Determinants of QRS duration in a diverse cardiomyopathy population of the Western Cape – Implications for eligibility for cardiac resynchronization therapy

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AUTHOR'S DECLARATION

This study represents original work by the author. It has not been submitted to any other tertiary institution. Where the work by others is made use of, this has been duly acknowledged.

The research described in this research was carried out in the Division of Cardiology at Tygerberg hospital under the supervision of Dr Hellmuth Weich (Senior interventional cardiologist, TBH), Prof. Anton Doubell (Head of Department, TBH) and Mr Jan Steyn (Assistant Director, TBH) and under the supervision of Dr Rosaley Prakaschandra in the Department of Biomedical and Clinical Technology, Faculty of Health Sciences, Durban University of Technology.

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DEDICATION

I dedicate this work to:

My parents, siblings and their families for their love, support and patience.

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ABSTRACT

Determinants of QRS duration in a diverse cardiomyopathy population of the Western Cape – Implications for eligibility for cardiac resynchronization therapy

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Background

Cardiac resynchronization therapy (CRT) improves quality of life in heart failure patients who have a QRS duration ≥120 ms. Relatively few patients presenting with heart failure to the Division of Cardiology at Tygerberg Hospital are candidates for CRT, mainly because of a QRS duration <120 ms.

Objectives

The objectives of this study were to determine the QRS duration in a diverse cardiomyopathy population served by Tygerberg Hospital and to identify possible determinants of QRS duration in this cardiomyopathy population.

Method

Approval for this study was obtained from Stellenbosch University Health Research Ethical Committee and Tygerberg Hospital and all patients signed informed consent. Patients with a left ventricular systolic function (LVEF) ≤35% were recruited prospectively from the cardiac clinic. LVEF was determined by echocardiography using Simpson's biplane method. QRS duration was measured on a standard 12 lead ECG.

Results

Two hundred patients were included. The mean age was 52 years (range 18-84). Self-identified ethnicity revealed 63% coloured, 22% black and 15% white patients. The mean QRS width was 105 ms. On univariate analysis, parameters associated with a QRS width ≥120 ms included: ethnicity (White >Coloured >Black) (p = 0.01), ischaemic heart disease

(<0.01), age (<0.01), left ventricular size (p = 0.03) and male gender (p = 0.05). After correcting for covariates in a multivariate analysis, ethnicity and sex were no longer predictive of a broad QRS.

Conclusion

Although it appeared on first evaluation that there was a gender and ethnic disparity in candidates for CRT, multivariate analysis revealed that this is more likely due to differences in age, ischaemic aetiology and LV size.

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LIST OF DEFINITIONS

Term	Meaning
Mitral regurgitation	A condition in which the mitral valve does not close tightly, which allows blood to flow backward from the left ventricle into the left atrium.
Myocardial infarction	Tissue death (infarction) of the heart muscle (myocardium) caused by ischaemia, that is lack of oxygen delivery to myocardial tissue.

LIST OF ABBREVIATIONS

AV	Atrioventricular
CI	Confidence Interval
CRT	Cardiac Resynchronization Therapy
CRT-P	Cardiac Resynchronization Therapy – Pacemaker
CRT-D	Cardiac Resynchronization Therapy – Defibrillator
ECG	Electrocardiogram
HR	Hazard Ratio
ICD	Implantable Cardioverter Defibrillator
IHD	Ischemic Heart Disease
IQR	Interquartile Range
IVCD	Intraventricular Conduction Delay
LBBB	Left Bundle Branch Block
LV	Left Ventricle
LVEF	Left Ventricular Systolic Function
MR	Mitral Regurgitation
ms	Milliseconds
NYHA	New York Heart Association
RBBB	Right Bundle Branch Block
RCT	Randomised Controlled Trial

RV	Right Ventricle
TBH	Tygerberg Hospital
USA	United States of America

CHAPTER 1: INTRODUCTION

1.1 Rationale

The prognosis of heart failure is generally poor. The Olmsted County cohort showed that between 2000 and 2010, all forms of heart failure patients had 1-year and 5-year mortality rates following diagnosis of 20% and 53%, respectively (Gerber et al., 2015). A study that pooled the cohorts from the Framingham Heart Study and Cardiovascular Health Study found that 67% of patients died within five years of their diagnosis (Tsao *et al.,* 2018). The EuroHeart Failure survey and Italian Network on CHF registry have shown that patients with heart failure and LVEF ≤35% are more likely to have a broad QRS complex (>120 ms) (Rao *et al.,* 2007). Patients who develop conduction abnormalities, especially left bundle branch block (LBBB) in a setting of severely impaired left ventricular systolic function (LVEF) have an additional problem of dyssynchronous activation of the left ventricle (LV) and this can have a marked effect on the effectiveness of the LV (Oh *et al.* 2018).

Heart failure patients with broad QRS complexes and consequent dyssynchrony of ventricular contraction can benefit from cardiac resynchronization therapy (CRT) (Daubert *et al.,* 2012). As such, in accordance with the European Society of Cardiology (ESC) guidelines, CRT should only be considered if a patient has a QRS complex of at least 120 ms, LVEF ≤35%, New York Heart Association (NYHA) functional class II-IV, and the patient must already be on optimal medical therapy (Beshai *et al.,* 2007).

Large, randomized control trials (RCTs) like the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) study and the CARE-HF (Cardiac Resynchronization - Heart Failure) study have clearly demonstrated the favorable effects of CRT (Bristow *et al.,* 2004). The COMPANION study was conducted to test the hypothesis that prophylactic cardiac resynchronization therapy in the form of biventricular

stimulation with a pacemaker or with a defibrillator would reduce the risk of death and hospitalization among patients with advanced chronic heart failure and intraventricular delays (Bristow *et al.,* 2004). 1 520 patients with advanced heart failure (New York Heart Association (NYHA) class III or IV) caused by ischaemic or non-ischaemic cardiomyopathies with a QRS length of ≥ 120 ms were enrolled in their study. These patients were enrolled in a 1:2:2 ratio to receive the best pharmacological treatment (diuretics, ACE inhibitors, beta blockers, and spironolactone) either alone or in conjunction with cardiac resynchronization therapy using either a pacemaker or a pacemaker-defibrillator. The time to death from or hospitalization for any cause was the main composite end point (Bristow et al., 2004).

The findings of this study demonstrated that cardiac resynchronization therapy and CRT with a pacemaker both reduced the risk of the primary end point when compared to optimum pharmacologic therapy alone (hazard ratio [HR], 0.81; $p = 0.014$).

The conclusion of the COMPANION study was that in patients with advanced heart failure and a broad QRS duration, CRT decreased the combined risk of death from any cause or first hospitalization, and when combined with an implantable cardiac defibrillator (ICD), reduced mortality significantly (Bristow *et al,.* 2004).

In the CARE-HF research, 813 patients with LVEF ≤ 35%, QRS duration ≥ 120 ms, and NYHA functional classes III and IV were enrolled to receive either optimum HF pharmaceutical therapy or cardiac resynchronization therapy with a pacemaker (CRT-P) (no cardiac resynchronization therapy – defibrillator [CRT-D] arm). This trial was a randomized, multicenter, multinational trial. From January 2001 to March 2003, patients were enrolled at 82 European centers. This investigation was not blinded. However, the end-points committee members were unaware of the patients' assigned treatments. For ethical concerns and so that the experiment could evaluate the full impact of cardiac resynchronization, including issues related to the device's installation, patients in the control group were not scheduled to get a device.

For a mean of 29.4 months, the patients were monitored. 159 patients in the cardiac resynchronization group met the primary end point, which was a composite of all-cause death and hospitalization for a major cardiovascular event, as opposed to 224 patients in the medical therapy group (39% vs. 55%, HR, 0.63; 95% confidence interval (CI), 0.51 to 0.77; p <0.001). In the CRT group, 82 people died, compared to 120 in the group receiving medical therapy (20% vs. 30%; HR 0.64; 95% CI, 0.48 to 0.85; p <0.002). CRT raised the left ventricular ejection fraction (LVEF) in comparison to medical therapy, decreased the interventricular mechanical delay, end-systolic volume index, and area of the mitral regurgitation (MR) jet, and improved symptoms and quality of life (p <0.01 for all comparisons).

In the conclusion of the CARE-HF study, CRT therapy was better than pharmacological therapy alone at all QRS durations, although the benefit was greater in those with QRS duration ≥160 ms. These studies were landmark studies as they both played a crucial role in determining the benefits of CRT.

Although Tygerberg Hospital (TBH) serves a large population of heart failure patients, relatively few patients presenting with heart failure to the hospital's Division of Cardiology are candidates for CRT, precluded mainly by a QRS duration <120 ms, which forms part of the criteria for CRT selection. This observation raised the question about the QRS duration in the local heart failure population and whether they have less prolonged QRS durations (i.e., QRS durations ≥120 ms) than the international norm. To the knowledge of the researcher, no such study has been performed in South Africa, and the potential benefit of this data would be to determine the QRS duration of the heart failure population served by TBH. Another potential benefit of this data is that it will provide information about the relationship between the demographics, aetiology of cardiomyopathy and the QRS duration in a diverse cardiomyopathy population served by TBH – information which is currently not available.

The aims and objectives of this study, therefore, were to identify similar studies conducted in first world countries; to determine the QRS duration in a diverse cardiomyopathy

population served by TBH; to identify determinants of QRS duration in this population served by TBH; and to compare the QRS duration in this cohort with the international norm to determine if the reason that fewer CRT devices are implanted in TBH could be attributed to fewer numbers of patients with prolonged QRS durations in the heart failure population served by TBH.

1.2 Summary of chapters

Chapter 1 – Introduction: In this chapter the importance of CRT is described as well as its benefits as proven by some previous studies. This chapter includes a brief overview of heart failure, and the rationale, aims and objectives of this study.

Chapter 2 – Literature Review: This chapter contains information about heart failure and the problems it causes. The benefits of CRT and the CRT guidelines are described. Studies that were conducted in first world countries are used to support the benefit of CRT.

Chapter 3 – Materials and methods: This chapter describes the materials and methods used in this study, including ethical issues such as the use of consent forms. Echocardiography is described in detail considering that it was the tool used to measure the LVEF in order to select the suitable participants for this study.

Chapter 4 – Results: In this chapter the study findings are described using histograms and percentages. The median, mean and standard deviations are also provided.

Chapter 5 – Discussion: In this chapter the results of this study are interpreted and discussed. All of the study aims and objectives were achieved since the QRS duration of the cardiomyopathy population served by TBH was obtained, the determinants of QRS duration were identified and the comparison of the QRS duration of the cardiomyopathy population served by TBH to the QRS duration of other countries was done.

Chapter 6 – Conclusion: Main conclusions based on the study findings are reported. The QRS duration of the cardiomyopathy population served by TBH and the determinants of QRS duration are reported.

CHAPTER 2: LITERATURE REVIEW

This chapter describes heart failure, cardiac resynchronization therapy and the guidelines for this specific type of a pacemaker. The benefits of CRT are stated in this chapter. There is also an overview of studies conducted in First World countries.

2.1 **Introduction**

Heart failure is one of the leading causes of death around the world. Cardiac resynchronization therapy is a special type of a pacemaker given to patients with heart failure with severely reduced LVEF and a broad QRS complex. Multiple studies have proven that cardiac resynchronization therapy improves quality of life and reduces hospitalizations when given to the right patient.

2.2 Heart failure

Heart failure develops as result of an abnormality in cardiac structure, function, rhythm, or conduction (Jessup and Brozena 2003). Valvular heart disease, ischaemic heart disease, idiopathic cardiomyopathy and alcohol induced cardiomyopathy are some of the major causes of heart failure. The heart depends on preload and afterload to function well. When cardiac output falls, either the heart rate or stroke volume must change in order to maintain perfusion. The pathophysiology behind heart failure includes the cardiovascular response to poor perfusion with the activation of the neurohormonal system (Jessup and Brozena 2003).

The renin-angiotensin system is activated in an attempt to increase preload by stimulating retention of salt and water, increasing vasoconstriction (and, thus, afterload) and augmenting cardiac contractility. In the beginning, this response will suffice, but prolonged activation results in loss of myocytes and maladaptive changes in the surviving myocytes and the extracellular matrix (Eichhorn and Bristow 1996). In response to the insult, the stressed myocardium undergoes dilatation and remodelling, and this process also has a

detrimental effect on other vital organs such as kidneys and lungs (Eichhorn and Bristow 1996). This remodelling results in additional cardiac decompensation from complications, MR secondary to annular dilatation, and cardiac arrhythmias from atrial remodelling (Jessup and Brozena 2003).

Although frequently fatal, the typical heart failure symptoms (excessive fatigue, dyspnea, and swelling limbs) are typically less severe than those linked to a myocardial infarction (Wasywich et al., 2010). Up to one in five people in economically developed nations are predicted to experience heart failure at some point in their lives, and even more people will be impacted as family members, friends, or medical professionals because treating heart failure patients is emotionally and financially draining (Lloyd-Jones et al., 2002). Globally, between 17 and 45 percent of people with heart failure who are hospitalized to hospitals pass away within a year of being treated there, with the majority passing away within five years (Wasywich et al., 2010).

In recent years, survival rates for patients with heart failure have improved in many parts of the world, in parallel with the introduction of modern evidence-based therapies and patient-management systems (Wasywich *et al.,* 2010). However, about 2-17% of patients with heart failure who are admitted pass away in the hospital, usually due to sudden cardiac death as a result of arrhythmias such as ventricular tachycardia and ventricular fibrillation. Survival rates are better for those treated in outpatient clinics who typically have less severe symptoms than those treated in hospital (Maggioni *et al.,* 2013). The outlook for patients with heart failure remains dire, and survival rates are significantly worse than those for colon, breast, or prostate cancer, despite advancements in care over the previous 20 years (Brenner et al., 2012).

Heart failure is graded using the NYHA functional class and the classes range from class I to class IV (Table 2.1).

Table 2.1: NYHA grading

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations or dyspnoea.
Class II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitations or dyspnoea.
Class III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitations or dyspnoea.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, physical discomfort increases.

Source: Adapted from Dolgin et al. (1994).

According to the latest American Heart Association guidelines which were published in April 2022, heart failure has different categories and these categories are based on the LVEF.

