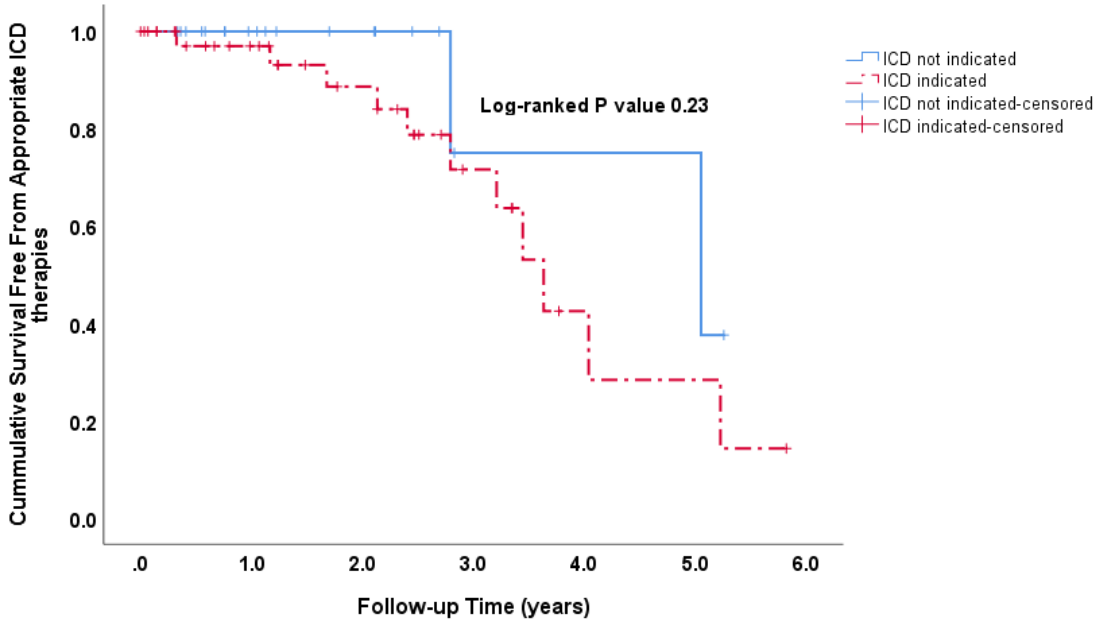
Figure 26: Subsequent ICD therapies after elective unit generator replacement in patients with prior ICD therapies compared with those without prior ICD therapies



Number At Risk

Year	0	1	2	3	4	5	6
Prior ICD Therapies	18	14	9	4	2	1	0
No Prior ICD Therapies	43	24	16	6	2	1	0

Figure 27: Subsequent ICD therapies after elective unit generator replacement in patients with no ICD indications compared with patients with ICD indications



Number At Risk

Year	0	1	2	3	4	5	6
ICD not indicated	20	11	7	2	1	1	0
ICD indicated	41	27	18	8	2	1	0

