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Cardiac Resynchronization Therapy
Risk stratification and long-term outcome

Cardiac Resynchronization Therapy

Risk stratification and long-term outcome

by Christian Reitan

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DOCTORAL DISSERTATION

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Cardiac Resynchronization Therapy: Risk stratification and long-term outcome

Abstract

Heart failure is a condition that will affect 2-3% of the population. Around one third of the patients have a decreased LVEF and a widened QRS complex as a sign of ventricular dyssynchrony. CRT has emerged as a treatment that reduces morbidity, mortality and improve functional status in this population. However, a substantial amount of treated patients do not respond satisfactory after implantation. This thesis sought to assess characteristics and factors associated with long term mortality and outcome in a cohort of CRT patients.

The thesis includes four papers:

Paper 1 assessed the association between early subjective response after implantation and long term outcome in CRT-P patients. We found that those who exhibited a self-assessed positive therapy response after 1-2 months had a significantly better survival rate compared with those who did not.

The second paper investigated long term mortality in CRT-P and primary prophylactic CRT-D patients. Patients with CRT-D had better crude survival rates than those with CRT-P. However, the CRT-P group was older and had more comorbidities. CRT-D was not significantly associated with better survival when adjusting for confounders, as compared to CRT-P.

The third paper assessed a method of estimating myocardial scar burden from a standard 12-lead ECG (Selvester QRS score) in patients with Left Bundle Branch Block. 401 patients were assessed and divided into a high-score and a low-score group. The group with high Selvester QRS score was found to have a worse survival rate compared to the group of patients with lower scores.

The last paper found that the CHA_2DS_2-VASc score, which is commonly used for stroke risk estimation in atrial fibrillation patients, was associated with long term mortality and a composite endpoint of mortality or hospitalization for heart failure in a CRT population. When comparing CHA_2DS_2-VASc to other, CRT-specific scores, it performed approximately as well in predicting mortality and the composite endpoint.

Key words

Cardiac Resynchronization Therapy, outcome, survival, follow-up, subjective improvement, ICD, Selvester QRS score, CHA_2DS_2-VASc

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Cover illustration front: *Left Bundle Branch Block* by Christian Reitan

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I love deadlines. I like the whooshing sound they make as they fly by.

Douglas Adams

Contents

List of Publications

This thesis is based on the following publications, referred to by their Roman numerals:

I Patient-assessed short-term positive response to cardiac resynchronization therapy is an independent predictor of long-term mortality

C Reitan, Z Bakos, PG Platonov, CJ Höijer, J Brandt, L Wang, R Borgquist
Europace (2014) 16, pp. 1603–1609

II Long-Term Results of Cardiac Resynchronization Therapy: A Comparison between CRT-Pacemakers versus Primary Prophylactic CRT-Defibrillators

C Reitan, U Chaudhry, Z Bakos, J Brandt, L Wang, PG Platonov, R Borgquist
PACE journal. (2015) 38, pp. 758–67

III Semi-automated QRS score as a predictor of survival in CRT treated patients with strict left bundle branch block

C Reitan, C. U Chaudhry, B Atwater, J Jacobsson, JP Couderc, X Xia, J Carlson, PG Platonov, R Borgquist
Journal of Electrocardiology (2018) 51, pp. 282-287

IV The CHA_2DS_2-VASc score and its association with long-term outcome in a Cardiac Resynchronization Therapy population

C Reitan, PG Platonov, R Borgquist
Submitted

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In addition to the above papers, the author has co-authored seven other articles in international peer-reviewed journals.

Populärvetenskaplig sammanfattning på svenska

Hjärtsvikt är ett tillstånd som drabbar 2-3% av populationen någon gång under livet. Det är ett syndrom som kan innebära ett stort handikapp, och har en dödlighet som är jämförbar med till exempel tjocktarmscancer. Vanligen visar den sig med symtom som t.ex andnöd, trötthet och svullna underben.

Hjärtsvikt är ingen enskild sjukdom utan snarare ett syndrom med olika symptom som uppstår då kroppens behov av blodflöde inte kan upprätthållas av hjärtat. Det kan därför finnas flera bakomliggande orsaker, exempelvis genomgången hjärtinfarkt som skadar en del av hjärtat och därför gör att det inte klarar av att pumpa så bra som krävs.

Diagnosen misstänks ofta vid typiska symptom, men ställs nu för tiden oftast med hjälp av blodprover, röntgenundersökningar eller ultraljud, som får anses vara det viktigaste diagnostiska verktyget.

Vid ultraljudsundersökning kan man ofta bilda sig en uppfattning av vilken typ av hjärtsvikt som föreligger, och tillskansa sig viktig information för hur den undersökta patienten bäst behandlas. Hos ungefär hälften av hjärtsviktspatienterna ser man att hjärtats kammare har sänkt s.k. *ejektionsfraktion* (LVEF). Det innebär att hjärtat inte pumpar ut lika stor andel av blodet ur kamrarna vid varje hjärtslag som hos den friska patienten, man kan säga att hjärtat har sänkt förmåga att dra ihop sig.

Hjärtats rörelse styrs i stor utsträckning av *retledningssystemet*, specialiserade hjärtmuskelceller som har till uppgift att sprida en elektrisk signal snabbt ut till hela hjärtat för att det ska dra ihop sig på ett kontrollerat och effektivt sätt. Hur denna signal sprider sig över hjärtat kan vi uppskatta med hjälp av EKG-mätning. Vissa patienter har en förlångsammad spridning av signaler ut till hjärtats kammare, vilket man ser genom att den del av EKG-kurvan som representerar kamrarnas sammandragning blir bredare, det vill säga att det tar längre tid från det att kamrarna börjar aktiveras till att den sista delen av kamrarna aktiverats.

Om en patient med hjärtsvikt och sänkt LVEF samtidigt har en förlångsammad aktivering av kamrarna kan man misstänka att den sänkta ejektionsfraktionen helt eller delvis beror på *dyssynkroni*. Man tror att den förlångsammade aktiveringen ger en ineffektiv pumpfunktion som vi kan se som sänkt ejektionfraktion och som i sin tur ger en sämre pumpförmåga och de symptom vi kallar för hjärtsvikt. Man har därför uppfunnit en särskild sorts pacemaker, CRT (*Cardiac Resynchronization Therapy*) som har till uppgift att snabba upp kamrarnas aktivering för att på så vis åstadkomma en mer effektiv pumpfunktion. Detta görs genom att man placerar två separata elektroder på var sin (motsatta) sida om hjärtat och skickar en signal till dessa samtidigt i varje hjärtslag för att få en *synkronisering* av kammaren, därav namnet.

Många studier har visat på CRTs positiva effekter för dessa hjärtsviktspatienter, både vad gäller symptom, ultraljudsmässiga mått och överlevnad. Kriterierna för vilka patienter som anses

lämpliga för behandlingen har förändrats något genom åren, bland annat har tiden för hur lång kammaraktiveringen som krävs på EKG ökats. Dock är det fortfarande så att många patienter, i vissa material så mycket som 30-50%, inte svarar på behandlingen. Det finns därför ett intresse i att försöka reda ut vilka som har nytta, och vilka som inte har nytta av behandlingen.

Denna avhandling bygger på ett material om cirka 800 patienter som fått inopererat en CRT-dosa vid Skånes Universitetssjukhus i Lund 1999-2012. Den har som övergripande mål att undersöka faktorer som påverkar långtidsprognosen hos dessa patienter.

Patienterna tillfrågades vid ett återbesök strax efter implantationen huruvida de kände någon skillnad i sin förmåga att anstränga sig. I delstudie I fann vi att de patienter som känt en tidig subjektiv upplevelse av förbättring också hade en signifikant bättre överlevnad. Resultaten höll även när vi korrigerade för faktorer som kan påverka patientens hälsa oberoende av hjärtsjukdomen, som bland annat ålder och kön. Att tidigt upptäcka vilka som svarar och inte svarar på behandlingen kan vara av stort värde då man kan justera behandlingen därefter. Vi hoppas att våra resultat kan bidra till just det.

I delstudie II jämförde vi patienter som fått en "vanlig"CRT-dosa (kallad CRT-P) med de som fått en kombinerad CRT och defibrillator (CRT-D), som även kan behandla elakartade rytmrubbningar (arytmier). Den senare typen har ökat kraftigt i användning på senare år. Man vet nämligen att arytmier är vanliga hos patienter med sänkt LVEF och att implanterbara defibrillatorer kan förbättra överlevnaden i denna grupp, även om man aldrig haft några kända arytmier sedan tidigare. Man vet också att CRT i sig kan minska risken för arytmier. Det finns dock inte lika många studier som har studerat kombinationen av de två behandlingarna, och eftersom tillägget av defibrillatorfunktion kan vara förenat med biverkningar, etiska dilemman och högre kostnad har det diskuterats om man verkligen bör erbjuda kombinationsbehandlingen på bred front. Vi jämförde därför överlevnaden mellan patienter som fått CRT-P och patienter med CRT-D (dock uteslöt vi patienter som hade haft arytmier tidigare). Vi fann då att patienter som hade fått CRT-D i snitt levde längre än de som fått en CRT-P. Vi såg dock också att patienterna i CRT-P-gruppen var äldre, sjukare och hade ett antal faktorer som påverkade överlevnaden. När vi korrigerade för dessa faktorer såg vi inte längre en fördel för CRT-D. Det såg alltså ut som, i vårt material, att det inte fanns någon vinst med att ge patienterna CRT-D i stället för CRT-P.

I den tredje delstudien beräknade vi ett särskilt score (Selvester score), som med hjälp av EKG-kurvan kan uppskatta mängden ärr i hjärtats muskel, till exempel efter hjärtinfarkt. Mängden ärr har föreslagits vara en viktig faktor för om CRT fungerar eller ej. Vi undersökte därefter om höga Selvester score korrelerade med högre dödlighet. Vi fann att det inte fanns något sådant samband om man betraktade Selvester score som en kontinuerlig skala. Dock såg vi att risken verkade vara ökad för patienter med riktigt höga score och vi delade därför in dem efter höga och låga score. De som hamnade i gruppen med höga Selvester score hade då en försämrad överlevnad om man jämför med de i gruppen med låga, och resultaten höll även

när vi korrigerade för annan sjuklighet. Resultaten tyder på att patienter med höga Selvester scores som ett mått på ärrvävnad i hjärtat har högre risk än de som har lägre poäng.

Delstudie IV undersökte ett annat scoringsystem, CHA_2DS_2-VASc. Detta scoringsystem är egentligen utvecklat för att uppskatta risken för stroke hos patienter med rytmrubbningen förmaksflimmer. Det består av olika kliniska faktorer som även kan spela roll för patienter som behandlas med CRT, och vi ville undersöka hur väl det kunde skilja mellan patienter med hög och låg risk. Vi ville även jämföra CHA_2DS_2-VASc med andra, liknande scoringsystem som dock utvecklats för just CRT-patienter. Vi fann att det fanns en relativt god korrelation mellan poängen och överlevnaden. Vidare fann vi också att CHA_2DS_2-VASc presterade i princip lika bra som CRT-specifika scoringsystem. Våra resultat visar att CHA_2DS_2-VASc, som är ett mycket välanvänt verktyg för läkare som jobbar med pacemakers och rytmrubbningar, även kan indikera låg eller hög risk för CRT-patienter, och att de scoringsystem som finns är ungefär lika bra.