Table 2.2: Heart failure categories

Type of HF according to LVEF	Criteria
HFrEF (HF with reduced EF)	LVEF ≤40%
HFimpEF (HF with improved EF)	Previous LVEF ≤40% and a follow up measurement of LVEF >40%
HFmrEF (HF with mildly reduced EF)	LVEF 41%-49% Evidence of spontaneous or provokable increased LV filling pressures (eg, elevated natriuretic peptide, noninvasive and invasive measurement)
HFpEF (HF with preserved EF)	LVEF ≥50% Evidence of spontaneous or provokable increased LV filling pressures (eg, elevated natriuretic peptide, noninvasive and invasive measurement)

Source: 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

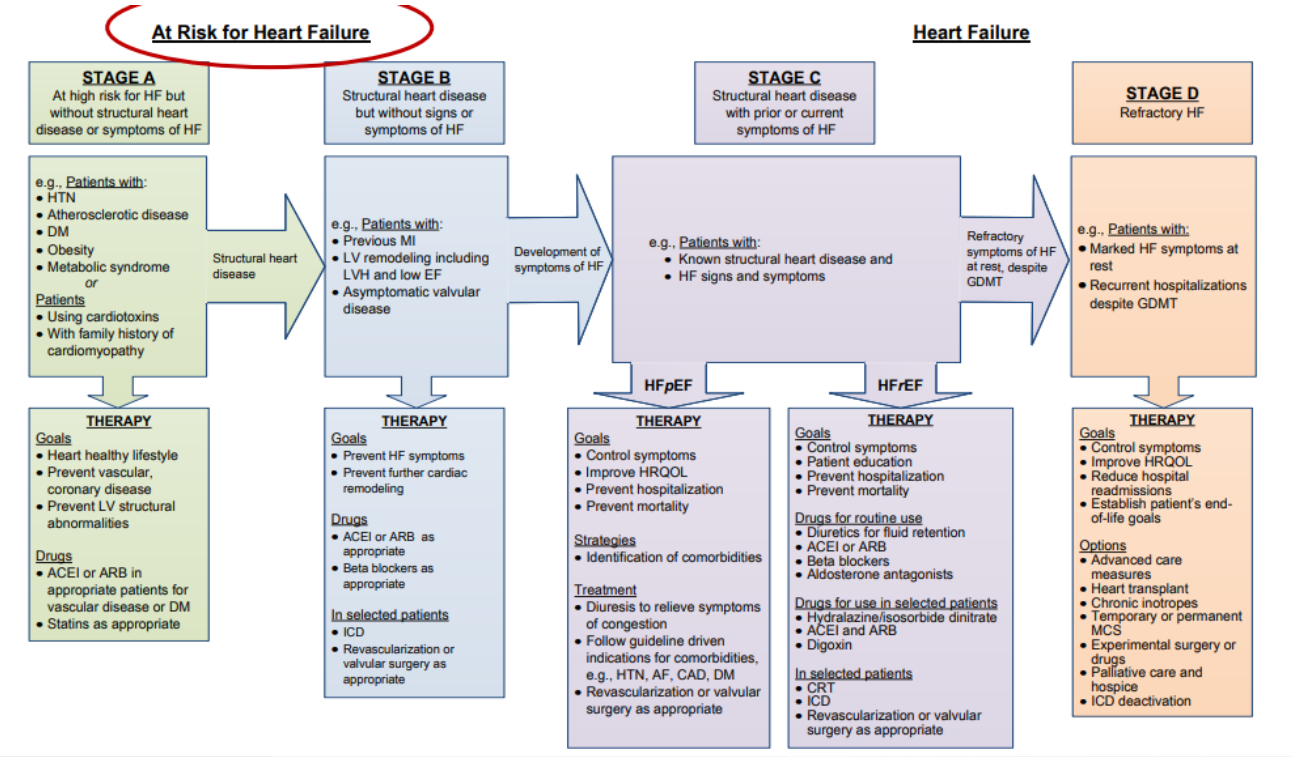

Figure 2.1: Stages of heart failure and management
Source: Yancy *et al*. (2013)

Heart failure affects over 26 million persons worldwide, prompting some to call it a global pandemic (Ambrosy et al., 2014). The risk of heart failure rises with age. Few heart failure patients in North America and Europe are under the age of 50, and more than 80% are 65 or older (Bui, Horwich and Fonarow 2011). In nations with aging populations, there will likely be a rise in the number of heart failure patients. Japan has the oldest population among all the economically advanced countries (Shiba and Shimokawa 2008). In the United States of America (USA), there were 5.8 million patients living with heart failure in 2012, and this is expected to rise to 8.5 million by 2030 (Heidenreich *et al.,* 2013). The advancements in treating heart attacks and other cardiovascular conditions that harm or put more strain on the heart are another element in the rising numbers. Despite the fact that many patients with these illnesses are now surviving, they still have a high chance of developing heart failure in the future (Ambrosy et al., 2014).

In economically developing areas, such as parts of Latin America and Asia, the numbers of patients with heart failure are increasing (Sakata and Shimokawa 2013). The change

to a Western lifestyle and its related illnesses, such as diabetes, which raises the risk of developing heart failure, are mostly to blame for the rise. This is despite a decline in the number of Chagas disease cases in Latin American cities as well as declines in the number of Davies disease cases in tropical regions (Vijayaraghavan and Sivasankaran 2012).

2.3 QRS width

QRS duration is measured from the beginning of the Q wave to the end of the S wave. A normal duration of a QRS complex is from 60 milliseconds to 100 milliseconds. A QRS duration of ≤100 ms means that the rhythm is of supraventricular origin. A QRS duration ≥120 ms can be due to ventricular tachycardia, idioventricular rhythm, ventricular escape, bundle branch block (LBBB and right bundle branch block [RBBB]), aberrant conduction (rate related bundle branch block), pre-excitation (antidromic atrioventricular re-entry tachycardia and Wolf Parkinson White syndrome), ventricular pacing, premature ventricular complex, hypothermia, hyperkalaemia and poisoning with sodium channel blocking agents (e.g trycyclic antidepressants) (Mattu, Tabas and Brady 2019). In a normal heart, the impulse is generated by the sinoatrial node which is found in the right atrium, and then the impulse travels to the atrioventricular node, where a delay of 120 ms to 200 ms takes place to allow adequate ventricular filling. From the atrioventricular node the impulse is transmitted to the bundle of His whereafter it is transmitted to the left and right branches and finally reaches the Purkinje fibres. Widening of the QRS complex can be due to disturbance or blockage in the normal specialized conduction resulting in a cell to cell conduction (Jastrzebski *et al.,* 2012).

Normal circumstances result in synchronous depolarization of the ventricles as a uniform, high-velocity electrical waveform that travels via the His-Purkinje circuit activates the myocardium (Shenkman et al., 2002). Affected electrochemical substrate and compromised conduction fibers in sick hearts can alter the speed and homogeneity of electrical propagation, leading to regions of activation delays (Shenkman et al., 2002). If the delay is substantial enough, the QRS complex on the 12-lead surface

electrocardiogram will lengthen (ECG). A prolonged QRS complex indicates electrical dyssynchrony and possibly reduced conduction velocity (Shenkman et al., 2002). QRS duration and decreased LVEF are directly correlated (Shenkman et al., 2002). Furthermore, a longer QRS duration is associated with worsening symptoms.The prevalence of a prolonged QRS (>120 ms) is approximately 20% in the general heart failure population, but it is approximately 35% in the symptomatic heart failure population (Silvet *et al.,* 2001).

Patients who develop LBBB in a setting of heart failure with reduced systolic function have an additional problem of dyssynchronous activation of the LV and this can have a marked effect on the effectiveness of the LV function. In order to bring back synchrony of the LV, a cardiac resynchronization therapy device is implanted. Cardiac resynchronization therapy (CRT) is a well established mode of device therapy in advanced heart failure patients who are on optimal medical therapy.

Electrical dyssynchrony may appear physically as mechanical dyssynchrony (Ypenburg et al., 2008). Three different kinds of mechanical dyssynchrony exist (Hawkins et al., 2006). The first one is intraventricular dyssynchrony involving the left ventricle (LV), which frequently manifests itself most clearly in individuals with LBBB due to a delay between early activation of the interventricular septum and late activation of the posterolateral wall. The second form is interventricular dyssynchrony, which frequently results from the LV's activation being delayed as a result of LBBB. The His-Purkinje system may be involved in the third form of mechanical dyssynchrony, AV dyssynchrony, which results from prolonged or missing AV nodal conduction (Ypenburg et al., 2008). Any type of mechanical dyssynchrony can lengthen the times between isovolumic contraction and relaxation (during which no blood movement occurs) and therefore reduce the effectiveness of the heart's pumping activity (Ypenburg et al., 2008). Additionally, the malfunction of the papillary muscle and absence of leaflet coaptation in a dyssynchronized dilated LV might lead to MR (Hawkins et al., 2006). Even while a prolonged QRS length is the strongest indicator of dyssynchrony, some research indicates that mechanical dyssynchrony can still exist (Hawkins et al., 2006).

Despite receiving the best possible medical care, patients are currently eligible for CRT based on QRS length, LVEF, and signs of chronic heart failure (Thibault et al., 2011). These requirements are based on the important CRT studies' enrollment requirements. The effectiveness of CRT in patients with LV dyssynchrony but relatively short QRS length (130 ms) has been studied in numerous major studies using echocardiographic criteria intended to determine mechanical dyssynchrony (Beshai et al., 2007). Overall, these studies have been unable to show any reduction in morbidity or death in this cohort when using CRT. Resynchronization Therapy in Normal QRS (RethinQ) research, a randomized trial that evaluated the effectiveness of CRT in patients with a QRS duration of less than 130 ms, is one study that has used echocardiographic criteria to do so.. The other study which used echocardiographic criteria to assess the efficacy of CRT in patients with a narrow QRS complex is the Evaluation of Screening Techniques for Electrically-Normal, Mechanically dyssynchronous HF patients receiving CRT (ESTEEM-CRT) which was a multi-centre, single arm study in 68 patients (Donahue *et al.,* 2012). The EchoCRT (Echocardiography-guided Cardiac Resynchronization Therapy) study revealed an increase in mortality following CRT implantation in this group, which is noteworthy (Ruschitzka et al., 2013). As a result, the only verified indicator of dyssynchrony that currently qualifies patients for CRT is a prolonged QRS duration.

Large-scale clinical investigations have thoroughly established the LVEF ≤ 35% threshold. There are currently no studies showing that CRT is helpful in patients with greater LVEF. A instance where a patient is anticipated to need regular cardiac pacing due to AV block is a notable exception to the aforementioned selection criteria (Beshai et al., 2007). It is desirable to implant a CRT device in these patients because continuous pacing with a single right ventricular (RV) lead can result in the same kind of dyssynchrony that CRT is intended to treat. In the BLOCK HF (Biventricular vs Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block) experiment, CRT and RV pacing were compared in patients with LVEF less than 50% in order to test this theory (Curtis *et al.,* 2013). The findings showed that, as compared to RV pacing alone, CRT significantly decreased the combined endpoint of mortality, HF-related urgent care visits, and

improved left ventricular end-systolic diameter by 26%. Therefore, CRT may be taken into consideration as a strategy of minimizing pacing-induced ventricular dysfunction in individuals who are planned for device implantation due to frequent AV block.

2.4 Mechanism of cardiac resynchronization therapy

Following the insertion of a biventricular pacemaker, CRT can lessen all three types of mechanical dyssynchrony (Moss et al., 2009). The preceding dyssynchronous heart immediately gains a mechanical advantage from coordinated ventricular contraction, increasing the cardiac output. In addition to the immediate hemodynamic advantages, CRT can improve the heart's structure and function even more over the course of months (Moss et al., 2009). Reverse remodelling, which refers to these long-term alterations, is frequently measured by a decrease in LV size and an improvement in LV function (Moss et al., 2009). In CRT-treated patients with baseline symptomatic HF and lengthy QRS duration, reverse remodelling is a common finding (Moss et al., 2009). Additionally, Yu et al. (2002) demonstrated that this effect ends after CRT withdrawal.

The level of reverse remodelling found with CRT is comparable to that reported after therapy with beta blockers and angiotensin-converting enzyme inhibitors. All groups with systolic HF have seen decreased morbidity and mortality as a result of these positive developments (Zweier, Chen and Talukder 2011). The resulting geometric modifications may also cause the mitral annulus to dilate less, which would lessen the severity of MR, a frequent concomitant disease in HF patients (Zweier, Chen and Talukder 2011). CRT enhances cardiac contractility and systolic function at the cellular level by increasing peak calcium levels that shorten sarcomeres (Zweier, Chen and Talukder 2011).

Additionally, CRT improves beta-adrenergic reactivity by increasing the density of beta receptors on the surface of cardiac cells. The increase in beta receptors is crucial because myocytes in failing hearts typically have decreased adrenergic responsiveness, which results in increased amounts of circulating catecholamine that might hasten HF (Zweier, Chen and Talukder 2011). By undoing mitochondrial oxidative post-translational

modification, cardiac resynchronization therapy can also boost the activity of mitochondrial adenosine triphosphate synthase. An improvement in myocyte function and a more effective energy metabolism are the results of this enzyme upregulation (Zweier, Chen and Talukder 2011).

Heart failure affects 2% of adults in developed nations, with the majority of patients being older than 70 and having an ejection fraction of less than 50% in half of them (Martin et al., 2012). In the EuroHeart Failure study, 41% of individuals whose LV function was evaluated had a QRS duration ≥ 120 ms, 7% of them had RBBB, 34% had LBBB or another type of intraventricular conduction delay (IVCD), and 17% had a QRS ≥ 150 ms. Of those who had LVEF assessment, 36% had an LVEF ≤ 35%. 1391 patients (25%) had complete LBBB, 336 (6%) had complete RBBB, and 339 (6%) had different types of IVCD in the Italian Network on CHF (IN-CHF) registry (Ritter et al., 2012). In ambulatory patients with left ventricular systolic failure and chronic HF, the annual incidence of LBBB is about 10%. (Gasparini et al., 2006). Only a small percentage of HF patients (perhaps 5–10%) are recommended for CRT based on current ESC guidelines, however this still accounts for a sizable patient population.

Based on information from two EuroHeart Failure surveys and extrapolation from hospital discharge data, it is thought that 400 patients per million people, or up to 400 000 patients annually in ESC nations, may be candidates for CRT. In 2011, the average number of cardiac resynchronization treatment (CRT) implants per million people in western and central Europe was 140, with 107 of those implants being CRT-D and 33 being cardiac resynchronization therapy with pacemakers (CRT-P) (Boriani et al., 2012).