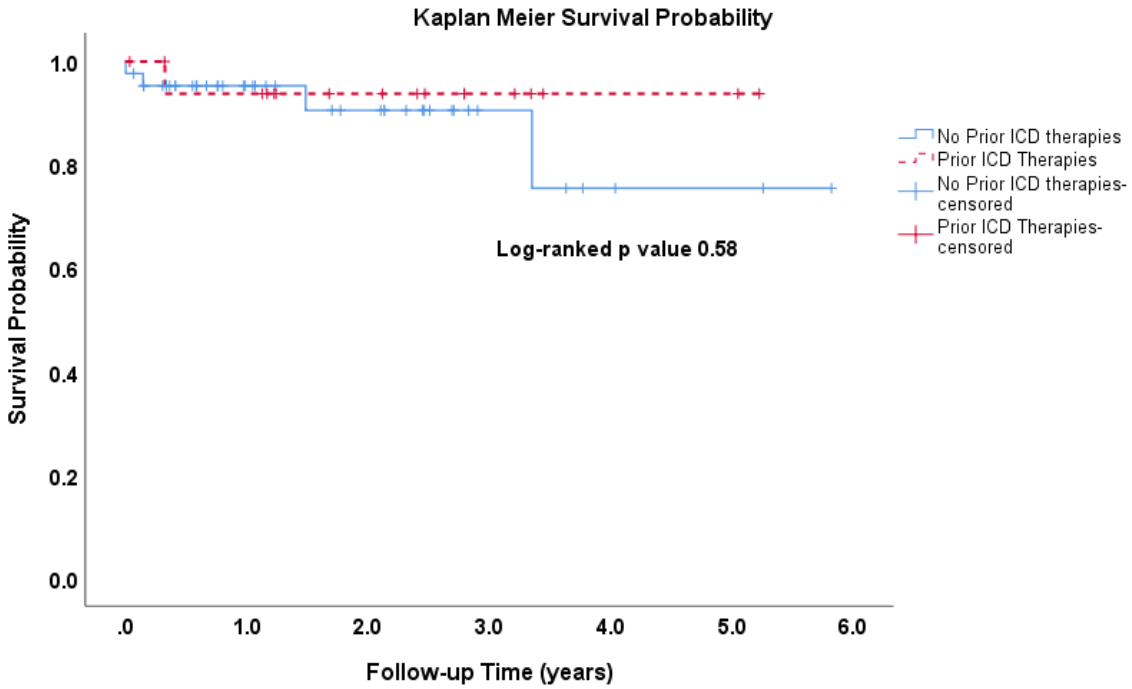
Complications

There were total of 6 (9.8%) procedure-related complications with 3 (50%) of these complications occurring in patients undergoing additional transvenous lead during replacement or upgrade to CRT-D. Early complications (<30 days after generator replacement) occurred in 1 (1.6%) patients who developed haematoma that was treated conservatively on an outpatient basis. Other complications (8.2%) (>30 days) included the need for reoperation resulting from lead malfunction due to increasing threshold and poor sensing in 4 patients (6.6%) and infection requiring intravenous antibiotics in 1 patient (1.6%).

Mortality

A total of 5 patients (8.2%) died during follow-up after generator replacement, all from end stage HF. The mean time from death after generator replacement was 1.1 ± 1.3 years. The 1-year,3-year and 5-year mortality risk was 5.2%, 8.2% and 18.4%, respectively. During follow-up, 1 (5.6%) of the 18 patients who received prior ICD therapy died after generator replacement. Of 48 with no prior ICD therapy, 4 patients (8.3%) died after generator replacement. There was no difference in mortality rate between the two groups (log-rank p=0.57, HR 5.14; 95% Confidence interval [CI], 4.54 to 5.75, p=0.33) (**Figure 28**). No predictors of survival were identified.

Figure 28: Kaplan Meier survival curve in patients with prior ICD therapies compared with patients without prior ICD therapies



Number At Risk

Year	0	1	2	3	4	5	6
Prior ICD Therapies	18	14	9	4	2	1	0
No Prior ICD Therapies	43	23	16	6	2	1	0

Discussion

Unsurprisingly, we found that patients who had previously undergone primary prevention ICD/CRT-D implantation were likely to develop significant co-morbidities during follow up until the time of elective ICD/CRT-D unit generator replacement. Although 32.8% patients no longer met primary prevention guideline indications at the time of generator replacement, the risks of subsequent appropriate ICD interventions were not different compared to those who continued to meet primary prevention ICD indications. 21.3% of patients received appropriate ICD therapy after generator replacement and the occurrence of appropriate ICD therapy was considerably higher for those with prior ICD interventions. However, there were no predictors found to stratify those at lower risk of needing ICD therapy, in whom avoidance of ongoing ICD support might have been an option.

Current guidelines do not distinguish between de novo ICD implantation and those undergoing elective unit generator replacement. The study by Kini et al. showed that approximately 26% of patients who receive primary prevention ICDs no longer met guideline-driven indications for an ICD at the time of generator replacement. Furthermore these patients had a significantly lower rate of subsequent ICD therapies.[373] Our study shows that a significant proportion (32.8%) of patients who receive their initial ICD for primary prevention on the basis of a low LVEF undergo generator replacement despite improved LVEF and not requiring ICD therapy in the intervening years. However, the cumulative risks of appropriate ICD interventions after generator replacement were no different than those with ongoing indications. This may be explained by the small number of patients, and our results would be consistent with lower subsequent ICD therapies rate observed in those no longer meeting guideline-driven indications.