Nomenclature

6MWT	six-Minute Walk Test
ACE	Angiotensin Converting Enzyme
AMI	Acute Myocardial Infarction
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor Neprilysin Inhibitors
AUC	Area Under the Curve
AVJA	Atriventricular Junction Ablation
CABG	Coronary Artery By-pass Graft
CAD	Coronary Artery Disease
CHF	Congestive Heart Failure
COPD	Chronic Obstructive Pulmonary Disease
CRT	Cardiac Resynchronization Therapy
CRT-D	CRT with Defibrillator
CRT-P	CRT-Pacemaker
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
eGFR	estimated Glomerular Filtration Rate
GE-MRI	Gadolinium-Enhanced Magnetic Resonance Imaging
Hb	Hemoglobin concentration

HFmrEF	Heart Failure with mid-range Ejection Fraction
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
HR	Hazard Ratio
HTx	Heart Transplantation
ICD	Implantable Cardioverter-Defibrillator
ICD-10	International Classification of Diseases, Tenth Revision
IHD	Ischemic Heart Disease
LAE	Left Atrial Enlargement
LBBB	Left Bundle Branch Block
LV	Left Ventricle
LVEDV	Left Ventricular End-Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
LVESV	Left Ventricular End-Systolic Volume
LVH	Left Ventricular Hypertrophy
MRA	Mineralocorticoid Receptor Antagonist
NICM	Non-Ischemic Cardiomyopathy
NT-proBNP	N-terminal pro-B type natriuretic peptide
NYHA	New York Heart Association functional classification
OMT	Optimal Medical Therapy
PCI	Percutaneous Coronary Intervention
QoL	Quality of Life
RAS	Renin-Angiotensin System
RBBB	Right Bundle Branch Block
ROC	Receiver Operating Characteristics

RV	Right Ventricle
SCD	Sudden Cardiac Death
SSc	Selvester Score
SUS	Skåne University Hospital
VAD	Ventricular Assist Device

Cardiac Resynchronization Therapy: Risk stratification and long-term outcome

Introduction

The foundation for a modern understanding of the heart's functions were laid out by the 17th century physician William Harvey, who in 1628 was the first to describe the circulation of blood in the body caused by a pumping heart in his book *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*. [1] Harvey did not provide evidence that the blood was, in fact, circulating; he hypothesized it:

> *"There must be a motion, as it were, in a circle."*

Earlier scientists generally believed that the main function of the heart and arteries was to generate and distribute air and heat to the rest of the body. This physiological theory made it harder for pre-Harvey researchers to understand the link between the malfunctioning heart and the symptoms the malfunction causes. [2]

After the publication of *de Motu Cordis*, the scientific community was provided a solid foundation for understanding the circulatory system. Thereafter, the French anatomist Raymond Vieussens (1635 – 1715) followed with accurate anatomical descriptions of the heart and provided some of the first explanations for heart failure symptoms caused by structural changes of the heart. [3, 4]

For a long time, studies of the heart focused on describing structural changes, especially hypertrophy and its correlation to clinical disease. A turning point was arguably Frank and Starling's theory in early 20th century (published in 1918) that described the relationship between end-diastolic volume and stroke volume, and was the beginning for the understanding of hemodynamics. [5]

Since then, extensive research has further elucidated the nature of the heart's functions and its diseases and our ability to examine and treat them. Discoveries that merit mentioning in the context of this thesis is the electrocardiogram (ECG), mostly credited to Willem Eindthoven, awarded the Nobel Prize in Medicine in 1924. [6] A notable contribution from Lund was the work of Inge Edler and Helmuth Hertz who showed the clinical value of echocardiography in the 1950's. [7] The method has since become one of the most important tools for examining the heart.

The first known heart failure patient was an Egyptian dignitary buried in the valley of Queens, whose 3,500 year-old mummified remains, when examined, exhibited signs of pulmonary oedema as a probable cause of death. [8] The heart failure syndrome is complex and heterogeneous. Today, treatment options for heart failure are still being intensely researched.

Heart Failure

Heart failure (HF) is often described as a syndrome in which the body's demand for blood flow exceeds the flow the heart is capable of supplying, although different definitions exist. The European Society for Cardiology (ESC) defines it in its 2016 heart failure treatment guidelines:

> "HF is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress." [9]

This definition is vague, but it postulates that the patient must be symptomatic, and the causes of the symptoms must be cardiac. However, the symptoms may arise in different parts of the body depending on how the blood circulation is affected (some are shown in Figure 1). A patient may be asymptomatic yet exhibit structural or functional cardiac abnormalities such as hypertrophy of the heart or reduced ejection fraction (see below), which is considered to be a precursor to HF.

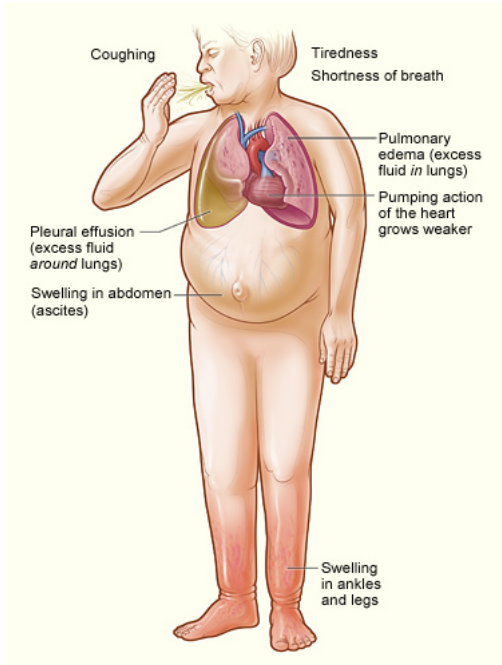

Figure 1: Some of the clinical signs of heart failure. Source: National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services.

In clinical practice, heart failure is suspected when typical symptoms are present: shortness of breath, ankle swelling and fatigue may all lead the physician to suspect HF. These findings are assessed together with other anamnestic information, such as previous myocardial infarction. [10]

Other tools for assessing HF include X-rays that may show widening of the pulmonary vessels indicating elevated pulmonary pressure, and cardiac enlargement, indicating ventricular dilatation or hypertrophy. Biochemical analyses, such as elevated NT-proBNP levels, may indicate high filling pressures of the ventricles. Magnetic Resonance Imaging (MRI) can visualize myocardial function and structure (such as prior myocardial infarction). ECG visualizes the heart's rate and rhythm (regular or irregular – e.g. atrial fibrillation) and depolarisation pattern, which is relevant when considering medical and/or device therapy. [9]

Echocardiography is a useful tool that is fast, non-invasive and can be used bedside. While MRI is a more accurate imaging method, echocardiography has the benefit of convenience and can be used in a variety of acute and non-acute clinical situations. Echocardiography also lets the physician visually examine the heart's structures and its movements. Specific causes of heart failure can sometimes be found using echocardiography, such as heart valve diseases, which can often be successfully treated. [11–15] Echocardiography can also locate regional impairment of wall movement, *dyskinesia*, a sign of localized scar tissue in the myocardial wall as a result of previous myocardial infarction. Echocardiography is considered crucial in assessing HF and selecting the correct treatment in daily practice. [16]

Heart Failure classification

The structure and movement of the ventricles are often among the most clinically relevant parameters (often obtained from echocardiography), and different types of HF are often classified based on these parameters. [9] Echocardiography of a patient with HF may show dilated ventricles and a *reduced ejection fraction* - the percentage of blood that is ejected from the ventricles with each heartbeat. [17] A healthy heart will exhibit a left ventricular ejection

Table 1: Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF) in the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Abbreviations available on page vi. [a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics. [b]BNP >35 pg/ml and/or NT-proBNP >125 pg/mL. Reprinted with permission from European Heart Journal (2016) 37, pp. 2129–2200

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

fraction (LVEF) of >50%, while a failing heart may not be able to eject more than <35% per beat. This type of HF is called heart failure with reduced ejection fraction (HFrEF).

Nearly half the patients presenting with HF symptoms will have a normal LVEF. This condition is called *HF with preserved ejection fraction* (HFpEF). Such patients often show other signs of cardiac disease upon echocardiographic examination. Typically, such patients will have signs of elevated filling pressures either in the left or right ventricle, indicating diastolic dysfunction, an impaired relaxation of the myocardium in diastole. These patients may also have elevated NT-proBNP levels and widened pulmonary vessels on chest X-ray. This condition is often related to a thickened and 'stiff' myocardium.

An intermediate class of HF has recently been introduced, *HF with mid-range ejection fraction* (HFmrEF). The LVEF-based classification is used in the ESC guidelines as etiology, demographics and treatment differ between the groups. The classification is described in Table 1. Many heart failure studies since the 1990's based their inclusion criteria on LVEF. [9]

HF is also often classified by underlying etiology. Coronary artery disease or previous myocardial infarction may lead to regional or global ischemia of the myocardium, causing an impaired ventricular function. Non-ischemic causes include exposure to toxic substances or drugs, infections, valvular, idiopathic or hereditary disease, and can lead to ventricular dysfunction. Etiology can also have implications for HF management. [10, 18–23]

One of the most widely used classification systems is the New York Heart Association Functional Classification (NYHA class), which stratifies HF patients based on limitation of physical ability. [24] The system is commonly used in clinical trials for describing the extent of heart failure. See Table 2.

Table 2: NYHA functional classification. [24] Adapted from Raphael et. al. [25]

NYHA class	Symptoms
I	Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.
III	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain
IV	Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased

HF can also be described as right or left-sided, depending on what part of the heart and circulation is affected. In some contexts, it is also meaningful to use such terms as acute, chronic, stable, decompensated or compensated HF. [8, 26, 27]

This thesis will focus on patients with left-sided HFrEF as it is one of the main criteria for Cardiac Resynchronization Therapy.