Cardiac resynchronization therapy aids in the restoration of AV, inter-, and intraventricular synchrony, which enhances LV function, lessens functional MR, and induces LV reverse remodelling as seen by increases in LV filling time and LVEF. The LV end-diastolic and end-systolic volumes, MR, and septal dyskinesis all decrease as a result of this treatment (Moss et al., 2009). It's possible that the primary mechanism of benefit will change over time both within and across patients. Given that the mechanisms of benefit are so diverse,

it's probable that no single measure will be able to predict the response to CRT with accuracy (Moss et al., 2009).

A number of RCTs have provided strong proof that CRT is beneficial for patients with NYHA class III HF in the short- and long-term (Auricchio et al., 2003). The advantages of CRT on symptoms, exercise capacity, and LV structure and function were shown in the first randomized trials. The effects of CRT-P on HF hospitalizations and all-cause mortality were examined in the CARE-HF and COmparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) studies (Bristow et al., 2004). In these patients, CRT improved symptoms and decreased all-cause mortality by 22% (risk ratio 0.78, 95% confidence interval (CI) 0.67-0.91) and HF hospitalizations by 35% (risk ratio 0.65, CI 0.50-0.86), according to a recent meta-analysis (Al-Majed et al., 2011). Due to the poor enrollment of patients in RCTs (7–15%), the data for NYHA class IV heart failure patients is sparse. In a COMPANION trial sub-study, class IV patients (referred to as "ambulatory" class IV) who had no scheduled or unscheduled HF hospitalizations within the previous month demonstrated a significant decline in the combined primary endpoint of time to all-cause mortality and hospitalization, but only a trend for all-cause mortality and HF deaths (Höijer, Meurling and Brandt 2006).

The majority of RCTs adopted an inclusion criterion of a QRS interval duration of ≥ than 120 ms. In a recent meta-analysis assessing the effect of QRS duration on the effectiveness of CRT, subgroup analysis demonstrated that in NYHA class III–IV HF patients, CRT significantly decreased all-cause mortality or hospitalization in patients with QRS duration ≥ 150 ms (data extracted from COMPANION and CARE-HF). With lower QRS duration, the strength of the effect and the certainty of benefit decreased. In addition, more patients in the RCTs exhibited LBBB morphology than non-LBBB patients, which was linked to a greater effect (Gervais et al., 2009). Therefore, more research is needed to understand the relationship between QRS duration and morphology.

Four RCTs have shown that CRT helps patients with moderate HF symptoms (NYHA classes I–II), sinus rhythm, LVEF ≤ 30–40%, and QRS duration ≥ 120–130 ms improve

LV function, all-cause mortality, and HF hospitalizations. However, for patients randomly assigned to CRT, improvement in functional status or quality of life was only moderate. Only 15% of patients in REsynchronisation reVErses Remodelling in Systolic left vEntricular dysfunction (REVERSE) and 18% in MADIT-CRT exhibited NYHA class I symptoms, while the majority of patients that were enrolled had NYHA class II HF symptoms (Moss et al., 2009). In individuals in the NYHA class I, cardiac resynchronization therapy did not lower all-cause mortality or HF events. Therefore, only patients in NYHA class II are eligible for the recommendation. Patients with a QRS length of ≥ 150 ms benefited most by CRT, according to pre-specified subgroup analyses of data from the MADIT-CRT, REVERSE, and Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT) trials (Moss et al., 2009). Using aggregate data from randomized trials, meta-analyses revealed that CRT reduced adverse clinical outcomes in patients with baseline QRS duration of ≥ 150 ms and suggested that it might not in patients with a QRS <150 ms (Moss et al., 2009). This meta-analysis of five randomized studies involving individual patients compared CRT with either no active device or a defibrillator. They looked into sex, age, NYHA class, aetiology, QRS morphology, QRS width, LVEF, and systolic blood pressure in this meta-analysis. The results included all-cause mortality and first hospitalization for heart failure or death (Moss et al., 2009).

Patients with complete LBBB appeared to benefit more from CRT on the overall composite of morbidity/mortality, according to sub-group analyses based on QRS morphology in the MADIT-CRT, RAFT, and REVERSE trials, as well as a meta-analysis of COMPANION, CARE-HF, MADIT-CRT, and RAFT. This was in contrast to patients with non-specific IVCD or RBBB (Sipahi et al., 2012). Analysis of morphology may be complicated by QRS duration because patients with LBBB had higher QRS duration. In particular, the MADIT-CRT trial shown that non-LBBB patients did not benefit clinically from CRT therapy (statistically not significant with 24% increased risk), however CRT-D reduced the risk of death or HF hospitalization in patients with LBBB by 53% when compared to ICD alone (Zareba et al., 2011). The pre-specified subgroups based on age, QRS length ≥ 150 ms, LV volumes, and LVEF all demonstrated consistent results that indicated a therapeutic benefit of CRT-D compared to ICD-only therapy in all subgroups

of LBBB patients, with the exception of NYHA functional class I. Regardless of the subgroup examined, there was no proof of a therapeutic advantage from CRT-D in the non-LBBB patients. The RAFT and REVERSE trials had similar findings (Tang et al., 2010). Based on this data, patients with complete LBBB were the only ones who could use the current class I recommendations.

According to the 2013 European Society of Cardiology guidelines in patients with sinus rhythm, CRT is classified and indicated as follows: class I level A in patients with LBBB with QRS duration >150 ms, LVEF ≤35%, NYHA functional class II, III and ambulatory class IV despite adequate medical treatment. Class I level B is for patients with LBBB with QRS duration 120-150 ms, LVEF ≤35%, NYHA functional class II, III and ambulatory IV despite adequate medical treatment. Class IIa level B is for patients who do not have LBBB but have QRS duration >150 ms, LVEF ≤35%, NYHA functional class II, III, and ambulatory IV despite adequate medical treatment. Class IIb level B is for patients who do not have LBBB but have QRS duration 120-150 ms, LVEF ≤35%, NYHA functional class II, III and ambulatory IV despite adequate medical treatment. According to these guidelines, CRT is not recommended in patients with chronic HF with QRS duration <120 ms (Beshai *et al.,* 2007).

Sridhar *et al.* (2016) conducted a study called “US Trends and Disparities in Utilization and Outcomes” where they used discharge data from the Nationwide Inpatient Sample database for the years 2002 to 2010 to identify all patients who underwent a CRT device implantation during their hospital stay. The Nationwide Inpatient Sample is the largest all-payer in-patient database in the USA and contains a 20% stratified sample of all discharges from USA non-federal short-term general hospitals, subspecialty hospitals and public hospitals which are stratified on the number of beds, ownership and hospital teaching status. This stratified random sampling ensures that the database is representative of the USA population and accounts for 90% of all hospitalizations in the USA. Sridhar *et al.* (2016) included patients who had CRT-P and those who had CRT-D. They only included de novo implantation of devices, and excluded generator changes,

redo procedures, lead revisions as well as stand-alone ICD implantations (Sridhar *et al.,* 2016).

Age (in five categories: 0-17, 18-44, 45-64, 65-84 and ≥ 85 years), gender, and ethnicity were the demographic factors in this study (whites, blacks and others). The age-independent Deyo-Charlson Comorbidity Index, which includes 17 comorbid conditions with varying weights, was used to measure patient comorbidity. Mild (Charlson score 0-1), moderate (Charlson score 2-3), and severe (Charlson score >3) comorbidity groups were created for the patients. Their study's main findings were (1) hospital mortality, (2) hospital duration of stay, and (3) hospital costs. They looked at the patterns of the three main CRT-related side effects: pericardial effusion, pneumothorax, and hematoma development. Additionally, they looked at trends in primary outcomes and contrasted them across subgroups based on demographic, clinical, and comorbidity data (Sridhar et al., 2016).

The total number of CRT implants estimated for the years between 2002 and 2010 showed that 2002 had a much lower number of CRT implants than the following years. Cardiac resynchronization therapy implantations in 2002 presumably represented a particular subset of early adopters of this new technology following its original FDA approval in 2001, and results from CRT's more widespread use in later years would not compare favorably. As a result, they decided not to include data from 2002 in their assessments of disparities and results.

A total of 374 202 CRTs, or an average of 41 578 per year, were implanted in the USA during the years of 2002 and 2010. Using a linear regression model, the overall number of CRT implants increased significantly between 2002 and 2006 (p value for the trend was 0.01), but has not increased significantly subsequently. CRT-P use gradually dropped from 2002 (28.8% of all CRTs) to 2010 (15.2% of all CRTs), while CRT-Ds made up the majority of implanted devices (n = 321 564 over 9 years, 14% of all CRTs) (Sridhar et al., 2016). (Figure 2.1).

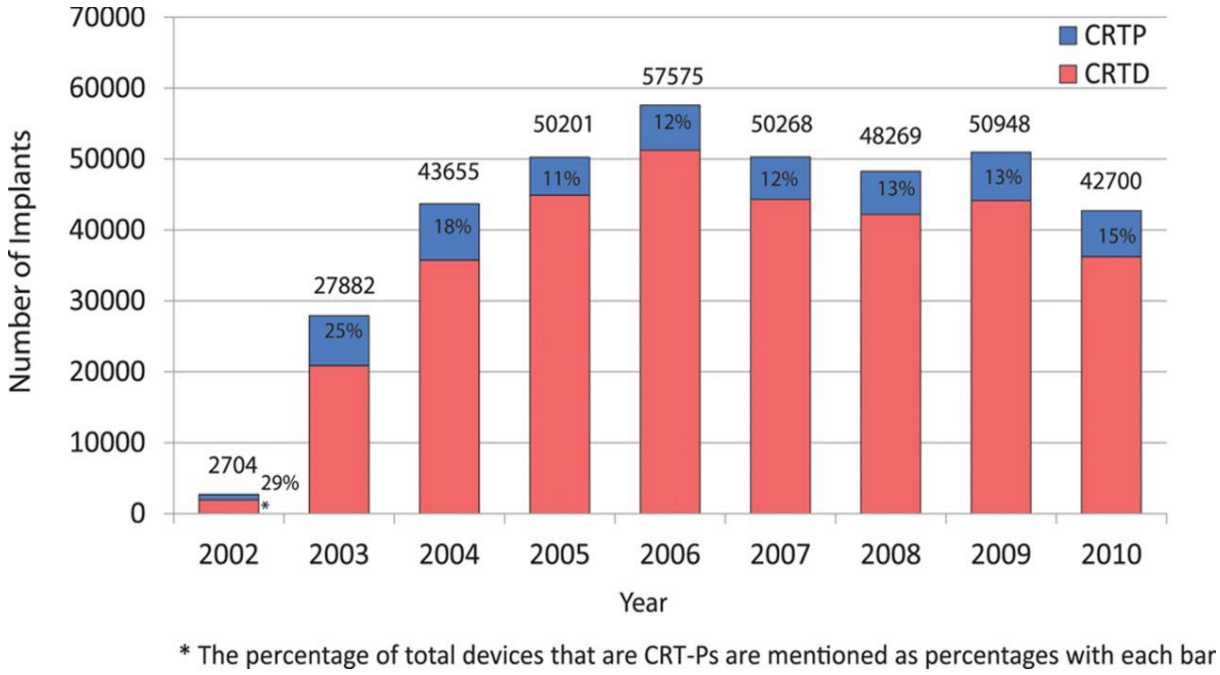

Figure 2.2: Trends in the USA regarding CRT implantation
Source: Sridhar *et al.* (2016).

The average age of CRT implantation was 69.94 ± 0.13, and this value remained stable over the course of their study's several years. The age groups 45-64 years (25.3%), 64-84 years (7%) and ≥ 85 years (7%) received the most CRTs overall (64.6% of all CRTs). The proportion of elderly patients who had CRTs implanted increased significantly from 4.95% [n = 1370] in 2003 to 8% [n = 3418] in 2010 (*p* 0.001) (Sridhar et al., 2016). (Figure 2.2).

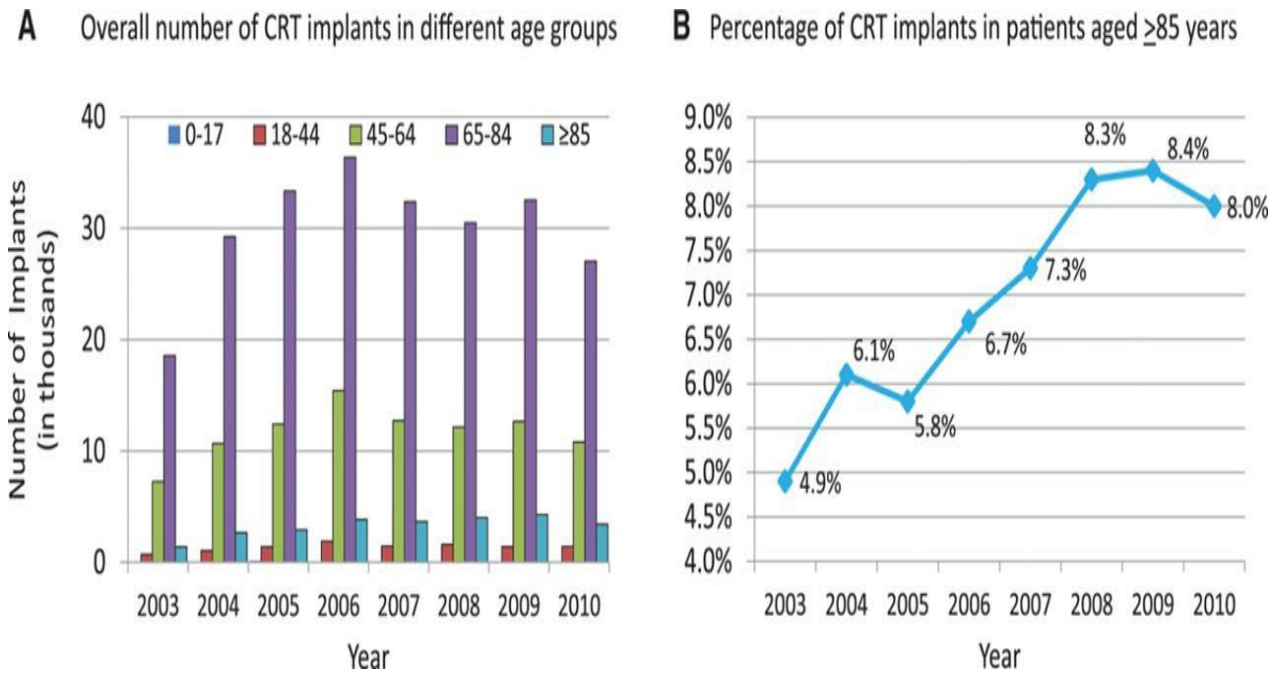

Figure 2.3: Age-stratified CRT implant trends. A. Implantation trends in five age groups: 0-17years, 18-44years, 45-64years, 65-84years and ≥ 85years. B. CRT devices implanted in age group ≥ 85years, expressed as a total percentage of CRT implants in the USA in each year
Source: Sridhar *et al.* (2016).