There is a general trend towards replacing ICD regardless of the patient's clinical evolution during the device lifetime. In the results of the European Heart Rhythm Association survey, the overwhelming majority of centres in Europe reported that they replaced ICDs at the end of battery life.[374] Only in a small subset (<10%) of patients with ICD for primary prevention and without ventricular arrhythmias since implantation, ICD was not replaced.[374] Similar in our study, 32.8% of the patients who no longer met the guidelines for primary prevention ICD had their ICD replaced at the end of battery life. Only 2 patients required appropriate ICD therapies in this group after generator replacement. Patients without ICD therapies are at significantly lower risk of ICD therapies post generator replacement, especially if the LVEF has improved, and the risk of appropriate ICD therapy and/or rapid ventricular arrhythmia, albeit persisting over time, decreases significantly over the years.[375] Shared discussions should occur with patients about the evidence, healthcare goals, risk tolerances, and feelings about life and death trade-offs to enable high-quality decisions about ICD replacement. ICD unit generator replacement is an ideal time to re-evaluate health care goals and explore personal preferences regarding continuing ICD therapy. However, not many health care professions feel comfortable about this discussion. Furthermore, many patients due for replacement of their ICD unit generator did not realise they could opt out and many underestimated the risks of ICD replacement. A study by Lewis et al. showed that 51.9% of the patients did not know that ICD unit generator replacement was optional.[376] Of these, 27% would have considered no replacement. In the study, 20% of the patients believed ICD replacement carried no surgical risk and 17% perceived there was no risk of surgical infection.[376] Therefore it is important to discuss risk and benefits before deciding whether to continue with ICD therapy as such a discussion would allow a patient and the treating physician to review their healthcare goals and reassess their views on risk and benefits. By exploring these topics, physicians can better integrate patient preference into decision-making.

Although primary prevention patients are at risk of developing ventricular arrhythmias, studies showed that only 35% receives appropriate ICD therapy for ventricular tachycardia (VT) or ventricular fibrillation (VF).[377,378] Therefore, a significant number of patients have not developed ventricular arrhythmias requiring therapy during the first ICD service-life. This raises the issue of whether or not such patients actually need a replacement. In two large ICD registries of all primary prevention patients who underwent first ICD unit generator replacement without prior ICD therapies, 11% experienced appropriate ICD therapy during follow-up after generator replacement.[379] Van Welsenes et al reported that although the majority of primary prevention ICD patients do not have ventricular arrhythmias during first battery service-life, a substantial number of these patients subsequently get appropriate ICD therapy after replacement with a cumulative 5-year incidence for appropriate ICD therapy of 37% (95% CI: 33–42%)).[380] The results of the INcidence free SUrvival after ICD REplacement (INSURE) trial showed that at least 20% of patients without prior ICD therapies received appropriate ICD therapies within 3 years of generator replacement.[371]. Similarly, in our cohort, 21.3% of patients received appropriate ICD therapy after generator replacement and the 5-year cumulative incidence of appropriate therapies was 29.9%. No predictors of appropriate ICD therapy after replacement were identified in our study, precluding the ability to identify patients who may not benefit from ICD replacement. These results are consistent with previously published data.[371,379]

The results from the National Cardiovascular Data Registry (NCDR) ICD Registry showed that >40% of patients died within 5 years following routine ICD unit generator replacement.[381] AF, HF and LVEF were independently associated with poorer survival in patients following routine ICD unit generator replacement at the end of expected battery life.[381] In addition, non-cardiac comorbidities including chronic lung disease, cerebrovascular disease, diabetes, and worsening renal function were also independently associated with worse survival.[381] At time of generator

replacement, our cohort patients had developed more comorbidities. Although no predictors of survival could be identified, the 1-, 3- and 5-year mortality risk in our patients following ICD unit generator replacement were 5.2%, 8.2% and 18.4%, respectively. These findings underscore the importance of evaluating patients' entire clinical history at the time of ICD generator replacement, with particular attention to accumulated comorbidities that may limit life expectancy and the potential of benefiting from ongoing treatment with ICD therapy.