Epidemiology

The prevalence of HF depends on HF definition, but it is estimated to be around 1-2 % of the population in developed countries. [28] The prevalence increases with higher age. In the US, around 14% of those 80 and older have HF. The prevalence is slightly lower among women than among men. [29]

A study from 2013 estimated the prevalence in Sweden to be 2.2%, based on ICD-10 codes from a regional administrative health data register. The incidence was 3.2/1,000 person-years for females and 3.0/ 1,000 person-years for males. Total 5-year survival was 48%, and mortality was higher among males. The study found a decrease in incidence and mortality between 2006 and 2010 (-24% and -19%, respectively). [30]

In a 2015 report from the Swedish RiksSvikt HF registry (a national quality of care registry reporting a 54.3% coverage of all Swedish HF patients), 16% of all HF patients had Left Bundle Branch Block. 32% had QRS duration above 120 ms, regardless of QRS morphology. A widened QRS complex was more common among patients with a decreased LVEF. The registry reports that only 6.3% of patients fulfilling class 1A recommendations receive CRT treatment, suggesting a substantial under-utilization of CRT. [16] (See guidelines in Table 6)

Pathophysiology

The heart failure syndrome has been subject to different explanatory models, but the exact mechanisms are not yet fully understood. As described in *Braunwald's Heart Disease*, one view is that an index event either damages the myocardium or disrupts the heart's ability to generate force, thereby preventing it from contracting properly and generating a normal stroke volume. [10] HF onset can be abrupt or slow depending on the underlying etiology, but the result is always a decline in the heart's pumping capacity. Initially, the patients may be asymptomatic, but the altered hemodynamic situation leads to an activation of a chain of compensatory mechanisms. These include nervous mechanisms, such as sympathetic activation due to decreased signaling from baroreceptors in the aortic arch, the carotid sinuses and atrial wall, leading to an increase in heart rate and contractility of the myocardium, and thus to an increased cardiac output. Renal hypoperfusion and increased sympathetic activity lead to an activation of the hormonal Renin-Angiotensin-Aldosterone System (RAAS), which through the Angiotensin II peptides and the Aldosterone mineral corticoid causes a retention of sodium, increased thirst, vasoconstriction and further activation of the sympathetic

nervous system. This, in turn, causes increased blood volume, blood pressure and venous return to the heart, which increases cardiac output, according to the Frank-Starling law (see Figure 2).

These compensatory mechanisms are, however, only dimensioned to compensate for 'normal' or short-term variations in cardiac function and blood volume. When activated for a long time, they can become harmful and may cause organ damage. For instance, an increased heart rate causes a shortened diastole, which can lead to hypoperfusion of the myocardium that, in the long run, causes impaired ventricular function and cell death. A continued activation of RAAS can cause an accumulation of fluid in the body, which the heart cannot handle due to its position on the Frank-Starling curve. Peripheral vasoconstriction increases the resistance against which the heart has to pump (increased *afterload*). The heart then has to work harder and its demand for oxygen increases. Higher aldosterone levels contribute to dysfunction of the baroreceptors and development of fibrosis in the myocardium, as well as causing sodium and fluid retention. HF is therefore not only a disease of the heart, but it also affects vascular, neural and endocrine systems. The activation of compensatory mechanisms may explain why patients can be asymptomatic at first, and this can also explain the progressive nature of the HF syndrome. [31]

Etiology and LV function

HF can have different underlying causes (or index events) that affect the heart in different ways. The heart will typically show signs of ventricular *remodeling*, macroscopic changes in ventricular geometry. (Figure 3, page 8) The myocardium exhibits signs of microscopic alterations, such as fibrosis. The common finding of ventricular dilatation can be explained as

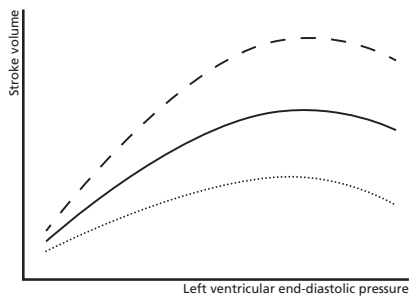

Figure 2: The Frank-Starling law states that with increased preload (here, left ventricular end-diastolic pressure, sometimes expressed as wall tension), the heart's output will increase up to a certain point, after which it will decrease (due to certain properties of the myofilaments). Each line represents how a heart will respond to preload in a given situation. Here, the solid line represents a normal heart in a normal nervous and hormonal state. If the heart's contractility is increased by sympathetic signaling or inotropic drugs, the curve is shifted 'upward' (dashed line), making the myocardium more responsive to changes in preload. In the situation of ventricular dysfunction, the curve is shifted 'downward' as a result of impaired contractility (dotted line). The maximum stroke volume is decreased, and the added benefit of venous return (increased end-diastolic pressure) is small. [5]

a compensatory mechanism; if the contractile function is impaired, additional stretch of the myocardium (dilatation) leads to an increased stroke volume, according to the Frank-Starling law. As the condition progresses, the dilatation becomes manifest. Different etiologies can lead to different types of remodeling. HF after myocardial infarction often exhibits a regional fibrosis and a secondary global dilatation. Non-ischemic dilated cardiomyopathy (i.e. after exposure to toxic substances, infiltrative, infective, genetic or idiopathic disease) can manifest as a global dilatation and thinning of the myocardium. [32]

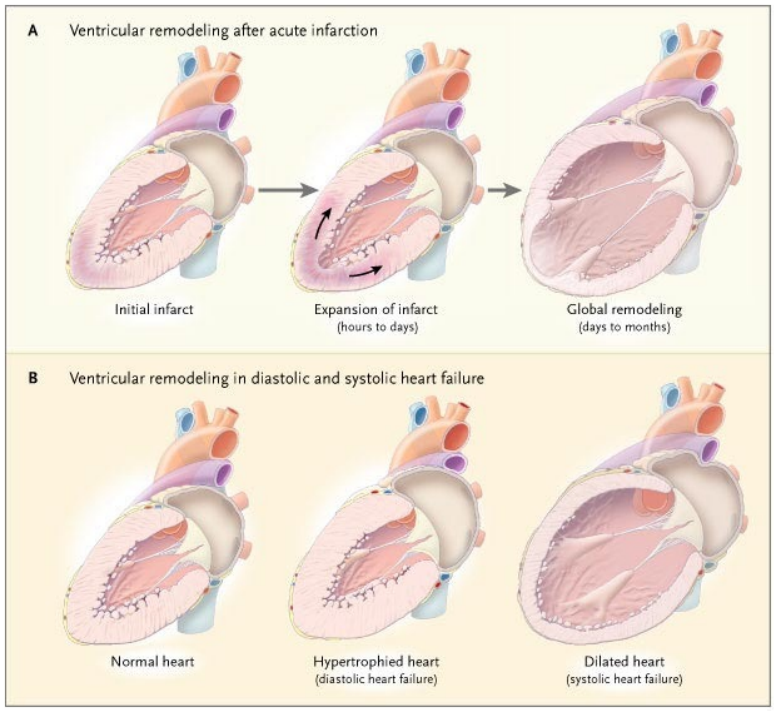

Figure 3: Ventricular remodeling. Panel A shows the remodeling process after an apical infarction. Soon after the infarction, the affected myocardium will expand and become thinner. Later, global remodeling can occur, resulting in a decreased LVEF, global ventricular dilatation and sometimes a ventricular aneurysm. Panel B shows a normal heart (left). Untreated hypertension sometimes leads to a hypertrophied heart (middle), commonly seen in patients with HFpEF. The 'classic' remodeling seen in patients with non-ischemic dilated cardiomyopathy is shown to the right. It leads to a rounding of the ventricles shape, thinning of the myocardium and resulting decrease in ejection fraction. Reproduced with permission from Jessup, Brozena, N Engl J Med 2003; 348:2007-2018, Copyright Massachusetts Medical Society.

Ventricular conduction disturbances

In order to efficiently deliver blood flow to the rest of the body, the heart's muscle fibers must be precisely coordinated during each heart cycle. This is accomplished through accurate myocyte activation by the heart's conduction system. The conduction system consists of

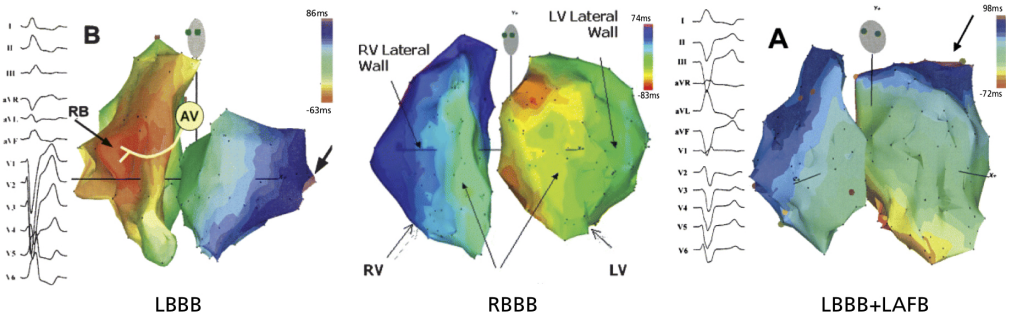

Figure 4: Endocardially mapped activation patterns for different ventricular conduction disturbances, anterior views. Red and orange color indicates the areas of first activation, blue color indicates last activation. In this case of LBBB, the lateral portion of the LV is activated approximately 150 ms after the septum, while the RV is activated much faster due to the rapid signal conduction by the intact right bundle. In RBBB, the RV lateral wall is activated late, but the LV is activated in a normal amount of time. The right panel shows a patient with RBBB and left anterior fascicular block, and shows late activation of both the lateral RV and the anterosuperior LV. Adapted with permission from Fantoni et al. and Peichl et al. [34, 35]

specialized myocytes able to rapidly conduct the signal and 'guide' the depolarization wave through the myocardium.

The normal activation sequence starts with the sinoatrial node depolarizing and activating the atria. After a short delay in the atrioventricular node, the signal enters the ventricles from the atrioventricular junction through the bundle of His in the ventricular septum, and spreads to the ventricles via the left and right bundle branches. Specifically, the left ventricle is activated by the left bundle branch, usually via one anterior, one posterior and, in some cases, a median fascicle. These deliver the signal to and activate the anterior/superior, posterior/inferior and septal aspects of the LV, respectively. The right ventricle is activated by the right bundle which runs towards the apex on the right side of the septum. When approaching the base of the right anterior papillary muscle, it ramifies and delivers fascicles to the right ventricular septum and free wall.

In HF with dilatation of the left ventricle, different kinds of ventricular conduction delay are common. [16] If some part of the main ventricular conduction system stops functioning, the depolarization wave front spreads through the myocardium via the 'normal' myocytes. These cells can also conduct the electrical signal, but much slower than the conduction system cells. Because of this, malfunction of different parts of the conduction system (*block*) will lead to abnormal activation patterns of the myocardium, usually with the latest activation of lateral parts of the heart that are farthest away from the AV junction (and thus the farthest distance for the wavefront to travel). Ventricular conduction disturbances may be caused by a number of reasons, such as infarction, fibrosis, calcification, or infiltrative lesions. [33]

The sequence of electrical activation can be visualized by different methods, such as invasive

Table 3: Table showing 'classical' ECG definitions of different types of ventricular conduction abnormalities. Adapted from Marriott's Practical Electrocardiography (12th edition) by Wagner and Strauss, 2014 [36]

Block Type		Criteria
RBBB	QRS duration	$\geq$ 120 ms
	Lead V1	Late intrinsicoid (R' peak or lateR peak), M-shaped QRS (RSR'); sometimes wide R or qR
	Lead V6	Early intrinsicoid (R peak), wide S wave
	Lead I	Wide S wave
LBBB	QRS duration	$\geq$ 120 ms
	Lead V1	QS or rS
	Lead V6	Late intrinsicoid (R or R' peak), no Q waves, monophasic R
	Lead I	Monophasic R wave, no Q
LAFB	QRS duration	Minimal QRS prolongation (20 ms) from baseline
	Electrical axis	Left-axis deviation (usually $\geq$ 60 degrees)
	Leads I and aVL	Small Q
	Leads II, III, and aVF	Small R
	aVL	Late intrinsicoid (R wave peak) deflection in aVL (>45 ms)
	Limb leads	Increased QRS voltage
LPFB	QRS duration	Usually normal
	Electrical axis	Right-axis deviation (usually$\geq +$ 120 degrees)
	Leads I and aVL	Small R
	Leads II, III and aVF	Small Q
	aVF	Late intrinsicoid deflection in aVF (>45 ms)
	Limb leads	Increased QRS voltage
		No evidence of RVH

mapping, which provides 3D maps of the heart's electrical activity, as in Figure 4. The main method of recording the heart's electrical activity is the ECG, which measures the electrical potential of the heart from 12 different angles. The different conduction disturbances have definitions by their appearance on ECG. [36]

If the right bundle branch is blocked, the signal will spread to the right ventricle slower than to the rest of the heart, resulting in a late activation of the RVs lateral parts. This is called Right Bundle Branch Block (RBBB). Similarly, if the left bundle malfunctions (Left Bundle Branch Block (LBBB)), the lateral wall of the left ventricle will activate later than normal. Blocks can also be present at fascicular levels as Left Anterior or Posterior Fascicular Block (LAFB and LPFB). Partial blocks also occur, as do combinations of different blocks. ECG criteria exist for different block types (see Table 3), but they are heterogeneous and ECG have limitations. An accurate diagnosis therefore requires knowledge of the underlying physiology.