Male patients were implanted with CRTs at a higher rate than female patients in the USA (71.4% of all CRTs). The large gender gap persisted throughout the whole study period.

The bulk of CRTs implanted in the USA were done so on white people (79.6% of all CRTs), followed by black people (9.9%) and all other racial groups combined (10.4%). This racial disparity in CRT implantation rates persisted over the course of the whole study period (Sridhar et al., 2016).

To ascertain whether there are differences in response to CRT based on sex, Cheng et al. (2014) did a meta-analysis to compile all published research. They conducted an unrestricted search of the literature using MEDLINE (January 1966 to March 2014) and EMBASE (January 1980 to March 2014). Random-effect meta-analysis was used to get pooled effect estimates. It was discovered that 33 434 patients were covered by 72 studies. Overall, female patients responded to CRT better than male patients, with a significant 33% reduction in risk of death from any cause (HR, 0.67; 95% CI, 0,67-0.74;

$p < 0.001$), 20% reduction in death or hospitalization for heart failure (HR, 0.80; 95% CI, 0.71-0.90; $p < 0.001$), 41% reduction in cardiac death (HR, 0.59; 95% CI, 0.42-0.84; $p <$ 0.001 Women consistently showed better responses to CRT than men, and there was more echocardiographic evidence of reverse cardiac remodelling in women than in men.

Other studies assessing sex differences in response to CRT showed conflicting results. For example, evidence from COMPANIAN (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) and REVERSE (Resynchronization reVErses Remodelling in Systolic left vEntricular dysfunction) showed that women with HF might receive the same benefit as men from CRT for reduction in the risk of death or hospitalization for HF, while a sex analysis in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) trial demonstrated that women with HF benefitted more from CRT than similarly selected men.

Heart failure hospitalization is a significant public health issue in developed nations, with the USA and Europe reporting more than 1 million admissions annually (Rosamond et al., 2007). Early post-discharge is when fatality rates are highest for patients who survive, with progressive heart failure and sudden cardiac death accounting for the majority of fatalities (Solomon et al., 2007). Additionally, three months after being discharged, almost one third of patients are readmitted (Fonarow et al., 2007).

In the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST), an event-driven, randomized, double-blind, placebo-controlled study in patients hospitalized for heart failure and having an LVEF 40%, Wang et al. (2008) performed a retrospective, post hoc analysis. In this study, individuals with decreased LVEF who were hospitalized for heart failure were examined to determine the predictive relevance of QRS length. Between October 7, 2003, and February 3, 2006, 4 133 patients in total were enrolled in this trial in 359 locations across North America and Europe.

Both the patient and the person doing the screening assigned an ethnicity to the patient. The alternatives included being white, black, Hispanic, Asian, or other, according to the investigators. After 10 minutes of supine rest, 12-lead ECGs were taken. At the initial screening day, three genuine baseline 12-lead ECGs were taken at least five minutes apart, and one ECG was taken during the subsequent predetermined scheduled appointments. Each ECG reading was examined by the primary investigator or their designate. A cardiologist completed the final analysis and data reporting on twelve-lead ECGs that were collected at the study centers and sent them to the centralized ECG vendor. An integer representing the QRS duration was reported. The average of the three baseline tracings served as the final baseline QRS duration for analysis. A prolonged QRS duration was classified as 120 ms or more, while a typical QRS duration was less than 120 ms. Standard criteria were published and used to determine whether there was an RBBB or LBBB (Willems et al., 1985).

Two thousand nine hundred sixty-two patients were included in the analysis after eliminating 142 patients without a documented baseline QRS length and 1 029 patients who had pacemakers, implantable cardioverter-defibrillators, or both at the time of enrollment.

In 1 641 patients (55.4%), baseline QRS length was less than 120 ms, while in 1 321 patients (44.6%), baseline QRS duration was ≥ 120 ms. For all patients with a QRS duration of less than 120 ms, their mean QRS duration was 96.3 ms (SD = 10.6), and for all patients with a QRS duration of ≥ 120 ms, it was 144.6 ms (SD = 19.9), with a range of 120.0-228.7 ms. An older age, male sex, lower LVEF, lower systolic blood pressure, and greater serum urea nitrogen levels were all linked to a QRS length of ≥ 120 ms. The NYHA function class did not show any appreciable variation. Of the 1 321 patients with a QRS duration of ≥120 ms, 234 were classified as having a RBBB and 909 as having a LBBB. The remaining 178 were considered to have nonspecific ICVD.

All-cause mortality was 18.7% for patients with a normal baseline QRS duration and 28.1% for patients with a prolonged baseline QRS duration throughout the course of a

median follow-up of 9.9 months (HR, 1.61; 95% CI 1.38-1.87). The composite of cardiovascular death or hospitalisation for heart failure was 32.4% for patients with a baseline QRS duration <120 ms and 41.6% for patients with a baseline QRS duration of ≥120 ms (HR, 1.40; 95% CI, 1.24- 1.58). The increased risk associated with prolonged QRS duration was confirmed after adjusting for multiple variables for all-cause mortality (HR, 1.24; 95% CI, 1.02-1.50) and the composite of cardiovascular death or hospitalization for heart failure (HR, 1.28; 95% CI, 1.10-1.49). Only 105 patients (3.6%) who presented with a prolonged baseline QRS duration had a normal QRS duration on their last inpatient ECG.

In 2 463 black and white patients with heart failure and LVEF ≤ 35% who had coronary angiography and 12-lead electrocardiography at Duke University Hospital from 1995 to 2011, Randolph et al. (2017) studied the QRS duration and morphology. The study looked at 92 135 cardiac catheterizations performed at the DUMC between January 1, 1995, and December 31, 2011. The earliest qualifying catheterization for a certain patient was used to calculate the index catheterization. The Philips TraceMaster ECG program was used to analyze the 12-lead ECG data, which comprised computer generated measurements of the important electrocardiographic intervals (PP, QRS, QT, and RR). When there were multiple ECGs, the most recent one was selected. They only included ECGs that were performed within a month of the index catheterization. LVEF was mainly quantified using data from the Duke Echocardiography Database. If LVEF information wasn't available at the time of the index catheterization, it was obtained during the 3 months prior to and 1 month after the procedure from the nearest source. Nuclear imaging, magnetic resonance imaging, or left ventriculography were the sources of further LVEF data. Patients lacking a documented QRS interval or LVEF evaluation were eliminated. In the analysis, only patients with LVEF less than 35% were taken into account.

Due to missing information regarding race, significant baseline features, a myocardial infarction within 30 days of the index catheterization, or revascularization within the previous three months, patients were removed from the study. Additionally, they disqualified individuals who had ventricular pacing, an unclear ECG, or who were taking

flacainide or propafenone. To rule out potentially inaccurate QRS estimations, ECGs having a QRS interval that was missing or thought to be beyond the range of physiologically plausible values >200 ms were eliminated.

They looked into the interaction between race, QRS, and sex, as well as the link between QRS duration and all-cause mortality, using multivariable Cox regression models. Their median QRS time was 105 ms, with a range of 92 to 132 ms (interquartile range; IQR) ($p < 0.001$). White men had the longest QRS duration (111 ms; IQR, 98-139), whereas white women came in second (108 ms; IQR, 92-140), followed by black men (100 ms; IQR, 91-120), and finally black women (94 ms; IQR, 86-118). In this study, LBBB was more prevalent in women than in men (24% vs. 14%), and in white people (21% vs. 12% of the black population). For every 10 ms increase in QRS length up to 112 ms, the risk of mortality in blacks increased by 16% (HR, 1.16; 95% CI, 1.07, 1.25); white patients did not experience this (interaction, $p = 0.06$).

Shenkman *et al.* (2002) conducted a study in which data was abstracted from Resource Utilization Among Congestive Heart Failure Study, which identified 29 686 patients with heart failure from a large, mixed-model managed-care organisation during 1989 to 1999. A target population of 3 471 had echocardiographic data and ECG data obtained from automated sources during the first year of diagnosis. In this study systolic function was defined as heart failure with LVEF <45%. In this study, 20.8% of the subjects had a QRS duration ≥120 ms. A total of 425 men (24.7%) and 296 women (16.9%) had a prolonged QRS duration ($p <0.01$). There was a linear relationship between increased QRS duration and decreased ejection fraction ($p <0.01$). A prolonged QRS duration of 129 ms to 149 ms demonstrated increased mortality at 60 months ($p = 0.001$), when adjusted for age, sex and race ($p = 0.001$). Systolic dysfunction was associated with graded increases in mortality across ascending levels of QRS prolongation.

The studies mentioned above show that QRS duration is a very important parameter when assessing the probability of benefit from CRT in patients with heart failure. These studies show that the broader the QRS width, the higher the chances of benefiting from CRT.

A study conducted by Sridhar *et al.* (2016) in the USA showed that there are disparities in the demographics of patients who qualify for CRT. The data from the current study has the potential to show if there are disparities in the demographics of patients who qualify for CRT in South Africa since it is the first study of this nature to be conducted in this country.

To the knowledge of the investigator there is no study that has been conducted on the African continent to investigate the QRS duration in the African population. The current study is the first study of this nature to be conducted on the African continent. There is a perception that fewer CRT devices are implanted at TBH than the international norm and the investigator hypothesised that this could be attributed to less prolonged QRS durations in the heart failure population served by TBH. In addition, there is a perception that there is an imbalance when it comes to age and ethnicity of the patients who get CRT implants at TBH. Whenever there is a CRT implant at TBH, the patient receiving the device is very likely to be an old white male, whereas the majority of patients who are seen in this hospital are of black and coloured ethnicity. The aims and objectives of this study, therefore, were to identify similar studies conducted in first world countries to act as reference, determine the QRS duration in a diverse cardiomyopathy population served by TBH, identify the determinants of QRS duration in a diverse cardiomyopathy population served by TBH, and compare the QRS duration in this cohort with the international norm.

CHAPTER 3: MATERIALS AND METHODS

This chapter is an overview of the study design, sampling methods, analytical test methods and data analysis that was completed to determine the QRS duration and investigate the determinants of the QRS duration in a diverse cardiomyopathy population of the Western Cape. The investigator decided to conduct this study because it was thought that, despite a large number of patients with severe left ventricular impairment in the population served by TBH, fewer CRT devices appear to be implanted than the international norm. The main requirement for CRT therapy is prolongation of the QRS complex. The majority of the population of the Western Cape are blacks and coloureds, but the majority of CRT implants in TBH appear to be whites, raising the question if racial variation in QRS width impacts on the number of heart failure patients qualifying for CRT therapy in local population. This study was conducted to investigate the QRS width of the local heart failure population and to assess their demographics to identify the determinants of QRS width in this population.

3.1 **INTRODUCTION**

This was a prospective study which was conducted at Tygerberg Hospital to investigate the determinants of QRS duration in a diverse cardiomyopathy population served by Tygerberg Hospital and to compare the QRS duration in this cohort with the international norm. This study consisted of 200 patients with heart failure with LVEF ≤35%.

3.2 STUDY AREA

This study was conducted at the Division of Cardiology at Tygerberg Hospital in Cape Town, Western Cape, South Africa. Tygerberg Hospital is the largest hospital in the Western Cape and second largest hospital in South Africa, with the capacity for 1 899 beds, officially opened in 1976. This was a quantitative non-experimental study which

was conducted in the Division of Cardiology at TBH between October 2020 and May 2021.

3.3 STUDY POPULATION AND SAMPLE SIZE

After a discussion with a statistician, it was felt that too little is known about the topic to do a sample size calculation. The investigator was advised to recruit 100 new patients and submit the data to the statistician. After recruiting the first 100 patients and submitting the data to the statistician, the statistician did a formal sample size calculation and decided that 200 patients were going to be enough for this study. The investigator then included 200 new patients seen at the Division of Cardiology with LVEF ≤35%. To have 200 patients, the investigator added 100 patients to the previous 100 patients. Patients seen at the Division of Cardiology with LVEF ≤35%, with good echocardiogram images and above 18 years of age were given the patient information leaflet and consent form (Appendices 3, 4 and 5) and invited to participate, after consent was acquired. The ethnicity was self-identified by the participants.

3.3.1 Inclusion criteria

- Patients with LVEF ≤ 35%

3.3.2 Exclusion criteria

- Patients under the age of 18 years
- Patients with poor/suboptimal echo images
- Patients with no informed consent
- Patients with accessory pathway and those with third degree AV block in ECG

3.4 ETHICAL IMPLICATIONS

Ethical approval was obtained from the Durban University of Technology Institutional Research Ethics Committee, University of Stellenbosch Health Research Ethical Committee (Ethics approval number: S20/07/162) (Appendix 1), and TBH (Appendix 2). All the participants were asked to sign a consent form and self-identify their ethnicity. The consent forms were written in English, Afrikaans and IsiXhosa to accommodate all potential participants (Appendices 3,4 and 5).

3.5 DATA COLLECTION

A purposive sampling strategy was used. The data collection began in October 2020 after full ethical approval of this study. The collected data was anonymised by removing all the patient identifiers such as name, surname and hospital number for confidentiality purposes. The data collection period ended in May 2021. The suitable participants for this study were identified by doing echocardiograms on GE echocardiography machines (GE Vivid E9, GE Vivid E95 and GE Vivid S6). These machines were used because of their reliability in giving high quality images. The patients with good echocardiographic images and who were above the age of 18 years were asked to sign informed consent to be part of this study. Those who agreed were taken to an ECG room where their ECGs were done by highly trained ECG technicians using the GE ECG machines (GE MAC 1200 ST and GE MAC 2000) using the standard 12-lead ECG placement format. The 12-lead ECGs were taken with the participant lying in supine position with standard paper speed of 25 mm/s and standard calibration of 10 mm/mV. QRS width was measured from the global QRS onset to the global QRS offset, i.e. from the earliest onset in any of the 12 leads to the latest offset in any of the 12 leads (Salerno *et al.,* 2003). In this study, British Society of Echocardiography (BSE) guidelines were followed. According to the latest BSE guidelines, the LVEF should be classified as follows: LVEF = 55-70% is normal, LVEF = 50-54% is borderline, LVEF = 36-49% is impaired, and LVEF ≤35% is severely impaired (Harkness *et al.,* 2020). In this study all patients had LVEF ≤35%. Normal QRS duration on an ECG is 60-100 ms, QRS duration of 101-119 ms is in the grey zone and a QRS duration ≥ 120 ms is a broad QRS duration. In this study, the patients that were included had QRS durations ranging from normal to abnormal (Jastrzebski *et al.,* 2012).