In our study, 24.7% of the patients had died prior to end of battery service life and 3.9% patients had their ICD/CRT-D devices deactivated prior to their deaths or as part of ACP. HF is chronic disease and can progressively deteriorate, resulting in poor long-term prognosis. ICDs improve prognosis by treating life-threatening ventricular arrhythmia, but do not modify HF progression nor contribute positively to quality of life of these patients. The 2013 British Heart Foundation guidelines state that the appropriateness of maintaining ICD therapy must be regularly reviewed as part of monitoring of the patient's progressive disease if there is any change in clinical status including the development of a life-limiting disease.[382] Similarly, Joint guidance from Resuscitation Council UK, Heart Rhythm UK/Arrhythmia Alliance and British Cardiovascular Society advises that patients approaching end of life should be offered a choice of ICD deactivation to avoid shocks in the latter stages of their illness.[383]

Careful decision making before ICD replacement is important because there is a potential risk of complications related to ICD replacement.[109,384] In the REPLACE registry, there was a major complication rate of 4.0% in patients who had a generator replacement without a plan to add a transvenous lead.[109] Complications were highest in patients who had an upgrade to or a revised CRT device (18.7%; 95% CI, 15.1 to 22.6).[109] Our cohort had a higher complication rate due to additional transvenous lead or upgrade, similar to published data that adverse event rates increase from pacemaker to ICD to CRT.[210,385]

Limitations

Our study should be interpreted in light of its potential limitations. Our study cohort was retrospectively recruited but prospectively followed up. The numbers of patients in our study were small, and the number of patients followed out after two years was small. Our population of patients receiving primary prevention ICD was also generally younger than in most Western Countries, especially the United States. Our study was observational and involved patients in the Northern Region of New Zealand; with a different socio-economic and ethnicity mix and will be different from other regions in New Zealand. Given the paucity of data on ICD unit generator replacement in New Zealand, this study represents real-world data on the outcomes of these patients.

Conclusion

Most patients who undergo primary prevention ICD unit generator replacement in Northern Region of New Zealand did not receive appropriate ICD therapy during the first generator longevity. One-third of patients who receive ICDs for primary prevention may no longer meet guideline criteria for continued ICD use at time of elective generator replacement. However, these patients appear to still be at risk of SCD. Notably, there were no predictors for lower occurrence of ventricular arrhythmias. Our findings alone should not guide clinical decision-making for patients eligible for ICD replacement. However, these data may support ACP discussion with potential ICD patients about life expectancy and accumulated comorbidity as this will allow each patient to choose in advance what interventions they wish to receive as part of end-of life care.

Chapter 7 : SUMMARY AND PERSPECTIVE

7.1 KEY RESULTS AND SIGNIFICANCE

The literature review and data presented in Chapters 1 to 3 demonstrated that ICDs can reduce all-cause mortality in HF patients with impaired LVEF. Moreover, there is robust evidence for favourable survival benefits and symptom improvement of CRT in the management of selected HF patients. However, which group of HF patients with impaired LVEF should receive a CRT-P alone or a CRT-D device remains a key question.

Chapter 4 describes the role of a simple risk score to identify HF patients who are more likely to benefit from CRT-D versus those who should be treated with a CRT-P, even when fulfilling ICD implantation criteria. Co-morbidities have an important impact on selection for prescription of devices given the potential for device-related complications against the potential benefit from the ICD.

Chapter 5 reports three observational studies describing the trends of health utilisation outcomes of HF patients with ICD/CRT-D and CRT-P in the Northern Region of New Zealand. It showed that effective ICD/CRT-D in appropriately selected HF patients resulted in a very low incidence of arrhythmic death. The incidence of hospitalisation for both ventricular arrhythmias and HF was significantly lower in the CRT-D group suggesting that where appropriate this should be the device of choice for HF patients. Significant challenges remain with improving access to device therapy and optimising the prescription of appropriate devices to maximise the benefit and minimise the harm to those who do get devices implanted. We have also demonstrated a difference between the use of a CRT-D and CRT-P in this region. CRT devices are commonly used in HF patients, but the coverage of the eligible populations is found to be low currently. Although there has been a significant increase in ICD implantation rates, gender imbalances remain in New Zealand, in keeping with the demographics of ischaemic heart disease and systolic dysfunction between genders. The study showed that

despite the higher perioperative complications in women who received primary prevention ICDs, they derived similar benefits in terms of long-term survival to men.