Table 4: Proposal for 'strict' LBBB criteria by Strauss, 2011. [37]

	Criteria
QRS duration	$\geq$ 130 ms for females, 140ms for males
Lead V1	QS or rS
In at least two of leads I, aVL, V1, V2, V5 or V6	Mid-QRS notching/slurring

LBBB

LBBB is common among patients with HFrEF, and a higher incidence is seen in patients with lower LVEF. [9, 16, 38] LBBB has been correlated to worse outcome in HF populations. [39]

The bundle blocks were described in the early 20th century, first in dogs, and then in humans. Wilson and Herrman presented ECG criteria for bundle branch block in 1920, observing delayed ventricular activation times of >100 ms. [40] Initially, the diagnoses of LBBB and RBBB in humans were mistakenly switched because of anatomical differences between humans and dogs. [41, 42] Wilson studied LBBB in canine models and found rS complexes in V1 and V2, and broad, notched R deflections in V6 and V5, as well as prolonged QRS durations. However, precordial leads were not standard at the time, and Wilson therefore proposed that in the absence of precordial leads, the key to distinguishing a "complete bundle branch block" from an "incomplete bundle branch block" and other disturbances of intraventricular conduction was having a prolonged QRS duration. Derived from studies on dogs, the QRS duration threshold $\geq$120 ms has since been a common criteria for defining LBBB (in humans). [10, 36] A "classical" definition of LBBB (in humans) is presented in Table 3, although refinements (such as mid-QRS notching) have been included in some definitions. [33]

Strauss et al. argue in a 2011 article that the classical definition of LBBB with a threshold of $\geq$120 ms is not specific enough for distinguishing LBBB from other abnormal conduction patterns in humans. [37] Strauss et al. cite studies of LBBB where up to 1/3rd of patients did not have actual block of the left bundle despite meeting ECG criteria for LBBB. Some patients may fulfill the criteria because of LV hypertrophy, which has a prolonged QRS duration because of greater myocardial mass activated, but the conduction system is intact. Strauss et al. therefore propose a new definition of LBBB on ECG that takes into account the fact that, in LBBB, the LV activation starts from the right side of the septum and spreads through the septum to the LV endocardium. The wavefront then proceeds to activate the LV before reaching the posterolateral epicardium. When the wave front reaches the septal endocardium (of the LV) and the posterolateral epicardium, it cannot travel further in that direction. This produces characteristic notches (or slurs) in the QRS complex on the ECG curve, which are included in the proposed definition. Furthermore, Strauss et al. propose that a true LBBB will increase QRS duration to even more than 120 ms in humans and that the QRS duration

criterion should be increased. The threshold in their definition is increased more for males than for females, as the larger heart takes longer to depolarize. Strauss et al. do acknowledge that it may be even better to adjust these thresholds based on body size, but choose sex as criteria for practical reasons. Below, the definition by Strauss et al. will be referred to as "strict" LBBB. It is presented in Table 4.

Ventricular Dyssynchrony

As discussed above, LBBB is common among HF patients with reduced EF. In healthy subjects, LV contraction starts at the septal endocardium and apex (the parts first activated by the left bundle) and spreads toward the base of the heart in order to "squeeze" the blood through the aortic valve. Upon echocardiographic examination of patients with LBBB and HFrEF it can sometimes be observed that the LV lateral wall contracts substantially later than the septum. This has led to the hypothesis that the reduced EF is caused by *dyssynchrony* of the ventricle – a mismatch in timing between contraction of the walls. Because of this dyssynchrony, the ventricle fails to eject as much blood from the ventricular cavity as if the walls were synchronized, and the stroke volume is decreased. [43, 44] As discussed above, the heart's conduction system is crucial in synchronizing the heart's contraction, and dyssynchrony is therefore often suspected as a contributing factor in patients with HFrEF and ventricular conduction delay. Dyssynchrony in HF patients has been linked to a worse prognosis. [45]

LV dyssynchrony is most often suspected in HFrEF with typical LBBB, but can also occur in situations of nonspecific ventricular delay, or with artificial pacing. Pacemaker leads intended to treat rhythm disorders, such as AV block or bradycardia, are typically placed near the apex in the right ventricle, which can lead to dyssynchrony by inducing an abnormal conduction pattern. [46] Dyssynchrony is often measured by the duration of the QRS complex on ECG, as it represents the time it takes for the ventricles to fully depolarize. QRS duration quantifies the ventricular activation time but it does not characterize how or which ventricle is affected. It is often argued that QRS morphology is as important as QRS duration in assessing intraventricular dyssynchrony. [47, 48]

The term "dyssynchrony" can also refer to a mismatch in timing between the activation of atria and ventricles (*atrioventricular* dyssynchrony) or between the right and left ventricles (*interventricular* dyssynchrony. In this text below, dyssynchrony will refer to intraventricular dyssynchrony of the left ventricle.

Heart Failure Treatment

Assuming that HF is a syndrome caused by one or several underlying etiologies, it can be argued that correct diagnosis and assessment of the underlying cause is the basis for HF treat-

ment. HF can in many cases be halted or reversed with specific therapy, such as valve replacement in valvular stenosis. [31] However, in many patients, the HF cause is permanent or irreversible, which creates a need for treating the HF syndrome and its symptoms. Great progress in medical, surgical and device-based treatment has been made over the last 30-40 years. [2] Treatment recommendations are published by the ESC (2016) and the AHA/ACCF (2013, updated 2016) every few years. The recommendations discussed below apply to the HFrEF subgroup. [9, 26]

Lifestyle and physical activity

Lifestyle factors are thought to influence the onset and progression of HF. Physical activity in particular has been inversely linked to the incidence of HF. [49] A lowered salt intake may slow HF progression and be associated with favorable hormonal changes. [50] Modest use of alcohol may lower the risk for HF, but excessive alcohol use increases this risk. [51] Lifestyle changes – such as cessation of tobacco use and blood pressure control through physical activity – can lower the risk of other cardiovascular diseases that can lead to HF. [52, 53]

Drug therapy

When initializing medical therapy in HF, beta-blockers and ACE inhibitors or Angiotensin Receptor Blockers are usually used first. Beta-blockers have negative chronotropic and inotropic properties, thus reducing the heart's workload and demand for oxygen. With a slower heart rate, diastole is prolonged, improving ventricular filling and coronary blood flow (especially in patients with coronary artery disease). The use of beta-blockers is indicated for patients with stable HF. [54] The ACE inhibitors and ARB complement the beta-blockers and work by inhibiting ACE and Angiotensin receptors, thereby blocking the effects of the activated RAAS system. Both beta-blockers and ACEi/ARB are recommended for use in all HFrEF patients who can tolerate them, and treatment should be initiated as soon as the diagnosis is made.

In addition to beta-blockers and ACEi/ARB, Mineralocorticoid Receptor Antagonists (MRA) are recommended for symptomatic patients with HFrEF. These substances further inhibit the RAAS system and have a diuretic function by blocking aldosterone receptors (and to some degree other steroid hormone receptors).

A common symptom of HF is the congestion of fluid in the lungs or peripheral tissue, and diuretics are therefore commonly used to relieve these symptoms. No randomized trials have investigated diuretics effect on morbidity and mortality in HF patients, but a meta-analysis suggests that treatment with diuretics may improve morbidity, mortality, and exercise capacity. [55]

Other drugs are recommended if the patient is still symptomatic or has a LVEF $\leq$ 35% after initiation of the "standard" HFrEF treatment – d beta-blockers, ACEi/ARB and MRA ($\pm$ diuretics). A new class of drugs called angiotensin receptor neprilysin inhibitors (ARNI) has been shown to improve morbidity and mortality better than ACEi, but ARNI is not widely implemented as standard therapy. [56] For patients in sinus rhythm with a heart rate of $\geq$ 70 beats per minute despite adequate dose of beta-blockers, treatment with ivabradine is recommended. It is a selective sinus node I_f-receptor inhibitor that lowers the heart rate, and improves morbidity and mortality. [57]

Heart transplantation and ventricular assist devices

Some patients progress in their HF syndrome despite optimal pharmacological and non-surgical device treatment, often called end-stage HF. Heart transplantation is a good treatment for many of these patients, and significantly improves mortality, quality of life, exercise capacity and return to work as compared to conventional therapy. However, due to the shortage of donor hearts and the high level of care, the risks and the costs associated with heart transplantation, transplantation is offered to few, carefully selected patients. It also requires lifelong follow-up and monitoring of the post-transplant immunosuppressive treatment. Patients of advanced age, comorbidities such as cancer or systemic diseases with multi-organ involvement, or patients with active infections are therefore usually not considered eligible for heart transplantation. [58]

Because transplantation is not widely available for, or indicated in, all severe HF patients, mechanical circulatory support systems have been developed. Temporary systems exist for patients in acute need of circulatory support where recovery can be expected or acute stabilization is wanted. Temporary systems range from percutaneous systems that reduce afterload on the LV to extracorporeal membrane oxygenation (ECMO) systems that can be used in patients with uni- or biventricular and/or pulmonary failure. The use of these systems is usually restricted to a few days or weeks. For patients with chronic end-stage HF, a ventricular assist device (VAD) may be implanted. These devices are typically offered to patients on the waiting list for transplantation (bridge to transplantation), but due to advances in technology, these devices' role as a destination therapy (i.e. for patients not eligible for transplantation) is currently discussed. Like transplantation, VAD treatment is associated with high costs, tedious follow-up routines and many potential complications. However, VAD treatment does not depend on the availability of donor hearts, and can therefore be offered to a larger – albeit still select – patient population. [59, 60]