LV size according to the latest BSE guidelines is as follows:

Table 3.1: LV size in males

Diastolic LV diameter (mm)	Grade
35-57	Normal
58-60	Mildly dilated
61-66	Moderately dilated
>66	Severely dilated

Table 3.2: LV size in females

Diastolic LV diameter (mm)	Grade
35-53	Normal
54-57	Mildly dilated
58-62	Moderately dilated
>62	Severely dilated

In terms of echocardiograms, the echocardiograms were performed by highly trained clinical technologists who specialize in cardiology, cardiology senior registrars, and consultant cardiologists. All of these echocardiograms were performed following BSE guidelines (Harkness *et al.,* 2020). All of these echocardiograms were full studies which include all the echocardiography views. The LVEF was measured using Simpson's biplane method due to its reliability and reproducibility. In Simpson's biplane method, LVEF is measured by calculating the volume inside the LV at the end of diastole (LVIDd) and volume inside the LV at the end of systole (LVIDs). These measurements are done in a zoomed apical four chamber image and a zoomed apical two chamber image by carefully tracing the endocardial border. All of these echocardiograms were reviewed by the principal investigator.

Since TBH is the biggest hospital in the Western Cape, the Division of Cardiology provides advanced cardiac care for a very large percentage of the Western Cape population.

3.6 DATA ANALYSIS

Descriptive statistics was used for data analysis. Descriptive statistics are brief descriptive coefficients that summarise a given data set, which can be either a representation of the entire or a sample of a population (Trochim 2006). Descriptive statistics are broken down into measures of central tendency and measures of variability. Measures of central tendency include the mean, median and mode. The measures of variability include standard deviation, variance, minimum and maximum variables, kurtosis and skewness.

All results obtained from the data collection process was captured on a Microsoft excel spreadsheet. Assistance from a professional statistician was used and analysis was conducted using STATA version 14. Other statistical methods that were used include Chi-square and Fisher exact test. Univariate and multivariate analysis was conducted. Odds ratio and the 95% confidence interval were calculated. A *p*-value of ≤0.05 was considered statistically significant.

Table 3.3: Summary of data analysis

Objective number		Statistical test used	Parameters analysed
1. Determine the QRS duration of the cardiomyopathy population served by TBH.		Median, mean, standard deviation and p value.	QRS width of the cardiomyopathy population served by TBH.
2. Identify the determinants of QRS duration of the cardiomyopathy population served by TBH.		Percentages, median mean, standard deviation, Levene's test for homogeneity of variances, Chi square and Fisher Exact test.	Demographics such as self-identified ethnicity, gender and age. Other parameters are the aetiology of the cardiomyopathy, and LV size.
3. Compare the QRS duration in this cohort with the international norm.		Percentages, median, mean, standard deviation and *p* value.	QRS width of the cardiomyopathy population served by TBH.

CHAPTER 4: RESULTS

Although TBH serves a large population of heart failure patients, the number of patients qualifying for CRT is relatively low, and those receiving devices are predominantly elderly men of Caucasian descent. The aims and objectives of this study were to identify similar studies conducted in first world countries to act as reference, determine the QRS duration in the diverse cardiomyopathy population served by TBH, and identify the determinants of QRS duration in that population.

An additional objective of this study was to compare the QRS duration in this cohort with the international norm to determine if the thought that less CRT devices are implanted in TBH, can be attributed to less prolonged QRS durations in our population. This chapter provides a detailed description of the results obtained in the QRS complex duration of a diverse cardiomyopathy population of the Western Cape. A total of 235 patients were asked to be part of this study, but 35 patients refused to sign an informed consent and were then excluded from this study (Table 4.1).

Table 4.1: Demographic data

Parameter	All (n = 200)	Men	Women	*p* value
Age	200 ± 14.47	52.8 ± 14.2	50.7 ± 14.72	<0.01
Gender	200	117 (59%)	83 (41%)	0.12
Ethnicity				0.33
Coloured	126	76		
Black	43	15		
White	29	24		
IHD	81	58	23	0.04

This study had 200 patients with heart failure. The majority of the participants in this study were males (117) and 83 females were part of this study. When it comes to ethnicity, coloureds were the largest group as they made up 63% of the sample. There was a statistically higher number of men presenting with ischaemic heart disease (IHD) than women.

Table 4.2 shows the cardiovascular risk factor profile of the sample. Out of the 200 participants in this study, 80 patients had IHD which was proven by coronary angiography.

Table 4.2: Cardiovascular risk factors (CVRFs)

CVRF	Total	Percentage (%)
Smoker	77	39
Illicit drug use	15	8
Diabetic	63	32
IHD	80	40
QRS ≥120ms	40	20

Illicit drug use was the least common cardiovascular risk factor in the cardiomyopathy population served by TBH.

All the echocardiograms in this study were performed in accordance with the BSE guidelines. The LVEF was calculated using the Simpson's biplane method due to its accuracy and the mean ejection fraction in this population was found to be 24.4%.

Table 4.3: Echocardiography parameters

Parameter	Range	Mean (%)
LVEF (%)	6-35	24.4
LVIDd* (mm)	32-98	60
LVIDs** (mm)	28-86	53.135
LA Area (cm²)	6.7-43.6	23.3
IVSd (mm)	4-19	8.2
LVPWd*** (mm)	3-14	8.2

* Left ventricular internal diameter at end of diastole
** Left ventricular internal diameter at the end of systole
*** End-diastolic left ventricular posterior wall thickness

Table 4.4. shows the classification of heart failure aetiology. This study reports that idiopathic cardiomyopathy (40.5%) and ischaemic cardiomyopathy (40%), respectively, were the most common causes of LVEF impairment, followed by tachycardia induced cardiomyopathy.

Table 4.4: Heart failure aetiology

Aetiology	Total	Percentage (%)
IHD	80	40
Idiopathic	81	40.5
Valvular disease/GUCH	4	2
Viral myocarditis	2	1
Alcohol induced	2	1
Peripartum	10	5
Tachycardia induced	12	6
Other causes	9	4.5

4.1 QRS DURATION

The QRS distribution is shown in Figure 4.1 below. The narrowest QRS complex was 64 ms, the largest QRS duration was 190 ms and the average QRS duration was 105 ms. When categorised using current guidelines, a total of 160 (80%) participants had QRS duration <120 ms and 40 (20%) participants had QRS duration ≥120 ms (Figure 4.2).

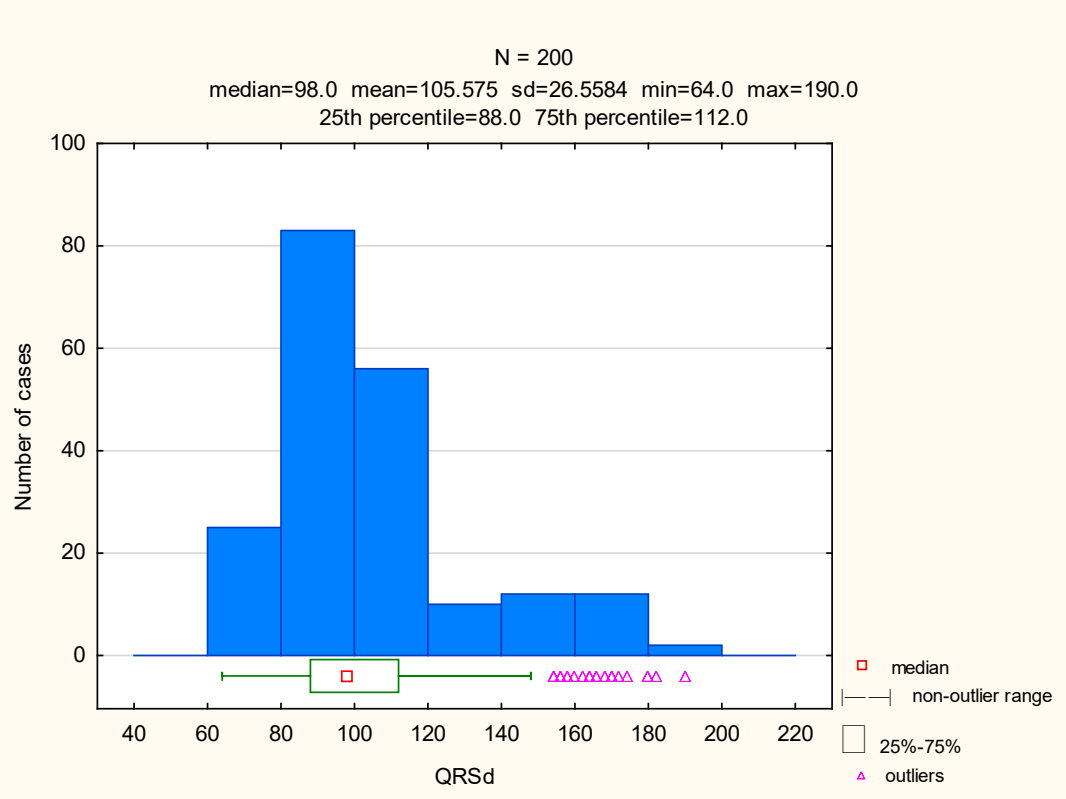

Figure 4.1: A histogram showing the QRS distribution

The mean QRS duration for females was found to be 96 ms and the range of QRS duration in females was 66 ms to 174 ms. The mean QRS duration for males was 111 ms and the range was 64 ms to 190 ms (Figure 4.2).

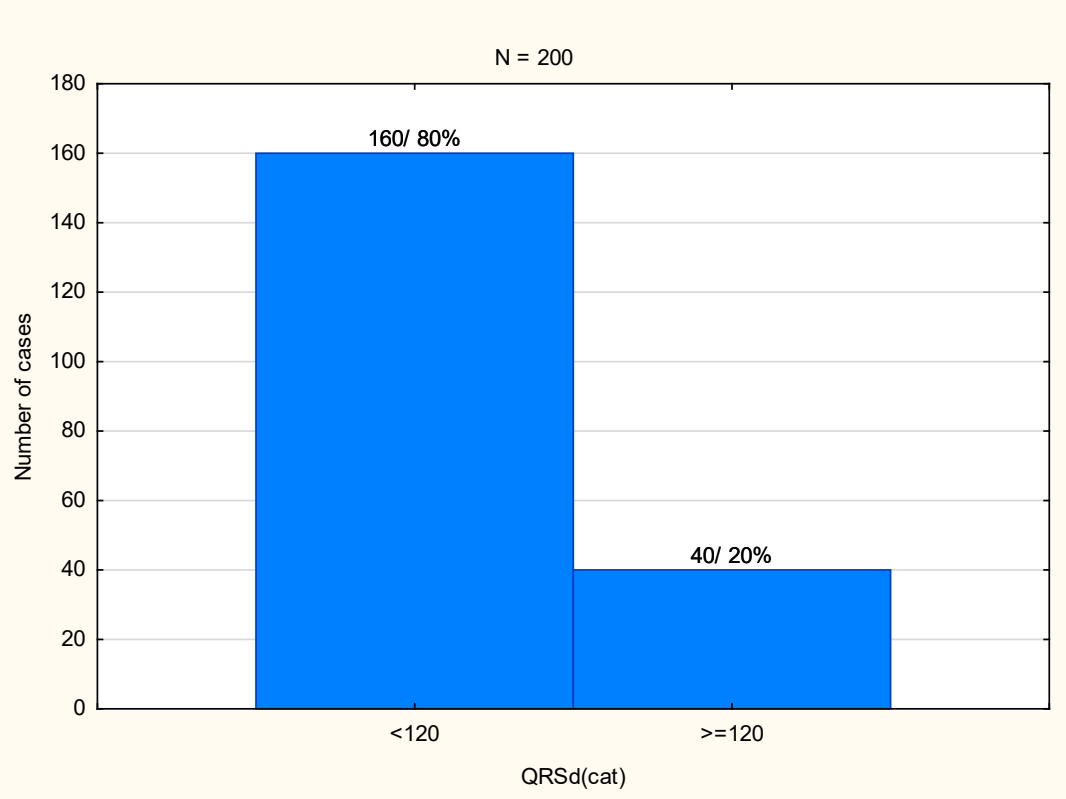

Figure 4.2: A histogram showing the number of patients with a narrow QRS complex and those with a wide QRS complex

4.2 LEFT VENTRICULAR EJECTION FRACTION (LVEF)

Figure 4.3 depicts the distribution of LVEF in the sample studied. A total of 8 (4%) participants had LVEF between 5 to 10%, 17 (9%) had LVEF between 10 to 15%, 28 (14%) participants had LVEF between 15 to 20%, 58 (29%) participants had LVEF between 20 to 25%, 45 (23%) participants had LVEF between 25 to 30% and 44 (22%) participants had LVEF between 30 to 35%.