In Chapter 6 the burden of hospitalisations is described, using the novel measure of "Days alive and out of hospital" (DAOH) in HF patients implanted with CRT devices in the Northern Region of New Zealand. Major findings are patients implanted with a CRT device have relatively favourable outcome with fewer total hospitalisation, fewer total hospital days and increase in DAOH within the 1-year follow-up compared to 12-months before implant.

The final study in Chapter 6 describes the outcomes of HF patients with primary prevention ICD/CRT-D who underwent ICD unit generator replacement due to battery depletion. These patients often developed significant co-morbidities during follow-up post initial implant and suffered high procedural complication rates at time of replacement generator procedures. Although one-third of these patients no longer met primary prevention guideline indications at the time of unit generator replacement, the risks of subsequent appropriate ICD interventions were no different compared to those who continued to meet primary prevention ICD indications. There were no identifiable predictors to select those at lower risk of SCD and of needing ICD therapy. The findings are important since decision-making about ICD replacement particularly given the concerns about the complication rates and appropriate use of resources is an area of clinical uncertainty. It highlights the needs for on-going research.

7.2 FUTURE IMPLICATIONS

The use of device therapy in the treatment of patients with HF adds a new dimension to the spectrum of treatment modalities for this increasingly prevalent condition. Device therapy provides incremental benefits to selected HF patients already receiving optimal medical therapy. Improvements in QoL and survival in these selected HF patients have been observed in multiple clinical trials.[63,84,87,218,346,351,386,387]

Given the growing evidence base, there has been a meaningful evolution of the indications for device therapy over the years. Not all HF patients meet the criteria for device therapy and not all patients who received CRT respond favourably to CRT. Current imaging modalities for ventricular dys-synchrony have not yet been shown to improve patient selection for CRT.[205] A key unanswered question is how to improve CRT patient selection criteria, by determining better predictors for CRT response. There are a still significant number of current issues that exist when assessing CRT response. Firstly, there is no consensus on CRT response definition and it is highly dependent on the criteria used to define the response.[365] Response rates tend to be higher when clinical measures, such as NYHA or LVEF, are used but are much lower when remodelling of the left ventricle measured by echocardiography or outcome measurements are used.[366] There is no consensus on the optimal timeline to assess CRT response in clinical trials. Secondly, response criteria vary greatly among clinical trials. Symptomatic improvement does not always correlate with improvement in echo or functional assessment parameters, and vice versa. In addition, the best criteria to determine CRT response remains unknown. Finally, different factors between individual patients can affect CRT response. Ultimately, the long-term goal of device therapy for HF patients should include improvement of symptoms, QoL and survival.

Having data to support clinical decision-making in this increasingly complex area requires a national registry. Patient registries provide an opportunity for quality improvement of service as well as for research into patient outcomes. Data can be used to highlight geographic areas of need. Clinicians should be committed to the continuous improvement of clinical practice and patient outcomes. Having a national registry can also provide real world clinical information to support the refinement of guidelines including practical application of selection/referral process that optimise patients' outcomes. The New Zealand Cardiac Implanted Device Registry has recently been developed on the All New Zealand Acute

Coronary Syndrome – Quality Improvement (ANZACS-QI) platform.[274] This registry collects consistent information on cardiac device implantations in New Zealand to aid quality improvement initiatives and to allow examination of equity of access to therapy. The New Zealand Cardiac Implanted Device Registry is mandated by the Ministry of Health and participation from all ICD/CRT implanting centres in New Zealand is now required.

7.3 CONCLUSION

The findings presented within this thesis provides further information on device implantation in HF population and outcomes in the local context of New Zealand Northern Region, highlighting the relative paucity of local data and lack of evidence-based medicine being applied in the NZ context. The thesis provides an overview of the current practice of device therapy in HF patients and the corresponding outcomes in the Northern region of New Zealand. It emphasises the need for database and registry data to enable future ongoing research examining equity of access to device therapy, outcomes and complications in "real-world" HF patients.