Cardiac Resynchronization Therapy

In the 1980s it was discovered that patients with LBBB often exhibited a delay in contraction between the septal and lateral walls of the LV, with a resulting decrease in ejection fraction. In the 1990s, researchers then acknowledged the poorly synchronous contraction as a therapy target. At the time, the effect on hemodynamics by different pacing modes and lead placements was discussed, and pacemakers were proposed to play a part in HF treatment. [61] Small studies indicated that ventricular pacing caused an ineffective ventricular conduction with a resulting decrease in cardiac output and other hemodynamic measures. [62]

Bakker et al. reported hemodynamic and clinical improvement in 5 patients who received a

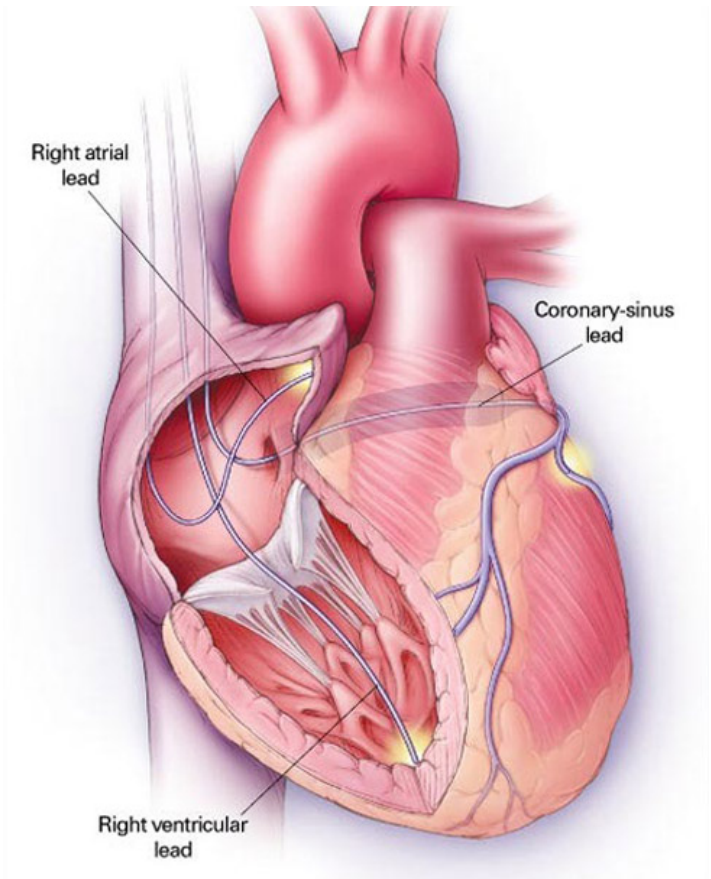

Figure 5: Cardiac Resynchronization Therapy. In this therapy, one lead is placed in the right atrium for atriventricular synchronization. The left ventricle is paced via a conventional pacemaker lead near the apex of the right ventricle, and an additional lead is placed in the coronary sinus or one of its branches on the posterolateral wall. Reproduced with permission from Hare. N Engl J Med 2002;346:1902-5, Copyright Massachusetts Medical Society.

lateral epicardial LV lead in addition to a standard transvenous RV apical lead. [63] Cazeau with colleagues implanted a man with acutely worsened HF due to dilated cardiomyopathy with LBBB in NYHA class IV with a pacemaker connected to four leads, one in each heart chamber. Hemodynamic evaluation was performed, and Cazeau et al. found an acute improvement of cardiac output and pulmonary capillary wedge pressure. After six weeks, the patient had lost 17 kg of fluid, and his functional status improved to NYHA class II with no peripheral edema. [64] A later pilot study confirmed the ability of biventricular pacing to improve cardiac function in select patients, and similar results were found in larger patient materials. [65–67]

The early studies in the 1990's used modified or custom-made pulse generators. The promising results of these studies prompted the cardiac device industry to produce purpose-made pulse generators with an additional lead connector for a LV lead. A common modern CRT configuration is presented in Figure 5, with one right atrial lead for optimization of AV delay, one RV apical lead for pacing the ventricular septum from the RV side, and one lead placed in one of the branches of the coronary sinus for pacing the LV from the posterolateral side. [68] The separate lead connectors for the RV and LV leads make it possible to control the ventricular leads independently of each other, as opposed to the earlier CRT trials in which both LV leads were often connected to the same connector. Such configurations (as in Figure 5) are used today, although some technical advances have been made. The pulse generators are usually smaller with refined internal technology, can incorporate ICD functionality and allow for individualized optimization. Combined CRT and ICD devices is often denoted CRT-D, and CRT-only devices CRT-P. New multipolar LV leads make it possible to adjust lateral LV pacing site to some degree even after implantation. New strategies for implanting and targeting the optimal pacing sites have been developed, as well as algorithms for individualized optimization and device programming. [69]

Clinical trials

After the initial exploratory studies, randomized clinical trials were soon initiated in the late 1990's. The earliest of these trials generally focused on patients with severe HF (NYHA III-IV). All the larger trials used a wide QRS complex (not morphology) and decreased LVEF as an indicator of ventricular dyssynchrony. The design and main results of the major CRT trials are presented in Table 5.

The MUSTIC studies were presented in 2001 and 2002. These studied two separate study populations – one in sinus rhythm, one in atrial fibrillation. The sinus rhythm population included 67 patients with widened QRS complexes, reduced LVEF in sinus rhythm and no indication for a conventional pacemaker. All patients received a CRT device. MUSTIC had a crossover design where the patients were randomized to three months of either CRT-on or CRT-off treatment, after which the patients crossed over to have their device turned either on

or off. The study found that during active biventricular pacing the mean distance the patients walked during the 6-minute walk test (6MWT) was 23% longer, Quality of Life (QoL) was improved, peak oxygen uptake increased, hospitalizations decreased by 2/3^{rds}, and 85% of the patients preferred active biventricular pacing to no pacing. [70] The other part of the study included patients with chronic atrial fibrillation and an indication for a conventional pacemaker due to slow ventricular rate, HFrEF and a prolonged QRS duration ($\geq$200 ms) with RV pacing only. That second part of the study reported similar results with improvement on 6MWT, peak oxygen uptake, hospitalizations. In that study, patients preferred active biventricular pacing.

The PATH-CHF study tested LV vs. RV vs. biventricular pacing in a similar crossover design, and followed 29 patients for one year. This study found that 6MWT and peak VO_2 improved with CRT, and that the improvements persisted for a longer period of time than previously shown.[71]

A preliminary report of the MIRACLE study were published in PACE journal 1998, and showed improvement in functional status as well as a longer walking distance in the 6MWT in patients with QRS duration >130 ms and LVEF $\leq$35% receiving CRT treatment. [81] It was the largest study at the time, and included 453 patients. The main results were published in 2002 and confirmed the results found in the preliminary report. The study had a double-blinded design; it compared CRT to optimal medical therapy (OMT). The study included patients with LVEF $\leq$35% and a QRS duration of $\geq$130 ms in NYHA class III-IV who were followed for 6 months. The investigators in that study established, along with improvement in functional status and a longer walking distance, that CRT improved LVEF and reduced hospital admissions for HF as well as the need for intravenous HF treatment. [72]

As mentioned earlier, the indications for primary prophylactic ICD are similar to the inclusion criteria for the CRT studies, apart from the added requirement of a wide QRS complex. Many patients fulfill the criteria for both treatments, and for that reason MIRACLE was followed by MIRACLE-ICD, which examined the potential benefit of CRT and ICD treatment over ICD alone. 369 patients were enrolled; the inclusion criteria were LVEF $\leq$35%, QRS duration of at least 130 ms, at high risk of life-threatening ventricular arrhythmias, and in NYHA class III or IV despite OMT. The patients were randomized to CRT and ICD or ICD alone and followed for 6 months. In the CRT + ICD group, improvement was seen in QoL and NYHA class, but there was no significant difference in 6MWT. Nor were any differences in LVEF change, overall HF status or rates of hospitalization found. [82]

MIRACLE-ICD II was designed to study the effect of CRT on patients with mildly symptomatic HF. This study enrolled 186 patients in NYHA class II. 85 patients received CRT-D and 101 ICD only. No significant differences were found in the primary endpoint peak VO_2, but the CRT-D group improved in ventricular modeling indexes (LVEF and systolic volumes) as well as in NYHA class and a clinical composite response measure. [76]

CONTAK-CD investigated ICD vs CRT + ICD (CRT-D) in 490 patients with NYHA class II-IV and a history of malignant tachyarrhythmia. The study began as a 3 + 3-month crossover design, after which the design was changed (due to regulatory concerns) to a phase of 6 months, with continuous treatment. The incidence of its primary endpoint – which was a composite of death, hospitalization for HF and VT/VF requiring device intervention – was not statistically different between the two groups. The CRT-D group did, however, significantly improve in peak VO_2-max, 6MWT and echocardiographic parameters such as LVEF and LV internal systolic and diastolic diameter. [74]

The COMPANION trial (2004) was the largest study at the time; it randomized 1,520 patients to either CRT-P, CRT-D or OMT. It is still the only randomized trial that included both a CRT-P and a CRT-D group. The study included patients with NYHA class $\geq$III, LVEF $\geq$35% and a QRS duration of 120 ms or more. It followed the patients for a mean of 16 months, and found a reduction of the primary endpoint (death or hospitalization by any cause) by 20% in both the CRT-P and the CRT-D group. The risk of crude mortality was reduced by 24% and 36% in the CRT-P and CRT-D group, respectively. COMPANION also assessed the combined endpoint of hospitalization or death from heart failure, and found that the incidence was reduced by 34% in the CRT-P group and by 40% in the CRT-D group.

In 2005, the CARE-HF study was published. It followed 813 patients in NYHA III-IV for a mean of 29 months. These patients received a CRT or OMT (control group) in an open-label study design. The primary endpoint was all-cause mortality or cardiac hospitalization; the hazard ratio was 0.63 in the CRT group. The risk of death was reduced by 36% with CRT. The CRT group also had a lower risk for HF hospitalization and an improvement of QoL, NYHA class, LVEF and LV End-Systolic Volume (LVESD). [77]

Although some studies included a small number of NYHA class II patients, all trials except MIRACLE ICD II focused on patients with severe HF (NYHA $\geq$III), and CRT's effect on long-term outcome was unclear for patients with mild or moderate HF. The REVERSE trial therefore included patients with LVEF $\leq$40%, QRS duration $\geq$120 ms and NYHA class I-II. 610 patients received a CRT device ($\pm$ defibrillator) and were randomized to have their device turned on or off. The patients were followed for 12 months. The primary outcome was defined as worsening of HF clinical composite response [83] after 12 months, and was seen in 16% in the CRT group and in 20% in the OMT group, but the difference was not significant. The study did, however, find a significant improvement in the LVESV index in the CRT group.

MADIT-CRT also included patients in NYHA class I-II. 1,820 patients were assigned to either CRT-D or ICD, and were followed for a mean of 2.4 years. The study was designed to assess whether CRT-D could reduce the risk of death or nonfatal HF event in mild to moderate HF compared to ICD. The investigators found that CRT-D had a 34% risk reduction for

the primary endpoint compared to ICD, and the result was mainly driven by a lower incidence of nonfatal HF events in the CRT-D group. The study found a significant interaction between sex and CRT treatment, with a better CRT outcome in females. Also, an interaction with QRS duration $\geq$150 ms was found, with a better outcome in patients with a wide QRS complex and a nonsignificant effect in patients with a QRS duration between 120 and 15. [79] The study was extended, and long-term results were presented for 854 of the original 1,820 patients with a median follow-up duration of 5.6 years. Those analyses showed that mortality was significantly better in patients with CRT-D and LBBB compared to ICD. No benefit – and possibly even harm – was seen for CRT treatments in patients without LBBB.