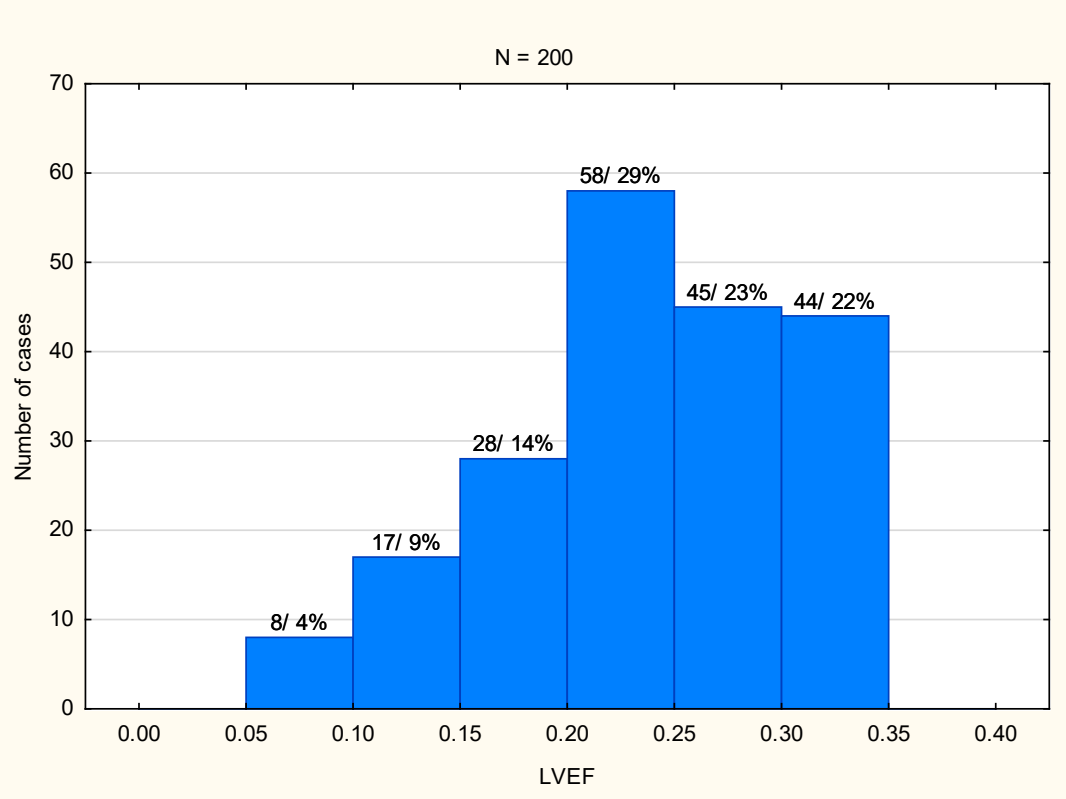

Figure 4.3: A histogram showing the distribution of left ventricular ejection fraction (n/%)

Univariate analysis (Table 4.5) was performed to determine the parameters that can be linked to a broad QRS duration. In univariate analysis the parameters associated with a broad QRS duration were ethnicity (p = 0.01; OR coloured = 0.69, white = 1.04), gender (0.05; OR = 1.21), age (p <0.01; OR = 1.07), ischaemic heart disease (p <0.01; OR = 2.7) and LV size (p = 0.03; OR = 1.08).

Table 4.5: Univariate and multivariate analysis

Parameter	Univariate analysis *p*-value	Multivariate analysis *p*-value	95% Confidence Interval	Odds Ratio
Ethnicity	p = 0.01	p = 0.63	Coloured: 0.22 – 2.16 White: 0.25 – 4.24	Coloured: 0.69 White: 1.04
Gender	p = 0.05	p = 0.68	0.48 – 3.06	1.21
LV size	p = 0.03	p<0.01	1.03 – 1.14	1.08
Age	p <0.01	p <0.01	1.03 – 1.11	1.07
Ischaemic heart disease	p <0.01	p = 0.03	1.12 – 6.52	2.7

Logistic regression was used after adjusting for all other variables. After doing multivariate analysis, age (p <0.01), ischaemic heart disease (p = 0.03) and LV size (p <0.01) were the only predictors of a broad QRS duration in this cohort. According to the odds ratios, there was no correlation between being coloured and a broad QRS duration, but there was a correlation between being white and a broad QRS duration since the OR was 0.69 for coloured and 1.04 for white. There was a correlation between gender, age, IHD, LV size and a broad QRS duration because the odd ratios were >1 in all these parameters.

CHAPTER 5: DISCUSSION

This was the first study of this nature to be conducted in Africa to investigate the QRS duration and determinants of QRS duration in a diverse cardiomyopathy population. The results from this study provide insight regarding the QRS duration in a diverse cardiomyopathy population of the Western Cape in South Africa.

The main findings were that in the Western Cape population, on univariate analysis, ethnicity, gender, age, ischaemic heart disease and LV size were all associated with QRS duration ≥120 ms. The multivariate analysis showed that only age, ischaemic heart disease and LV size were predictors of QRS duration ≥120 ms in the cardiomyopathy population served by TBH.

Our study reports that in the Western Cape cardiomyopathy population, 13% of females had QRS ≥120 ms and 25% of males had QRS ≥120 ms. Even after adjusting for body size, healthy men and women have clearly differing left ventricular (LV) dimensions and function (Moss 2010). Although women's LV chambers are smaller and their stroke volumes are correspondingly lower, their higher resting heart rates maintain a similar cardiac output to men (Beale et al., 2018). In addition, women have higher systolic and diastolic LV elastance than men at a given age, and these disparities become more apparent as women's LV elastance increases more rapidly than men's does as they age (Rao et al., 2021). Both sexes have an increase in LV ejection fraction with aging, however women experience this to a higher extent (Beale et al., 2018). But while having a higher LVEF overall, women had a bigger loss of systolic long axis contraction velocity with ageing. (Beale *et al.,* 2018). At a cellular level, the number of cardiomyocytes are similar between sexes at birth, but ageing women have a relatively more noticeable decline in cardiomyocyte number and mass, with less tendency towards cardiomyocyte hypertrophy and eccentric LV remodelling compared with men (Beale *et al.,* 2018).

It is known that there are significant and meaningful differences when it comes to the measured ECG parameters between males and females, beginning in adolescence and persisting thereafter. In the first decade of life, the quantitative ECG parameters in males and females are quite similar with regard to resting heart rate, PR interval, ST-segment location, QRS duration, QRS voltage and QT interval (Moss 2010). There are ethnic-specific differences in some of these parameters, but within each ethnic group the ECG patterns are similar in preadolescent males and females. Beginning in adolescence, the resting heart rate is faster in females than in males, and the QT interval and the QTc interval become significantly longer in females than in males probably as a result of female hormones, and the QRS duration becomes larger in males than in females as a result of the male hormones and the associated increase in cardiac mass and left ventricular wall thickness (Moss 2010).

Healthy adult women have a narrower QRS duration that is, on average, about 10 ms shorter than men (Moss 2010). This is postulated to be due to the reduced cardiac mass in females, as suggested in the Framingham heart offspring cohort study, where left ventricular mass was smaller in women even after adjustment for height or body surface area (van Hout *et al*., 2020). In adult patients with ischaemic and non-ischaemic cardiomyopathy, women also have less intraventricular conduction disturbance and less QRS duration prolongation than men due to the effect of oestrogen which is thought to affect the expression of the hormone Connexin43 (Cx43), which may offer greater resilience to conduction abnormalities in females (Shimoni *et al*., 2009).

The magnitude of the QRS prolongation with cardiac disease has a direct effect on the magnitude of cardiac dyssynchrony, and for any given prolonged QRS duration value (Rao *et al.,* 2021). The Multicenter Automatic Defibrillator Implantation Trial - Cardiac Resynchronisation Therapy (MADIT-CRT) study has shown that for any given QRS prolongation, women receive a significantly greater beneficial effect from biventricular left ventricular pacing than their male counterparts (Moss 2010).

The mean QRS duration of females in this cohort was 96 ms, whereas it was 111 ms for males. These findings are in keeping with males having a broader QRS duration than females in accordance with the findings by Moss in 2010, due to intrinsic hormonal differences. The current study found that a wide QRS complex was more prevalent in whites compared to other ethnic groups, but this was not statistically significant ($p = 0.63$) when multivariate analysis was conducted. These were also reported by MacFarlane *et al.* (1994).

A wide QRS complex reflecting left-sided ICVD in patients with HF is associated with more advanced myocardial disease, worse LV function and poorer prognosis compared with patients with a narrow QRS complex (Kashani and Barold 2005). In this study, ischaemic heart disease was associated with a broad QRS complex ($p = 0.03$) after multivariate analysis.

In terms of gender, males had more prevalence of a wide QRS complex, but this was not statistically significant ($p = 0.68$) after multivariate analysis. When it comes to age this study found that broad QRS is more prevalent in the old age group (aged >56 years) compared to the younger population ($p <0.01$) after multivariate analysis, a trend which has been reported in other studies (Rijnbeek *et al.*, 2014). It has been reported that in healthy men with advancing age there is a narrowing of QRS (Levy *et al.*, 1987). However, the findings in our study confirm the presence of general age-related conduction pathway degeneration leading to conduction delays which manifest with a broader QRS complex.

In patients with HF, an inverse correlation exists between QRS prolongation and LVEF. A dilated LV was also associated with QRS duration ≥120 ms ($p <0.01$) after multivariate analysis. According to the BSE guidelines, a LV larger than 57 mm in males and larger than 53 mm in females is a dilated LV (Harkness *et al.*, 2020).

The results of this Western Cape cohort are similar to those of the first world countries such as the study conducted by Sridhar *et al.* (2016) in the USA where most CRT recipients were also males (71.4% of all CRTs), in that males were the most represented

gender in the Western Cape heart failure population. Other similarities were that the study conducted by Sridhar *et al.* (2016) showed that whites were the ethnic group that received most CRTs (79.6% of all CRTs) and the age group between 65 to 84 years received the majority of CRTs (64.6% of all CRTs). In the Western Cape population a broad QRS duration was associated with old age and whites.

The results of this study revealed that the majority of the patients with severe heart failure are males in terms of gender, 59% (n =117) of 200 participants. The median QRS duration was 98.0, mean QRS duration was 105 ms (standard deviation = 26.5). This means that there is an equal probability of falling above or below 98 ms in the Western Cape population and the average QRS in this population is 105 ms. The percentage of patients with QRS duration ≥120 ms was 20% in the Western Cape heart failure population. This percentage was almost similar to that of a study conducted by Shenkman *et al.* (2002) in which the percentage of patients with ≥120 ms was 20.8%. The difference between these two studies is that they had 3 471 patients in their study whereas in this study only 200 patients were included.

A study conducted by Alfraidi *et al.* (2019) showed that an increase in the QRS duration over time is associated with poor clinical outcomes which translates into the QRS complex widening as the LVEF deteriorates. The primary outcome of their study was mortality, with secondary outcomes being HF hospitalization and a composite of HF hospitalization, implantation of cardiac resynchronization therapy, left ventricular assist device and cardiac transplant. Multivariable analysis found that a rate of QRS duration change of ≥1 ms/month was independently associated with increase in mortality (odds ratio [OR] 2.26, 95% CI 1.04 to 4.91), HF hospitalization (relative risk [RR] 2.01, 95%CI 1.37 to 2.94), and the composite (OR 2.40, 95%CI 1.44 to 4.02) (Alfraidi *et al.,* 2019). In the Western Cape cardiomyopathy population, 20% of the population had a QRS duration ≥120 ms and this was very likely due to the fact that the mean LVEF of this population was 24.4%. It is very likely that if the mean LVEF of this population was lower that 20%, the percentage of patients with QRS duration was going to be higher than 20%. This is

due to the broad QRS duration being directly proportional to the poor LVEF; the more poor the LVEF, the more broad is the QRS duration.

One other possible reason only 20% of the Western Cape cardiomyopathy population was found to have a QRS duration ≥120 ms is because there is a link between ischaemic heart disease and a QRS duration of ≥120 ms, and only 40% of the Western Cape heart failure population had ischaemic heart disease. The study investigators believe that the percentage of those with a QRS duration ≥120 ms would have been higher if ischaemic heart disease was as prevalent in this population as it was in the study conducted by Farwell *et al.* (2000) in the United Kingdom heart population with QRS duration ≥120 ms which consisted of 721 patients, with 437 (61%) of that population having ischaemic heart disease.

In the Western Cape population, a QRS duration ≥120 ms was associated with older age and this is a similar trend in international studies like the study which was conducted by Sridhar *et al.* (2016) in the USA as well as the study conducted by Wang *et al.* (2008). In the Western Cape study, a QRS duration ≥120 ms was associated with ethnicity in univariate analysis, but became statistically insignificant after multivariate analysis (p = 0.63) (Table 4.5). Although ethnicity was statistically insignificant in this study, a similar trend was seen when compared to the international studies (Sridhar *et al.,* 2016). In the Western Cape population, a QRS duration ≥120 ms was more prevalent among whites and this was similar to the USA and European population as per Sridhar *et al.* (2016) and Randolph *et al.* (2017).

5.1 Strengths of this study

This study was a prospective study which was conducted in one of the best academic hospitals on the continent. The first strength of this study is that it heeds the call for investigating QRS prolongation for ethnicity-specific clinical decision-making as recommended by Gijsberts *et al.* (2016). Secondly, the investigator used Simpson's biplane method for calculation of ejection fraction. This method is the most reliable

method when doing a two-dimensional echocardiogram for LVEF assessment, when done correctly. The principal investigator reviewed all echoes to make sure that the LVEF assessment was done correctly without foreshortening the LV. The other studies that were compared with this study, did not mention the method used for LVEF assessment in echocardiography. The third strength of this study is that the ECGs were performed by the ECG technicians who are highly trained professionals and a standard calibration as well as same paper speed was used.

5.2 Weaknesses of this study

The weakness of this study is that only 200 patients were used, which is a much smaller number when compared to the international studies. Since this study had a small population, it means the findings should be regarded as hypothesis-generating only. The other limitation of this study is that a single value was used as a cut off point for the determination of a broad QRS duration in males and females, in accordance with established guidelines, although it is known that females have smaller hearts and narrower QRS duration when compared to males with similar health status.

CHAPTER 6: CONCLUSION

This was the first study investigating the QRS duration to be done on the African continent. The aims and objectives of this study were to identify similar studies conducted in first world countries to act as reference, to determine the QRS duration and to identify the determinants of QRS duration in a diverse cardiomyopathy population served by TBH. One other important objective of this study was to compare the QRS duration in this cohort with the international norm to determine if the thought that less CRT devices are implanted in TBH can be attributed to less prolonged QRS durations in the Western Cape heart failure population.

These aims and objectives of the study were achieved as this study was able to determine the QRS duration of the cardiomyopathy population served by TBH. This study showed that the QRS duration of the Western Cape population is similar to the international normal and this study also revealed the determinants of QRS duration, and these were found to be age, ischaemic heart disease and LV size.