In conclusion, reporting of follow-up data from the New Zealand Cardiac Implanted Device Registry is a critical tool to monitor the use of device therapy in HF patients. The regional variation of ICD /CRT implant in HF population can be a helpful starting point to discuss the possible treatment gaps in regard to the implementation of evidence-based guideline directed device therapy for HF patients in New Zealand. The follow-up data will enable more optimal patient selection in device therapy for HF management as well as ensuring adherence to the optimal management for patients with implanted devices.

APPENDIX

Editorial for the manuscript contained in Chapter 6

Primary prevention ICD generator at end of life: to replace or to not?

Santosh K Padala, Kenneth A Ellenbogen

Implantable cardioverter-defibrillators (ICDs) are the cornerstone of therapy for primary prevention of sudden cardiac death in patients with severely depressed left ventricular ejection fraction (EF) ≤35%, irrespective of the aetiology.[1–3] Current device guidelines and appropriate use criteria lay profound emphasis on the baseline left ventricular EF and New York Heart Association functional class in selecting appropriate candidates for primary prevention ICD implantation.[4 5] However, these society guidelines do not provide guidance regarding a decision about replacing ICD generators, especially in patients who have not had any appropriate ICD therapies during the lifespan of the device and/or in whom the left ventricular EF improves to >35% at the time of reimplantation. Prior studies have shown that among primary prevention ICD recipients, about 75% do not experience any appropriate ICD therapies during the lifetime of their first ICD generator[6 7] and about 25%–40% have improvements in their left ventricular EF >35% after ICD implantation.[7–12] Furthermore, patients requiring generator replacements are older and have significantly greater comorbidities compared with the initial recipients.[6 13 14] A significant proportion of ICD-related procedures in the USA, approximately 40%, involve ICD generator replacement based on the National Cardiovascular Data Registry data.[6] Device replacements are associated with substantial healthcare costs and greater risk of major complications compared with initial implant.[15 16] This raises a critical question as to whether the risk of sudden cardiac death warrants ICD generator replacement in patients who have not had any prior appropriate ICD therapies. Does improvement in left ventricular EF >35% lower the risk of sudden cardiac death negating the potential benefits of ICD?

In this issue of the *Journal*, Looi *et al*[17] report their single-centre outcomes in patients with heart failure after primary prevention ICD generator replacement. Of 385 patients with primary prevention ICD/CRT-D (cardiac resynchronization therapy-defibrillator) devices implanted between 2007 and 2015, 61 (16%) underwent pulse generator replacement. Twenty-one (34.4%) patients had a device upgrade. The mean time between the initial implant and generator replacement was 5.8 years. The mean longevity of the device did not differ between the device types (single chamber vs dual chamber vs CRT-D vs S-ICD (subcutaneous-ICD) device; p=0.24). Patients who presented for generator replacement had a significantly higher left ventricular EF (31.2±11. vs 24.8±5.2, p<0.01), higher prevalence of diabetes mellitus (p=0.04) and lower mean estimated glomerular filtration rate (p=0.02). Of 61 patients, 18 (30%) had received prior appropriate ICD therapies. When stratified based solely on left ventricular EF at the time of reimplant, 41 patients (67%) met the criterion for device replacement. Twenty patients (33%) had their left ventricular EF improved >35%. These patients were more likely to be women, with history of non-ischemic cardiomyopathy, had CRT-D devices, and had higher use of ACE inhibitors/angiotensin II receptor blockers and beta-blockers.

During a mean follow-up period of 1.8±1.5 years, 13 patients (21%) received appropriate ICD therapies (anti-tachycardia pacing/shock). Among the 20 patients who underwent ICD device replacement despite no longer meeting accepted indications for primary prevention ICD therapy, 10% (2/20) received appropriate ICD therapies compared with 26.8% (11/41) who continued to meet primary prevention ICD indications. The cumulative risks of appropriate ICD interventions after 1, 3 and 5 years after generator replacement in those who no longer met indications were 0%, 25% and 62.5% and in those who continued to meet primary prevention ICD indications were 3%, 28.4% and 85.9%, respectively (log-rank p=0.23). Although the authors state that 20 patients did not meet an indication for generator replacement based on improvement in EF, 5 of these patients received appropriate ICD therapy and would likely be considered to have an ongoing indication for secondary prevention ICD.