RAFT is the most recent of the larger randomized CRT trials. It was designed to assess a potential survival benefit of adding CRT for patients with OMT and a planned ICD implantation. Inclusion criteria were: LVEF $\leq$30%, QRS duration $\geq$120 ms (or paced $\geq$ 200 ms) and NYHA class II-III. The trial used crude mortality or HF hospitalization as primary endpoint and found a 25% risk reduction for the CRT-D group as compared to ICD. [80]

Other important trials have also been published. The EchoCRT trial investigated CRT in patients with narrow QRS complexes ($<$130 ms). The study was stopped due to possible harm to patients. The authors concluded that CRT in these patients may increase mortality and should be avoided. [84] A subgroup analysis of the same study found no benefit for patients with a QRS duration of 120-130 ms. [85] The LESSER-EARTH trial included patients with QRS duration $<$120 ms, but was also stopped early because of futility and safety concerns. [86]

The BLOCK HF trial randomized patients with an indication for pacemaker due to atrioventricular block, HF (NYHA II-IV) and LVEF $\leq$50% to CRT or conventional RV pacing. The patients had no classical indication for CRT (i.e. a widened QRS complex). The study found that biventricular pacing was superior to conventional RV pacing with regards to mortality and urgent care visits due to HF. [87] The BioPace trial went even further, randomizing patients with a conventional indication for permanent ventricular pacing, regardless of LVEF and QRS duration to CRT or conventional pacemaker. Preliminary results from the BioPace trial were, however, disappointing, showing a non-significant trend towards better outcome in the CRT-group. The official results have apparently not been published at the time of writing. [88, 89]

Table 5: Table summarizing the landmark clinical trials leading up to today's practice guidelines for CRT implantation. Modified from Ruwald et. al. Res Reports Clin Cardiol 2014, Volume 5, 305–317.

Trial (year)	Design	Patients	Months follow-up, mean	NYHA	LVEF inclusion criteria, mean	QRS inclusion criteria, mean	Primary end-point	Secondary endpoint	Significant improvement in intervention group
MUSTIC-SR [70] (2001)	CRT vs OMT crossover	29/29	3	II, III, IV	≤ 35%, 24%	≥150 ms, 174	6MWT	NYHA, QoL, peak VO_2, MR, LV improvement, hosp, mortality	Yes
PATH-CHF [71] (2002)	RV/LV/CRT-P crossover	41	12	III, IV	NA, 22%	≥120 ms, 175	6MWT, peak VO_2	NYHA, QoL, hosp	Yes
MIRACLE [72] (2002)	CRT-P/OMT	228/225	6	III, IV	≤35%, 22%	≥130 ms, 166	NYHA, 6MWT, QoL	Peak VO_2, LVEDD, LVEF, MR, CCR	Yes
MIRACLE-ICD [73] (2003)	CRT-D/ICD	187/182	6	III, IV	≤35%, 25%	≥130 ms, 164	NYHA, 6MWT, QoL	LVV, LVEF, MR, CCR	Yes
CONTAK-CD [74] (2003)	CRT-D/ICD	245/245	6	II, III, IV	≤35%, 22%	≥120 ms, 158	NYHA, 6MWT, QoL	LVV, LVEF, CCR	Yes
COMPANION [75] (2004)	CRT-P/CRT-D/OMT	617/595/308	16	III, IV	≤35%, 21%	≥120 ms, 159	All-cause mortality or hosp	Mortality	Yes/Yes
MIRACLE-ICD II [76] (2004)	CRT-D/ICD	85/101	6	II	≤35%, 25%	≥130 ms, 166	peak VO_2	NYHA, QoL, 6MWT, LVV, LVEF, CCR	Only for secondary endpoints
CARE-HF [77] (2005)	CRT-P/Med	409/404	29	III, IV	≤35%, 25%	≥120 ms, 160	All-cause mortality or cardiac hosp	NYHA, QoL, LVEF, LVESV, HF Hosp	Yes
REVERSE [78] (2008)	CRT-P or D/Med	419/191	12	I, II	≤40%, 28%	≥120 ms, 160	HF clinical composite response	LVESVi	Only for secondary endpoints
MADIT-CRT [79] (2009)	CRT-D/ICD	1089/731	29	I, II	≤30%, 25%	≥130 ms, 162	All-cause mortality or HF hosp	LVESV, LVEDV, LVEF	Yes
RAFT [80] (2010)	CRT-D/ICD	894/904	40	II, III	≤30%, 24%	≥120 ms, 158	All-cause mortality or HF hosp	Cardiac death, Non-fatal cardiac hospitalization	Yes

Response measures

The major CRT trials found that, on group level, CRT improved survival, clinical and QoL measures. However, later CRT studies frequently state that between 30% and 50% of the patients do not respond to therapy. [90–92] CRT response is not universally defined, and many studies use proprietary definitions with poor agreement on the definitions among the studies. Furthermore, the response rate depends on population characteristics. [93–95]

The randomized trials used both short-term clinical status (6 months - 1 year) and longer-term mortality rates as a measure of CRT effect. However, the concept of response is commonly attributed to the patient fulfilling some criteria after a given time period (often 6 months or 1 year). It is commonly divided into clinical response (improvement of NYHA class, 6MWT, hospitalization for HF or composite measures etc.) or echocardiographic response (improvement in LVEF, LVEDD or LVESV etc.). A lower mortality rate, which is considered to be the main objective for successful CRT treatment, is seldom included in the definition of response. Although short-term improvement, especially clinical status, is very important for the individual patients' quality of life, it is not always correlated to a long-term mortality benefit. (See also the descriptions of the major RCTs on page 20.)

Changes in echocardiographic measures are commonly used as a sign of therapy response. A sub-study from the MADIT-CRT cohort assessed response in LBBB patients and defined clinical 'hypo-response' as an HF event in the first year after CRT implantation, and echocardiographic hypo-response as a $\leq$35% reduction (median) in left ventricular end-systolic volume 1 year after CRT-D implantation without evidence of clinical hypo-response. The study found that 48% of patients in the cohort exhibited both response measures after 1 year. 47% of the patients did not fulfil criteria for echocardiographic response, and 5% had no improvement in clinical status. Echocardiographic hypo-response was associated with increased long-term mortality. [96] The PROSPECT trial found a poor agreement among the different echocardiographic measures of dyssynchrony and clinical response. [97] The PROSPECT study has, however, been criticized for using complex methodology without properly training the participating echocardiographers. [98]

Some researchers use the term *super-responder*, indicating patients with very good effect of CRT. This term is also not universally defined, although most authors define it as patients with near-normalization of LVEF (>50%). Such response is correlated to very good long-term outcome. [99]

A meta-analysis of 150 studies found that the mean reported response rate in terms of clinical improvement (NYHA class) was 66%. [100] The same analysis also examined several randomized trials with a total of 3,904 patients, and found that NYHA class improved in 51% of the cases in the CRT group, and in 35% of the cases in the control group. An EHRA/ESC consensus statement surveyed major CRT trials and found that response is highest when con-

sidering 'soft' functional measure endpoints (such as) at 70%-80%. Structural and event-driven endpoints resulted in response rates between 40% and 60%. [101] The difference in response rates among subjective response criteria and objective findings may be partially explained by the placebo effect. It is well-known that patients exposed to a surgical intervention and follow-up visits are prone to experiencing a positive effect, regardless of the actual effect of the treatment. [102]

Response rates of 50-70% are often cited, but they are generally derived from trials conducted in the 2000s. It should be noted that more recent trials report somewhat higher response rates, perhaps owing to modern technology and an individualized approach to determining CRT eligibility. [103] A non-responder rate of 30-50% may thus not be accurate for CRT patients today.

Recommendations for CRT

Updated clinical practice guidelines are published every few years by different entities. The guidelines discussed in this thesis are primarily those published by the European ESC. [9, 104–107] Current recommendations from the ESC with references are presented in Table 6, and they summarize the evidence for CRT in HF well (as of the time of publication).

The guidelines are based on the results of the major randomized trials, and the recommendations are therefore based on outcomes derived from those populations. CRT is mainly recommended as an elective treatment in patients with insufficient response to optimal medical

Table 6: Current treatment recommendations for Cardiac Resynchronization Therapy from the ESC. Reprinted with permission from European Heart Journal (2016) 37, pp. 2129–2200. Citations legend: 261: [70], 262: [77], 263: [108], 264: [109], 265: [75], 266: [110], 267: [80], 268: [79], 269: [111], 270: [78], 271: [112], 272: [113], 273: [114], 274: [87], 275: [115], 276: [46], 277: [116], 278: [117], 279: [118], 280: [119], 281: [120], 282: [121], 283: [84], 284: [85], 285: [110]

Recommendations	Class [a]	Level [b]	Ref [c]
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	I	A	261–272
CRT should be considered for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIa	B	261–272
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	I	B	266, 273
CRT may be considered for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIb	B	266, 273
CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class who have an indication for ventricular pacing and high degree AV block in order to reduce morbidity. This includes patients with AF (see Section 10.1).	I	A	274–277
CRT should be considered for patients with LVEF ≤35% in NYHA Class III–IV[d] despite OMT in order to improve symptoms and reduce morbidity and mortality, if they are in AF and have a QRS duration ≥130 msec provided a strategy to ensure bi-ventricular capture is in place or the patient is expected to return to sinus rhythm.	IIa	B	275, 278–281
Patients with HFrEF who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite OMT and who have a high proportion of RV pacing may be considered for upgrade to CRT. This does not apply to patients with stable HF.	IIb	B	282
CRT is contra-indicated in patients with a QRS duration < 130 msec.	III	A	266, 283–285

therapy. The recommendations apply to patients with a LVEF $\leq$35%, as most randomized trials were designed with this inclusion criterion. Therefore, CRT is not recommended for patients with a LVEF $\geq$35%. Due to the findings of the terminated EchoCRT trial and individual patient meta-analyses, CRT is not recommended when QRS duration $\leq$130 ms. Subgroup analyses on patients with QRS duration $\geq$150 ms indicate that these patients benefit from CRT the most.

Patients in sinus rhythm with a QRS duration $\geq$150 ms, LBBB and impaired LVEF have a class I recommendation, as numerous studies and meta-analyses have shown a clear improvement in mortality and morbidity after CRT treatment in this subgroup. The guidelines state that CRT should be considered in morphologies other than LBBB with a wide QRS complex, although it is widely considered to be a less optimal substrate for resynchronization than LBBB. When assessed as one group, the non-LBBB patients have shown some or no benefit with CRT, and therefore in this group the effect of CRT is not as strong. [75, 122, 123] If QRS duration is 130-150 ms, CRT is recommended in presence of LBBB. The recommendation is not as strong in non-LBBB morphologies as the effect in those morphologies is unclear.