The percentage of patients with QRS duration ≥120 ms in the Western Cape cardiomyopathy population is similar to what was found in the international studies. The study conducted by Shenkman *et al.* (2002) had 20.8% of patients with a QRS duration ≥120 ms, which is very close to the 20% that was found in the Western Cape population. The patients with LVEF <45% might have narrow QRS due to the LVEF not being severely impaired. In the Western Cape population univariate analysis, ethnicity, gender, age, ischaemic heart disease and LV size were all associated with QRS duration ≥120 ms. After doing multivariate analysis the results showed that only age, ischaemic heart disease and LV size are predictors of QRS duration ≥120 ms in the cardiomyopathy population served by TBH.

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APPENDICES

Appendix 1: Stellenbosch University Health Research Ethical Committee (HREC) Study Approval Letter

UNIVERSITEIT STELLENBOSCH UNIVERSITY

Approved with Stipulations

New Application

21/08/2020

Project ID: 16746

HREC Reference No: S20/07/162

Project Title: Determinants of QRS duration in a diverse cardiomyopathy population of the Western Cape - Implications for eligibility for cardiac resynchronization therapy.

Dear Mr Sanele Dlamini

The **New Application** received on 13/07/2020 09:20 was reviewed by members of the **Health Research Ethics Committee** via Minimal Risk Review procedures on 21/08/2020 and was approved with stipulations.

Please note the following information about your approved research protocol:

Protocol Approval Period: **21-August-2020 – 20-August-2021.**

The stipulations of your ethics approval are as follows:

1. Please provide an investigator declaration for Mr Dlamini that includes his name at the top.
2. It is recommended to use more reliable forms of data backup, such as portable hard drive or secure cloud-based storage.

Please remember to use your project ID 16745and ethics reference number S20/07/162on any documents or correspondence with the HREC/UREC concerning your research protocol.

Translation of the consent document(s) to the language(s) applicable to your study participants should now be submitted to the HREC.

Please note that this decision will be ratified at the next HREC full committee meeting. HREC reserves the right to suspend approval and to request changes or clarifications from applicants. The coordinator will notify the applicant (and if applicable, the supervisor) of the changes or suspension within 1 day of receiving the notice of suspension from HREC. HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review:

Please note you can submit your progress report through the online ethics application process, available at: https://apply.ethics.sun.ac.za and the application should be submitted to the Committee before the year has expired. Please see Forms and Instructions on our HREC website for guidance on how to submit a progress report.

The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility, permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Please consult the Western Cape Government website for access to the online Health Research Approval Process, see: https://www.westerncape.gov.za/general-publication/health-research-approval-process. Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.

For standard HREC forms and instructions, please visit: Forms and Instructions on our HREC website (www.sun.ac.za/healthresearchethics)

If you have any questions or need further assistance, please contact the HREC office at 021 938 9677.

Yours sincerely,

Mrs. Brightness Nxumalo

HREC 2 Coordinator

National Health Research Ethics Council (NHREC) Registration Number:

REC-130406-012 (HREC1)•REC-230208-010 (HREC2)

Page 1 of 2

Appendix 2: Tygerberg Hospital Approval Letter

Western Cape Government
Health

TYGERBERG HOSPITAL
REFERENCE:
Research Projects
ENQUIRIES: **Dr GG Marinus**
TELEPHONE:**021 938 5752**

Project ID: 16746

Ethics Reference: S20/07/162

TITLE: **Determinants of QRS duration in a diverse cardiomyopathy population of the Western Cape – Implications for eligibility for cardiac resynchronization therapy.**

Dear Mr Sanele Dlamini

PERMISSION TO CONDUCT YOUR RESEARCH AT TYGERBERG HOSPITAL.

1. In accordance with the Provincial Research Policy and Tygerberg Hospital Notice No 40/2009, permission is hereby granted for you to conduct the above-mentioned research here at Tygerberg Hospital.

2. Researchers, in accessing Provincial health facilities, are expressing consent to provide the Department with an electronic copy of the final feedback within six months of completion of research. This can be submitted to the Provincial Research Co-Ordinator (Health.Research@westerncape.gov.za).

DR GG MARINUS
MANAGER: MEDICAL SERVICES

CHIEF EXECUTIVE OFFICER
Date: 14.10.2020

Administration Building, Francie van Zijl Avenue, Parow, 7500 Private Bag X3, Tygerberg, 7505
Tel: +27 21 938-6267 fax: +27 21 938-4890 www.capegateway.gov.za

Project ID: 16746

Ethics Reference: S20/07/162

TITLE: **Determinants of QRS duration in a diverse cardiomyopathy population of the Western Cape – Implications for eligibility for cardiac resynchronization therapy.**

BY _____

An authorized representative of Tygerberg Hospital

NAME_____

Dr. P. Ciapparelli
MBChB (UCT),
MBA (UCT)
MP0244546
Director

TITLE_____

DATE 14. 10. 2020

Appendix 3: English Information Leaflet and Consent Form

PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM

TITLE OF RESEARCH PROJECT:	
Determinants of QRS duration in a diverse cardiomyopathy population of the Western Cape – Implications for eligibility for cardiac resynchronization therapy.	
DETAILS OF PRINCIPAL INVESTIGATOR (PI):	
Title, first name, surname: Mr Sanele Dlamini	**Ethics reference number:** S20/07/162
Full postal address: Tygerberg hospital, Francie van Zijl Avenue, Tygerberg, 7505, 8th floor cardiology	**PI Contact number:** 083 9559182/ 081 580 7125

We would like to invite you to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are completely satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is **entirely voluntary** and you are free to decline to participate. In other words, you may choose to take part, or you may choose not to take part. Nothing bad will come of it if you say no: it will not affect you negatively in any way whatsoever. Refusal to participate will involve no penalty or loss of benefits or reduction in the level of care to which you are otherwise entitled to. You are also free to withdraw from the study at any point, even if you do agree to take part initially.

This study has been approved by the **Health Research Ethics Committee at Stellenbosch University.** The study will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, the South African Guidelines for Good Clinical Practice (2006), the Medical Research Council (MRC) Ethical Guidelines for Research (2002), and the Department of Health Ethics in Health Research: Principles, Processes and Studies (2015).

What is this research study all about?

- *This study will be conducted at Tygerberg hospital in the Division of Cardiology, on the 8th floor. We will recruit 200 patients and take the data to the statistician.*
- *Cardiac Resynchronisation Therapy (CRT) is a type of a pacemaker given to patients with a left bundle branch block with a QRS duration > 120ms, LVEF ≤ 35%, New York Heart Association class II – IV (system used to grade heart failure symptoms) and on optimal medical therapy. This pacemaker helps the heart to pump more effectively in these patients. It has been our observation here at Tygerberg hospital that most of our CRT candidates are older white patients. The investigator aims to determine if the reason behind the large number of white patients who get resynchronisation therapy compared to other ethnic groups is due to high prevalence of left bundle block with QRS duration > 120ms among whites or wide QRS (> 120ms) duration being associated with certain age group, gender or the cause of severe heart failure.*
- *You will have an ultrasound of your heart (echocardiogram) which will be used to assess the cardiac function and an electrocardiogram which tells us about the electrical conduction in your heart.*
- *We plan to include all patients with left ventricular ejection fraction (LVEF) ≤ 35% and optimal echo images. We will exclude all those patients who are below the age of 18 years, those who have sub-optimal echo images, eccentric pathway/ third degree AV block on ECG, peripartum cardiomyopathy and those who did not sign informed consents.*
- *There will be no use of any medication in this study.*

Why do we invite you to participate?

- *We invite you to participate in this study because you have heart failure with LVEF that is required in this study and you also have optimal echo images.*

What will your responsibilities be?

- *Your only responsibility will be to sign this informed consent form.*

Will you benefit from taking part in this research?

- *You will not benefit from being part of this study, but the principal investigator might benefit by publishing this study in one of the journals.*

Are there any risks involved in your taking part in this research?

- *There are no risks.*

If you do not agree to take part, what alternatives do you have?

- *If you do not agree to take part in this study you will still receive the treatment suitable for you from Tygerberg hospital. It will not stop you in any way from getting proper treatment from the staff of Tygerberg hospital. There will be no treatment involved in this study.*

Who will have access to your medical records?

The collected data will be anonymised and aggregated for confidentiality. No other person will have access to your personal information except the principal investigator and supervisors.

Even though it is unlikely, what will happen if you get injured somehow because you took part in this research study?

- *There is no risk of injury in this study since we will not be doing any intervention.*

Will you be paid to take part in this study and are there any costs involved?

- *You will not be compensated to take part in the study. You will not have to pay for anything in this study.*

Is there anything else that you should know or do?

- *You can phone Mr Sanele Dlamini at 021 938 4332 if you have any further queries or encounter any problems.*
- *You can phone the Health Research Ethics Committee at 021 938 9677/9819 if there still is something that your study doctor has not explained to you, or if you have a complaint.*
- *You will receive a copy of this information and consent form for you to keep safe.*

Declaration by participant

By signing below, I ……..……. agree to take part in a research study entitled (Determinants of QRS duration in a diverse cardiomyopathy population of the Western Cape – Implications for eligibility for cardiac resynchronization therapy).

I declare that:

- I have read this information and consent form, or it was read to me, and it is written in a language in which I am fluent and with which I am comfortable.
- I have had a chance to ask questions and I am satisfied that all my questions have been answered.
- I understand that taking part in this study is **voluntary,** and I have not been pressurised to take part.
- I may choose to leave the study at any time and nothing bad will come of it – I will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan that we have agreed on.

Signed at (*place*) .....…..……. on (*date*) ……...…….. 2021.

....

Signature of participant **Signature of witness**

Declaration by investigator

I *(name)* ……..…… declare that:

- I explained the information in this document in a simple and clear manner to ……..
- I encouraged him/her to ask questions and took enough time to answer them.
- I am satisfied that he/she completely understands all aspects of the research, as discussed above.
- I did/did not use an interpreter. (*If an interpreter is used then the interpreter must sign the declaration below.)*

Signed at (*place*) .....…..……. on (*date*) ……...…….. 2021.

....

Signature of investigator **Signature of witness**

Appendix 4: Afrikaans Information Leaflet and Consent Form

INLIGTINGSBLAD EN TOESTEMMINGSVORM VIR DEELNEMERS

TITEL VAN DIE NAVORSINGSPROJEK:	
Verskille in QRS wydte in n diverse kardiomiopatie populasie in die Weskaap – implikasies vir geskiktheid vir kardiale hersinkronisasieterapie.	
INLIGTING OOR HOOFNAVORSER (HN):	
Titel, voornaam, van: Mr. Sanele Dlamini	**Verwysingsnommer vir etiese goedkeuring:**
Volledige posadres: Afdeling Kardiologie, Tygerberg Hospitaal & Stellenbosch Universiteit	**HN se kontaknommer:** 0219384400

Ons wil jou graag nooi om aan ’n navorsingsprojek deel te neem. Lees asseblief rustig deur die inligting hier onder, want dit verduidelik wat hierdie projek presies behels. Vra gerus die projekpersoneel of -dokter as daar enige deel van die projek is wat jy nie heeltemal verstaan nie. Dit is baie belangrik dat jy moet voel jy weet presies waaroor die navorsing gaan en wat dit gaan beteken as jy daaraan deelneem. Onthou ook, jou deelname is **heeltemal vrywillig**, en jy mag weier om deel te neem. Met ander woorde, jy kan kies of jy wil deelneem of nie. As jy nee sê, sal daar niks slegs van kom nie. Dit sal jou op geen manier benadeel nie. As jy kies om nie deel te neem nie, sal dit geensins veroorsaak dat jy benadeel word, sekere voordele verloor of swakker versorg word as waarop jy andersins geregtig sou wees nie. Jy kan ook op enige tydstip sê jy wil nie verder aan die projek deelneem nie, selfs al het jy aan die begin ja gesê.

Die **Universiteit Stellenbosch se Gesondheidsnavorsingsetiekkomitee** (GNEK) het hierdie navorsingsprojek goedgekeur. Die projek sal uitgevoer word volgens die etiese riglyne en beginsels van die internasionale Helsinki-verklaring, die Suid-Afrikaanse riglyne vir goeie kliniese praktyk (2006), die Mediese Navorsingsraad (MNR) se riglyne vir etiese navorsing en die Departement Gesondheid se dokument ‘Etiek in Gesondheidsnavorsing: Beginsels, Prosesse en Studies’ (2015).

Waaroor gaan hierdie navorsingsprojek?

- *Ons wil onersoek instel na die EKG-veranderinge wat mense met hartversaking ontwikkel. Verder wil ons kyk of hierdie veranderinge geassosieer is met ander faktore soos ouderdom, geslag en etnisiteit.*
- *Die studie word slegs in die Wes-Kaap gedoen by Tygerberg Hospitaal en verwysende hospitale.*
- *Daar sal geen prosedures of behandeling gedoen word op u vir die doeleindes van die studie nie. Ons gaan al die inligting van u mediese rekords kry.*

Hoekom nooi ons juis vir jóú om deel te neem?

- *Jou ondersoeke toon dat jou hartfunksie ingeperk is en dit is die groep pasiente wat ons wil ondersoek.*

Wat gaan ons van jou verwag?

- *Jy hoef niks te doen anders om toestemming te gee dat ons jou inligting gebruik en self identifiseer watter etniese groep u aan behoort.*

Watter voordeel is daar vir jou as jy aan hierdie projek deelneem?

- *Jy sal geen voordeel trek nie- die idee is dat pasiente met hartversaking in die toekoms voordeel trek.*

Watter gevare is daar vir jou as jy aan hierdie projek deelneem?

- *Daar is geen gesondheidsgevare verbonde aan die studie nie.*

As jy besluit om nié deel te neem nie, watter ander moontlikhede is daar vir jou?

- *Niks sal verander as jy besluit om nie deel te neem nie.*

Wie sal kan sien wat in jou mediese lêer staan?

- *Slegs jou dokters sal toegang he tot jou mediese inligting.*
- *Jou mediese inligting word anoniem deur die navorsers gestoor.*
- *Die navorsers sal slegs oor die hele groep se resultate rapporteer en nie individue nie.*

Die kanse is baie skraal dat dit sal gebeur, maar wat as jy tóg op die een of ander manier beseer word omdat jy aan hierdie projek deelgeneem het?

- *In hierdie studie bestaan daar geen risiko vir beserings nie*

Sal jy betaal word om aan hierdie projek deel te neem, of sal jý iets moet betaal?

- Jy sal nie betaal word om aan die projek deel te neem nie.

Is daar enigiets anders wat jy moet weet of doen?