There were a total of 6 (9.8%) procedure-related complications: 1 haematoma, 1 infection requiring intravenous antibiotics and 4 lead revisions. Half of these complications occurred in patients undergoing device upgrade at the time of generator replacement. A total of 5 patients (8.2%) died during follow-up after generator replacement from end-stage heart failure.

There are no randomised controlled trial data on outcomes in patients with primary prevention ICD who are referred for elective generator replacement due to battery depletion and had no appropriate therapies in the past and/or who had improvement in their left ventricular EF. Although a small, retrospective, single-centre study, the results of the present study adds to the existing knowledge, showing that at the time of reimplant, left ventricular EF as a sole risk marker for assessing future arrhythmic death is far from ideal.[17] Although the risk of ICD therapies was lower in patients with improved EF >35%, the cumulative risks of subsequent appropriate ICD interventions did not differ compared with those who continued to have persistently depressed EF ≤35%.[17] The present study, however, was unable to identify predictors that would identify lower risk individuals at the time of reimplant for future ICD therapies.

Few observational studies have analysed the outcomes of primary prevention ICD recipients who were referred for generator replacement and had improvement in the EF >35%.[7 9 11 12 18] Two large studies are worth mentioning. Madhavan *et al*[7] reported outcomes in 253 primary prevention ICD patients who never received an appropriate ICD therapy and were referred for generator replacement at two tertiary medical centres. EF improved to >35% in 28% of patients at generator replacement. During a median follow-up of 3.3 years after generator replacement, 27% experienced appropriate ICD therapy. Importantly, patients with EF >35% continued to be at a significant risk for appropriate ICD therapy after generator replacement (5% per year), although at a lower rate than patients with a persistently low EF ≤35% (12% per year).[7]

In the Sudden Cardiac Death in Heart Failure Trial substudy, 1273 patients with reduced EF ≤35% assigned to ICD versus placebo were analysed.[18] During a median follow-up of 30 months, EF improved to >35% in about 30% of patients in each group. Compared with placebo, the adjusted HR for the effect of ICD on mortality was 0.64 (95% CI 0.48 to 0.85)

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in patients with a repeated EF of ≤35% and 0.62 (95% CI 0.29 to 1.30) in those with a repeated EF >35%. These data suggest that patients who had an improvement in EF >35% during follow-up accrued a similar mortality benefit with ICD as those whose EF remained ≤35%.[18] Similar findings were reported in other smaller studies where improvement in EF >35% was associated with lower risk of ICD therapies; however, the residual arrhythmic risk was significant enough to warrant ongoing ICD therapy.[9 11 12] Furthermore, heart failure is a progressive disorder. The left ventricular EF may subsequently decline after an initial improvement, thus placing a patient at risk for sudden death if generator replacement is not considered.

We would like to echo the concern raised by the authors of the present study. The fact that the risk of sudden arrhythmic death among those with improved EF and no prior ICD therapies is not zero does not necessarily imply that generator replacement should be performed routinely in all of these patients. The decision to perform a generator replacement should be made after considering carefully the relative balance between competing risks of arrhythmic and non-arrhythmic death.[19] Compared with an initial ICD implant, patients receiving replacement devices are older, have more significant comorbidities and have shorter life expectancy, all of which may limit the benefit of ICD therapy following generator replacement.[19] Additionally, generator replacements are associated with significant healthcare expenditure and associated complications, including infection, which may increase the risk of mortality.[15 16]

The present study, along with previously published reports, underscores the limitations of left ventricular EF as a sole marker of future arrhythmic risk. These studies have taught us that patients continue to be at significant risk for ventricular arrhythmias despite improvement in left ventricular EF >35%. The pivotal randomised controlled trials of primary prevention ICD included only high-risk patients with left ventricular EF <35%.[1–3] There has been no randomised controlled trial to date of primary prevention ICD implantation in patients with EF >35%. If proven in a prospective study, it will have significant implications on risk stratification in patients with left ventricular EF >35%. Future prospective studies should also use other markers for better risk stratification, such as detection of myocardial scarring by cardiac MRI in addition to left ventricular EF prior to ICD implantation.[20 21] In conclusion, it is reasonable to offer generator replacement for primary prevention ICD patients with improved EF >35% after carefully considering the risks of arrhythmic and non-arrhythmic death with an individual patient.

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