In patients with atrial fibrillation, the effect of CRT is not as strong, but should still be considered. The recommendations emphasize that a strategy for ensuring biventricular capture is desirable.

The evidence and recommendation for CRT is also strong for patients with HFrEF with an indication for ventricular pacing, regardless of NYHA class, QRS duration or morphology in order to reduce morbidity. Furthermore, an upgrade to CRT for patients with conventional pacemaker may be considered if the patients develop worsening HF despite optimal medical therapy.

CRT response

Numerous studies have focused on finding variables that are associated with response to CRT. However, this requires a definition of response, yet there is no consensus on what constitutes therapy response, and no predictor is strong enough to, on its own, reliably predict outcome. There are however, different variables that correlate with different outcome measures.

Heart-specific measures, such as QRS morphology and QRS duration, have been discussed earlier, and have been shown to correlate to echocardiographic and clinical response, mortality and morbidity. The noted two measures represent different aspects of dyssynchrony of the ventricles and thus substrate for resynchronization. [48]

A decreased LVEF and other signs of LV dysfunction are considered to be prerequisites for CRT response. More specific echocardiographic measures have been proposed as potential

markers for dyssynchrony suitable for CRT, but the PROSPECT trial and further studies have not found reliable echocardiographic measures that predict outcome after CRT. [124, 125]

HF etiology has also been assessed, as it has been hypothesized that the ischemic myocardium is a worse substrate for reverse remodeling than the non-ischemic myocardium. Ischemic etiology has been correlated to less echocardiographic response (MADIT-CRT), but has not been correlated to mortality, NYHA class or hospitalization rates (CARE-HF). [126, 127] Presence of myocardial scar as a consequence of ischemic heart disease may correlate to a lesser CRT effect, especially if the lead is placed in a scarred area. [128–131]

An irregular atrial rate, such as in atrial fibrillation, may result in suboptimal biventricular pacing, and some evidence indicates that a near-100% biventricular pacing is required for optimal CRT effect. [132] It has also been proposed that atrioventicular junction ablation should be considered for patients where biventricular pacing >90% is not achieved in order to reduce native atrioventricular conduction. [133]

Clinical status when initiating treatment may naturally impact long-term prognosis in patients with CRT. Treatment is recommended for symptomatic patients (NYHA II-IV), but positive effects have been shown for patients in all NYHA classes. MADIT-CRT and REVERSE showed that in NYHA class I, echocardiographic measures improved, and so has the rate of hospitalization for HF, although crude mortality did not improve. NYHA Class II patients have been shown to derive a mortality benefit; subgroup analyses indicate that this effect is mainly seen in patients with LBBB. [123] Early CRT trials focused on patients with severe HF (NYHA III-IV). In this group, mortality, hospitalization for HF and clinical outcome measures improved.

The presence of comorbidity has also been linked to worse outcome. A newly published post-hoc analysis of the MADIT-CRT cohort indicated that the burden of comorbidity impacts survival and the HF event rate. A higher burden of comorbidity was inversely correlated to reverse LV remodeling, although it did not compromise the clinical benefits of CRT. [134] Other measures of the comorbidity burden, such as the Charlson comorbidity index, have also been shown to correlate to outcome in CRT patients. [135] One comorbidity that has been discussed is renal failure or chronic kidney disease, which negatively impacts mortality after CRT and ICD implantation. It is not a contraindication to CRT, but it may be associated with worse prognosis after ICD implantation. [136]

Female sex has commonly been found to be associated with CRT response. The underlying mechanisms have not been fully elucidated. It has also been reported that CRT is underutilized in females, and the major trials included between 10 and 30% females in their cohorts. [137] Females in the CRT trials have had a higher proportion of LBBB and non-ischemic etiology compared to males, which may account for some (although not all) of this effect. One recent meta-analysis suggested that the effect of female sex on CRT response was due to gener-

ally smaller body size in females than in males. [138] The study found a greater CRT benefit in shorter patients of both sexes. One explanation could be that the relative dyssynchrony would be larger if using the same inclusion criteria (QRS duration) as for males.

Case-specific circumstances may also influence the effect of therapy. Coronary sinus anatomy varies and may not always allow for optimal LV lead placement. Posterolateral myocardial scar. [128, 139] Suboptimal device programming may prevent effective resynchronization, but can in some cases be corrected. [140] Furthermore, it is important that patients receiving CRT also receive optimized medical therapy. [19, 94]

Post-implantation variables can also be of value. If non-responders are identified early, a multidisciplinary approach to optimizing CRT and/or planning for additional treatment may improve outcome. Such variables can include ECG, echocardiographic, biochemical or clinical response measures. [140]

CRT and ICD

Patients with HFrEF have an increased risk of sudden cardiac death (SCD), often due to malignant ventricular arrhythmias. The prevention of SCD by ICD is often divided into primary and secondary prophylactic; i.e. patients without or with recorded previous malignant ventricular arrhythmia. [9, 141] Superiority of secondary prophylactic ICD treatment as compared to pharmacological treatment (primarily Amiodarone) is widely accepted after randomized trials and meta-analyses. [142]

ICDs for primary prevention has been subject to more debate. The first trials, which focused mainly on patients with ischemic etiology, have shown risk reduction with ICD as compared to pharmacological treatment. [143] However, since the time of those studies, medical treatment of HFrEF significantly improved. The role of antiarrhythmic drugs, such as miodarone, have been questioned in HF patients with modern HF treatment. [144, 145]. Several trials of ICD in both ischemic and non-ischemic HFrEF have been conducted, with somewhat diverging results. [144, 146–152] Subsequent meta-analyses concluded that there was strong evidence for using primary prophylactic ICDs in patients with HFrEF, and guidelines recommend this treatment for patients with NYHA class I-III. [9, 26, 153]

Since these recommendations were published, the impact of etiology on ICD treatment has been discussed. The evidence for ICD in ischemic patients is considered to be strong, but the recommendations for non-ischemic patients are largely based on subgroup analyses, and no trial convincingly showed a mortality benefit for the non-ischemic subgroup. The DANISH study, published in 2016, addressed this question and randomized 1,116 non-ischemic patients to ICD or no ICD (and CRT if indicated). The study found no significant differences in mortality between the groups. [21]

Both CRT and ICD gained widespread use during the 2000s, and both treatments were soon available in a single device. ICD indications overlap CRT indications, with the exception of excluding the QRS duration criterion and patients in NYHA class IV. The utilization of CRT-D is substantially higher than CRT-P in the US and most of Europe, but not as high in Sweden. [154, 155]

Only one randomized comparison between CRT-P and CRT-D has been performed. COMPANION included both device types, but failed to show any survival benefit for CRT-D when compared to CRT-P. [75] The ICD component is indicated for patients with LVEF $\leq$35%, especially if the etiology is ischemic heart disease. [9] Some studies suggest that if pathological remodeling of the myocardium is reversed by optimized treatment, the risk of sudden cardiac death decreases, possibly diminishing the benefit of ICD. [156–158]

The results of the DANISH trial, which included patients with and without CRT, indicate that patients with a non-ischemic etiology may not derive benefit from ICD treatment. [21] One pooled multicenter observational study (which included the cohort used for the studies in this thesis) indicated that CRT patients with ischemic etiology may benefit from added ICD functionality, while this was not the case for the non-ischemic sub-population. Although guidelines have not changed since the results from DANISH were presented, utilization of ICD in patients with non-ischemic heart disease has decreased in Europe. [159]

Adding ICD functionality to CRT is associated with ethical concerns and risk for side effects such as ICD lead failure or inappropriate shocks, which can be life-threatening. Furthermore, the a CRT-D device costs around 20,000 SEK more than a CRT-P device, and a defibrillator lead costs around 10,000 SEK more than a standard pacing lead. For this reason, and due to the uncertain evidence for CRT-Ds superiority over CRT-P, some researchers have argued for a more restrictive use of CRT-D. [160, 161]

Complications

Nearly all treatments, especially invasive treatments, are associated with potential complications. Known complications include device or lead malfunction, programming issues, and implantation-associated complications such as infection, bleeding and pneumothorax. In the Swedish pacemaker registry's preliminary report for 2017, the total complication frequency was 3.8% for CRT-P and 6.3% for the CRT-D group. [162] In the CRT-P group, the most common complication was infection or perforation (1.1%), followed by pneumothorax (0.9%) and electrode displacement (0.7%). For CRT-D patients, electrode displacement was most common (2.9%), followed by infection or perforation (0.9%) and electrical dysfunction (0.9%). The DANISH trial reported a device infection rate of 4.7% and 5.6% for CRT-D and CRT-P, respectively. [21] Another known complication in patients with CRT-D (or ICD) is inappropriate shock therapy. Yearly incidence rates of 7-12% or higher is reported in materi-

als consisting mainly of ICD-only patients, although modern ICD programming may lower these numbers. [163–165] The occurrence of inappropriate shock is associated with worse QoL and increased mortality.

Selvester QRS score

One factor that has been proposed to correlate to worse outcome after CRT implantation is a high burden of myocardial scar, as a scarred myocardium may be a worse substrate for resynchronization and reverse remodeling. [166] Myocardial scars have been described in ischemic patients as replacement tissue after myocardial infarction, and in non-ischemic patients as regional or diffuse myocardial fibrosis. [167, 168]

Myocardial scarring is usually assessed using gadolinium contrast-enhanced cardiac magnetic resonance imaging (GE-MRI), and burden of scar using GE-MRI showed promise to predict CRT response in both ischemic and non-ischemic patients. [166, 169] However, GE-MRI is costly, time-consuming, and is not routinely used in CRT patients.

The Selvester QRS scoring system (SSc) is a set of criteria designed to quantify scar tissue by analyzing the morphology of a standard 12-lead ECG. [170] Each met criterion corresponds to 3% added scar burden (for instance, 5 points would correspond to 15% total scar). SSc has recently been updated to be used on measurements of ventricular conduction delay, which all CRT patients have. The score has been validated for identifying and quantifying myocardial scar compared to GE-MRI in patients with ischemic and non-ischemic heart disease, with and without ventricular conduction delay. [171] SSc can potentially predict CRT response in terms of echocardiographic LV remodeling, with scores ≥ 5 indicating a lower probability for remodeling. [172]

The scoring process is complicated and time-consuming, and must be performed by a trained clinician. New software ('QuaReSs') drastically simplified the scoring process, making it possible to score large materials quicker. [173] The score requires human validation and, in some cases, correction. It has been validated by comparing the computer-generated score to the score produced by trained clinicians.

Risk stratification tools

Because response to CRT depends on multiple variables, composite score prediction models have been developed in order to better stratify long-term risk after CRT implantation.