- Jy kan dr H Weich by 0219384400 skakel as jy enige verdere vrae het of enige probleme ondervind.
- As jou projekdokter nie alles verduidelik het wat jy wou weet nie, of as jy ’n klagte het, kan jy die GNEK bel: 021 938 9677/9819.
- Jy kan ’n afskrif van hierdie inligtingsblad en toestemmingsvorm kry wat jy kan saamvat huis toe.

Verklaring deur deelnemer

Deur hier onder te teken, stem ek, ……..……., in om aan ’n navorsingsprojek met die titel (Verskille in QRS wydte in n diverse kardiomiopatie populasie in die Weskaap – implikasies vir geskiktheid vir kardiale hersinkronisasieterapie) deel te neem.

Ek verklaar soos volg:

- Ek het hierdie inligtingsbrosjure en toestemmingsvorm gelees, of iemand het dit aan my voorgelees, en dit is geskryf in ’n taal wat ek maklik praat en verstaan;
- Ek het kans gekry om vrae te stel, en al my vrae is duidelik genoeg beantwoord.
- Ek verstaan dat ’n mens **vrywillig** aan hierdie studie deelneem, en niemand het my gedwing om deel te neem nie.
- Ek besef ek kan op enige tydstip ophou om aan die projek deel te neem sonder dat ek enigsins gestraf of benadeel sal word.
- Ek besef dat die navorsingspan my kan vra om op te hou deelneem voordat die projek afgehandel is as die projekdokter of -navorser dink dit sal vir my beter wees, of as ek nie die projekplan volg waarop ons ooreengekom het nie.

Geteken te (*plek*) .....…..…….. op (*datum*) ……...…….. 2021.

…… **……**

Deelnemer se handtekening **Getuie se handtekening**

Verklaring deur navorser

Ek, *(naam)* ……..……, verklaar soos volg:

- Ek het die inligting in hierdie dokument op ’n eenvoudige en duidelike manier aan …….. verduidelik.
- Ek het die persoon aangemoedig om vrae te stel, en het genoeg tyd daaraan afgestaan om dit te beantwoord.
- Ek is tevrede dat die deelnemer alle aspekte van hierdie navorsing, soos dit hier bo uiteengesit is, ten volle verstaan.
- Ek het (nie) ’n tolk gebruik (nie). *(Indien ’n tolk gebruik is, moet die tolk die verklaring hier onder teken.)*

Geteken te (*plek*) .....…..…….. op (*datum*) ……...…….. 2021.

…… **……**

Navorser se handtekening **Getuie se handtekening**

Appendix 5: IsiXhosa Information Leaflet and Consent Form

INCWADANA YEENKCUKACHA YALOWO UTHABATHA INXAXHEBA NEFOMU YOKUNIKA IMVUME

ISIHLOKO SEPROJEKTHI YOPHANDO:	
Ukuchonga kwexesha le-QRS kubuntu beentlobo ngeentlobo obunokwehla kokusebenza kwentliziyo eNtshona Koloni – Impembelelo zokufaneleka kunyango lokuvuselela kwentliziyo.	
IINKCUKACHA ZOMPHANDI OYINTLOKO (PI):	
Isihlonipho, igama lokuqala, ifani: Mr Sanele Dlamini	**Inombolo yesingqinisiso kwiNdlela yokuziphatha:**
Idilesi epheleleyo yeposi: Tygerberg hospital, Francie van Zijl Avenue, Tygerberg, 7505, 8th floor cardiology	**Inombolo epheleleyo yoMphandi oyiNtloko:** 0839559182/ 0815807125

Singathanda ukukumema ukuba uthathe inxaxheba kwiprojekithi yophando. Nceda uthathe ixesha ufunda iinkcukacha ezibhalwe apha, eziza kucacisa ngeenkcukacha zale projekthi. Nceda ubuze abasebenzi okanye ugqirha wophando malunga nayiphi imibuzo onayo malunga nayiphi na indawo ongayiqondi kakuhle kule projekthi. Kubaluleke kakhulu ukuba waneliseke ngokupheleleyo ukuba ukuqonda ngokucacileyo okuqulathwe kolu phando nendlela onokubandakanyeka ngayo. Kwakhona, ukuthabatha kwakho inxaxheba **ukwenza ngokuzithandela ngokupheleleyo** kwaye uvumelekile ukuba ungarhoxa ekuthatheni inxaxheba.Ngamanye amazwi, ungakhetha ukuthatha inxaxheba, okanye ungakhetha ukungathathi nxaxheba. Akukho nto imbi eza kwenzeka ukuba ukuba uthi hayi: oko akuzi kukuchaphazela kakubi nangayiphi na indlela. Ukwala ukuthatha inxaxheba akuzi kubandakanya sohlwayo okanye ukulahlekelwa kokuzuzwayo okanye ukuncitshiswa koncedo olufumanayo nofanele ukulufumana.Ukhululekile ukuba ungarhoxa kolu phando nanini na, nokuba uqale ngokuvuma ukuthabatha inxaxheba.

Olu phando luvunyiwe **yiKomiti yeeNdlela zokuziPhatha ngokuseSikweni kuPhando lwezeMpilo yeYunivesithi yaseStellenbosch**. Uphando luza kwenziwa ngokwezikhokelo neenqobo zeSaziso

saMazwe ngamazwe seHelsinki , iziKhokelo zaseMzantsi Afrika zokuQhutywa kakuhle kwezoNyango (2006), iziKhokelo zeBhunga loPhando lwezoNyango ezimalunga neNdlela yokuziPhatha ngokuseSikweni kuPhando (iMRC) (2002), neSebe lokuziPhatha kwezeMpilo kuPhando lwezeMpilo: Imithetho-siseko, iiNkqubo noPhando (2015).

Lumalunga nantoni olu phando?

- *Lolu phando luzakwenziwa eTygerberg hospital. Inani labantu abazothukatha inxaxheba lizakushiwo ingcali-manani.*
- *Ngalolu phando sihlose ukufumana ukuba ingabe ixesha leQRS kwi-electrocardiograph lihlobene yini nobuzwe, ubulili, iminyaka yobudala, okanye unobangela wokwehla kwamandla okubetha kwentliziyo.*
- *Sizakuhlola intliziyo yakho sisebenzisa umatshini wokubona intliziyo owakhiwe ngabakwaGE. Sizobuye siphinde sibale amandla okubetha kwentliziyo yakho. Emva koko sizokwenza i-electrocardiograph ukuze sibale ixesha leQRS.*
- *Ucelwe ukuba uthathe inxaxheba kolu phando ngokuba amandla okubetha kwentliziyo yakho ehlile. Kolu phando sizimisele ukufaka zonke izigulane izinokwehla kwamandla okubetha kwentliziyo okusezingeni lika ≤ 35%.*
- *Akuyi kubakho mayeza kolu phando.*

Kutheni uceliwe ukuba uthathe inxaxheba?

- *Ucelwe ukuba uthathe inxaxheba kolu phando ngoba amandla okubetha kwentliziyo yakho asezingeni lika ≤ 35%, nezithombe zentliziyo yakho zicacile*

Luya kuba yintoni uxanduva lwakho?

- *Uxanduva lwakho kuzakuba ukutyikitya ifomu yokunika imvume emva kokufunda incwadana yeenkcukacha.*

Ingaba uya kuzuza ngokuthatha kwakho inxaxheba kolu phando?

- *Awuzuxhamla ngokuthatha kwakho inxaxheba kolu phando, kodwa umphandi oyintloko angaxhamla ngokuba lolu phando lwamukelwe ukuba lufakwe kwenye yamajenali.*

Ingaba kukho imingcipheko ebandakanyekayo ekuthatheni kwakho inxaxheba kolu phando?

- *Akuyi kubakho bungozi ngokuthatha kwakho inxaxheba kolu phando.*

Ukuba akuvumi ukuthatha inxaxheba, zeziphi ezinye iindlela onazo ezinokulandelwa?

- *Akuyi kusetyenziswa mayeza okanye indlela yokunyanga kolu phando.*

Ngubani oza kukwazi ukufikelela kwiingxelo zakho zezonyango?

- *Akuyi kubakho mntu oza kukwazi ukufikelela kwinkcukacha zobuqu bakho ngaphandle komphandi oyintloko kunye nabaphathi bakhe. Iinkcukacha zobuqu bezigulane zizakuba imfihlo.*

Noxa kungaqhelanga kwenzeka, kuza kwenzeka ntoni xa unokwenzakala nangayiphi indlela kuba uthatha inxaxheba kolu phando?

Abukho ubungozi bokwenzakala uma uthatha inxaxheba kolu phando

Ingaba uza kuhlawulwa ngokuthatha inxaxheba kolu phando kwaye ingaba kukho iindleko ezibandakanyekayo?

- *Awuzakuhlawulwa ngokuthatha inxaxheba kolu phando.*
  Akuzi kudingeka ukuba uhlawulele nantoni na, ukuba uthatha inxaxheba.

Ingaba ikhona enye into ekufuneka ukuba uyazi okanye uyenze?

- *Ungatsalela umnxeba uMnu Sanele Dlamini ku 021 938 4332 ukuba uneminye imibuzo okanye ufumana naziphi na iingxaki.*
- *Ungatsalela umnxeba iKomiti yokuziPhatha kuPhando lwezeMpilo ku-021 938 9677/9819 ukuba kusekho into angakakucaciseli yona ugqirha wakho okolu phando, okanye ukuba unesikhalazo.*
- *Uza kufumana ikopi yezi nkcukacha nefomu yokunika imvume ukwenzela ukuba uzigcinele.*

Isifungo somthathi-nxaxheba

Ngokutyikitya apha ngezantsi, mna ……..……. ndiyavuma ukuthatha inxaxheba kuphando olunesihloko esithi (Ukuchonga kwexesha le-QRS kubuntu beentlobo ngeentlobo obunokwehla kwamandla okusebenza kwentliziyo eNtshona Koloni – Impembelelo zokufaneleka kunyango lokuvuselela kwentliziyo).

Ndibhengeza ukuba:

- Ndizifundile ezi nkcukacha nefomu yokunika imvume, okanye ndiyifundelwe, ibhalwe ngolwimi endilwaziyo nendiziva ndikhululekile kulo;
- Ndiye ndalifumana ithuba lokubuza imibuzo kwaye yonke imibuzo yami iphendulwe ngokwanelisayo.
- Ndiyaqonda ukuba ukuthatha kwami inxaxheba kolu phando **ndikwenza ngokuzithandela** kwaye khange ndinyanzeliswe ukuba ndithathe inxaxheba.
- Ndingakhetha ukuyeka kuphando nanini na kwaye akukho nto imbi eza kwenzeka ngoko - andisayi kohlwaywa okanye ndicalulwe nangayiphi na indlela.
- Ndisenokucelwa ukuba ndilushiye olu phando lungekapheli, ukuba ugqirha wophando okanye umphandi ucinga ukuba oko kundifanele ngcono, okanye ukuba isicwangciso sophando andisilandeli ngale ndlela kuvunyelwene ngayo.

Kutyikityelwe *(indawo)* e.....…..……. ngomhla (*umhla*) we- ……...…….. ngo-2021.

....

Utyikityo lomthathi-nxaxheba **Utyikityo lwengqina**

Isibhengezo somphandi

Mna *(igama)* ……..…… ndibhengeza ukuba:

- Ndizicacisile iinkcukacha ezikolu xwebhu ngendlela elula necacileyo ku……..
- Ndimkhuthazile ukuba abuze imibuzo ndaza ndathatha ixesha elaneleyo ukuyiphendula.
- Ndanelisekile kukuba uyiqonda ngokwaneleyo yonke imiba yolu phando, njengoko icacisiwe apha ngentla.
- Ndiyisebenzisile/andiyisebenzisanga itoliki. *(Ukuba kusetyenziswe itoliki, loo toliki mayityikitye esi sifungo singezantsi)*.

Kutyikityelwe *(indawo)* e.....…….. ngomhla (*umhla*) we- ……...…….. ngo-2021.

....

Utyikityo lomphandi **Utyikityo lwengqina**

Appendix 6: Research Questionnaire

RESEARCH QUESTIONNAIRE

Determinants of QRS duration in a diverse cardiomyopathy population of the Western Cape – Implications for eligibility for cardiac resynchronization therapy

Study number:

ETHNICITY:

WHITE	BLACK	COLOURED	INDIAN

Gender (Male, female or other)	
Age	
Diabetic (Yes/No)	
Smoker (Yes/No)	
Illicit drug (Yes/No. If yes please put the drug name)	

DATA COLLECTION

QRS duration	
LVEF	
LVIDd	
LVIDs	

DCMO Aetiology (Mark with X)

Ischaemic: _____

Idiopathic: _____

Severe Mitral Regurgitation: _____

Severe Aortic Regurgitation: _____

Patent Ductus Arteriosus: _____

Ventricular Septal Defect: _____

Peripartum: _____

Tachycardia induced: _____

Alcohol induced: _____

Viral myocarditis: _____

Other (Please specify): _____

Appendix 7: Letter from a Statistician

Prof Martin Kidd
Centre for Statistical Consultation
Dept of Statistics and Actuarial Sciences
University of Stellenbosch
Private Bag X1
Matieland 7602
South Africa
15 September 2021

Project ID: 16746
Ethics Reference: S20/07/162
Title: Determinants of QRS duration in a diverse cardiomyopathy population of the Western Cape: Implications for eligibility for cardiac resynchronization therapy

SAMPLE SIZE CALCULATION

A sample of 200 patients were decided upon which were based on comparing three groups (ethnic) with 80% power and medium effect size (ES=0.22).

Yours sincerely

Prof Martin Kidd

Appendix 8: Editing certificate

DR RICHARD STEELE
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EDITING CERTIFICATE

Re: **Sanele Maxwell Dlamini**
Durban University of Technology master's dissertation: **Determinants of QRS duration in a diverse cardiomyopathy population of the Western Cape – Implications for eligibility for cardiac resynchronisation therapy**

I confirm that I have edited this dissertation and the references for clarity and language. I returned the document to the author with track changes so correct implementation of the changes and clarifications requested in the text and references is the responsibility of the author. I am a freelance editor specialising in proofreading and editing academic documents. My original tertiary degree which I obtained at the University of Cape Town was a B.A. with English as a major and I went on to complete an H.D.E. (P.G.) Sec. with English as my teaching subject. I was a part-time lecturer in the Department of Homoeopathy at the Durban University of Technology for 13 years and supervised many master's degree dissertations during that period.

Dr Richard Steele
11 October 2022
per email