Such scores were constructed using different approaches, derived either from large multivariate regression analyses [174–178]or from previous knowledge about clinical variables.[135, 179] One publication took a different approach, focusing on accumulated comorbidity

LBBB		
Lead	**Criteria**	**Pts**
I	any Q	1
	R/Q ≤ 1	2
	R/S ≤ 1	
	R/Q ≤ 1.5	1
	R/S ≤ 1.5	
II	Q ≥ 40 ms	2
	Q ≥ 30 ms	1
	R/Q ≤ 0.5	1
	R/S ≤ 0.5	
aVL	Q ≥ 50 ms	2
	Q ≥ 40 ms	1
	R/S ≤ 0.5	2
	R/Q ≤ 0.5	
	R/S ≤ 1	1
	R/Q ≤ 1	
aVF	Q ≥ 50 ms	2
	Q ≥ 40 ms	1
	R/Q ≤ 0.5	1
	R/S ≤ 0.5	
V1	NchInit40	1
Ant.***	R ≥ 0.3 mV	2
	R ≥ 30 ms	
	R ≥ 0.2 mV	1
	R ≥ 20 ms	
V1	S/S' ≥ 2.0	3
Post	S/S' ≥ 1.5	2
	S/S' ≥ 1.25	1
V2	NchInit40	1
Ant.***	R ≥ 0.4 mV	2
	R ≥ 30 ms	
	R ≥ 0.3 mV	1
	R ≥ 20 ms	
V2	S/S' ≥ 2.5	3
Post	S/S' ≥ 2.0	2
	S/S' ≥ 1.5	1
V5	any Q	1
	R/R' ≥ 2	2
	R/R' ≥ 1	1
	R/S ≤ 2	
	R ≤ 0.5 mV	1
V6	Q ≥ 20 ms	1
	R/R' ≥ 2	2
	R/R' ≥ 1	1
	R/S ≤ 2	
	R ≤ 0.6 mV	1
Total	Points	

Figure 6: Scoring chart for manual Selvester scoring of LBBB showing the different criteria. Full details on the scoring process can be found in an article by Loring et al. (A Detailed Guide for Quantification of Myocardial Scar with the Selvester QRS Score in the Presence of Electrocardiogram Confounders. J Electrocardiol 2011, 44, 544–54). The figure is adopted from the same paper, with permission.

among CRT patients in the MADIT-CRT cohort. The authors found that outcome worsened for each added comorbidity. It was not explicitly intended as a risk stratification tool, but it predicted mortality or HF event fairly well. [134]

Even though several tools exist, it can be difficult getting clinicians to become familiar with them, and then to actually use them. Some scores are not very user-friendly, e.g. requiring a computer for calculating them, or incorporating variables not routinely gathered. Perhaps new uses can be found for tools already widely in clinical use.

One tool already widely used is the CHA_2DS_2-VASc score, originally developed for stratifying the risk for thromboembolic events in patients with AF. [180] The CHA_2DS_2-VASc score

is commonly used by clinicians across many specialties, especially among electrophysiologists. The score consists of common clinical variables known for most patients, and includes some of the known risk factors after CRT implantation. CHA_2DS_2-VASc includes a sex category variable which assumes higher risk for females, contrary to evidence for CRT response. [181, 182]

Aims

The general aim of this thesis was to study the relationship between preoperative/early clinical characteristics and long-term outcome after CRT implantation, measured either as mortality, or as a composite of mortality and time to hospitalization for heart failure or heart transplant.

Specific aims of the respective papers were:

- Paper I sought to investigate the relationship between short-term subjective response after CRT implantation and long-term mortality.
- In Paper II, we sought to assess the long-term prognosis for CRT patients. We also wanted to investigate whether patients who received a primary prophylactic CRT-D exhibited better outcome than patients receiving CRT-P, when adjusting for comorbidity and other clinical characteristics.
- Paper III investigated a possible correlation between an ECG-based scoring method for estimating the amount of ventricular myocardial scarring and long-term outcome after CRT implantation.
- Paper IV aimed to explore the scoring system CHA_2DS_2-VASc's ability to stratify long-term outcome for CRT patients. Its secondary aim was to compare CHA_2DS_2-VASc to other scoring systems designed for use in CRT populations.

Methods

The patient material that the studies in this thesis were based on was gathered from the Arrhythmia clinic at Skåne University Hospital (SUS) in Lund, Sweden (previously Lund University Hospital). The hospital serves the Southern healthcare district (Södra sjukvårdsregion-en), incorporating the counties of Scania, Blekinge, Kronoberg, and the municipalities of Halmstad, Hylte and Laholm in the county of Halland. [183] In 2009, the region had a total population of 1,681,247. [184] SUS' arrhythmia clinic was the region's sole CRT referral unit and was, to the best of our knowledge, responsible for all CRT implantations in the region during the study period. The project was approved by the local ethics board in Lund (Dnr 2013/236 and 2016/861).

For the base cohort, we included all consecutive patients who received a first-time CRT implant between 1999 (when the hospital first began offering CRT treatment) and 2012. We excluded patients younger than 18 years of age at the date of implantation and patients who received CRT due to reasons other than heart failure. Patients with unsuccessful CRT implantation (or implantation of the intended LV electrode in RVOT due to technical difficulties) and patients who had the CRT system explanted within the first two months (e.g. due to infection) were also excluded from analysis, as were patients lost during follow-up. The patient selection process is presented in Figure 7.

Baseline evaluation consisted of standard clinical evaluation before implant, and patients were selected for treatment based on current ESC guidelines at time of implantation. Guidelines changed during the study period. [9, 105, 106, 141, 185]

Paper I included patients with CRT-P, as the objective was to address whether an eventual difference in mortality between groups was due to the CRT treatment effect. Patients implanted with CRT-D were excluded. Paper II included patients with CRT-P or CRT-D, but excluded CRT-D patients with a secondary preventive ICD indication, in order to assess whether the ICD function was associated with better outcome in the absence of previous malignant arrhytmia. In Paper III, the method used for calculating the Selvester score was designed to

Figure 7: Flowchart describing patient selection for the cohort and the four studies.

be used only on LBBB that fulfilled the criteria specified by Strauss et. al. [37] The semi-automated method used required a preoperative digital ECG for each case.[173]Thus, only patients with available ECG data and a "true" LBBB were eligible for analysis and were included for final analysis. [37] For the final Paper, IV, all patients from the "base" cohort had available data for calculating the CHA_2DS_2-VAScscore, and were included.

Data sources

Electronic medical records for all patients were retrospectively screened, gathering clinical preoperative characteristics, including previous medical history, comorbidity, echocardiographic data, medications, ECG and biochemical data using the SUS electronic records system (Melior © Cerner Sverige). Electronic ECGs were gathered from local MegaCare and MUSE databases.

For follow-up data, including cause of death and pre- and postoperative diagnoses, we obtained records from the Swedish Cause-of-Death registry and the Swedish National Patient Registry (SNPR) in May 2013 for studies I to III. Implant data was cross-checked with the Swedish Pacemaker Registry. [162] For Paper IV, we again obtained data from the Cause-of-Death and SNPR registries in September 2017, adding four years to the follow-up period. [183, 186]

Errata

When obtaining follow-up data on mortality and diagnoses for Papers I-III, details regarding data formatting were not properly communicated. This led to 32 deaths being omitted from the analyses in Paper I and II. Errata have been published for both Papers. The error was discovered and corrected before Papers III and IV were written, and therefore Papers III and IV were not affected. All results presented in this thesis are calculated using the corrected endpoint.

Outcome measures

We used primarily two measures of outcome. The main endpoint used in all studies was crude mortality, and was used in Paper I and II. Cause of death analysis was also performed in Paper I. For Papers I and III, we used a combined endpoint of time to death or heart transplantation (HTx). For the last Paper (IV), we used two endpoints – crude mortality and a composite of time to mortality or hospitalization for heart failure. As an exploratory analysis, we also assessed correlations with the tested score and short-time subjective improvement (see paper I).

Statistics

The project was focused on finding predictors for time-dependent outcome measures, and we therefore used the Cox regression analysis (proportional hazards modeling) in all studies. [187] For binary outcomes, logistic regression modeling was used. [188] Survival curves were plotted using the Kaplan-Meier method, and differences among groups were assessed using the log-rank test. [189, 190] For Paper III, we also used a proportional hazards model incorporating a spline function of the third degree in order to visualize an eventual non-linear relationship between the tested score and the outcome. [191]

Continuous variables are presented as means $\pm$SD or as median (IQR). Categorical variables are presented as numbers and percentages. Differences in mean are assessed with Student's T-test, and medians were tested using the Mann-Whitney U test. Differences in categorical variables were tested with Fisher's exact test, the χ^2-test or Kruskal-Wallis analysis of variance for variables with multiple groups. A two-sided P-value of <0.05 was considered significant in all Papers.

The SPSS statistical package (versions 21-23 (IBM)) was used for data collection, project management and statistical analyses for Papers I and II. [192] Analyses for Papers III and IV were performed in R (R core team). [193] Analyses used base R and specific R packages. [194–197]

Method by Paper

Paper I

During the study period, the local protocol after CRT implantation included a follow-up evaluation within two months of implantation. During follow-up, patients were asked if they experienced an improved functional capacity after the CRT implantation ("early subjective improvement"). In the patients' medical records, this was documented as one of three possible answers; 'Yes', 'No, unchanged', 'No, worsened'. The patients were divided into two groups based on their answers – responders (the 'yes' group) and non-responders (the 'No, unchanged' and 'No, worsened' groups). Analyses were then stratified on the basis of this variable.

Kaplan-Meier curves were plotted for the whole cohort, and for the male and female subgroups, stratified by the early subjective response variable. Univariable Cox regression analysis was performed for all available variables. Those with a P-value <0.2 were then included in a multivariate Cox regression analysis with stepwise backward conditional elimination (highest P value out) in order to fit the final adjusted model.

Paper II

This study included all CRT-P and all primary prophylactic CRT-D patients. Univariable Cox proportional hazards models were fit for all available variables. Variables with high internal correlation were assessed manually, and the most clinically relevant variables was kept. All variables with a $P < .2$ were included in a multivariate model in order to identify individual predictors of mortality. Unadjusted survival over time was visualized using Kaplan-Meier plots. Baseline variables and survival Kaplan-Meier curves were stratified by CRT type.

Paper III

All available preoperative ECGs (0-6 months) were downloaded from SUS ECG databases. These were then processed to be analyzed in the QuaReSs software tool.[173] All ECGs were manually screened, and all patients with an ECG not fulfilling Strauss et. als. criteria for LBBB were excluded from further analyses, as the algorithm for calculating Selvester score in QuaReSs only supports this QRS morphology. (See page 8 and reference [37]) Selvester scoring was performed with QuaReSs for all eligible cases by one investigator (CR). The scoring process was validated by another investigator (RB).

Kaplan-Meier curves were plotted for SSc quartiles. The SSc variable was dichotomized into two groups: the high-score group and the low-score group, the quartile with the largest separation in the Kaplan-Meier curve was used as cut point. A Cox model incorporating a spline function for the SSc variable was fitted, the resulting spline was plotted in order to visualize the Hazard Ratio (HR) for mortality over the SSc variable. Uni and multivariate Cox proportional hazards models were fitted, one with the integral and one with the dichotomized SSc variable, as well as with other clinical variables. All variables with a $P < 0.1$ in univariate analysis were included in the multivariate model. All individual score criteria were also tested with Cox regression.

Paper IV

For all patients in the base cohort ($n = 796$), CHA_2DS_2-VASc score was calculated using aggregate data from the manual medical records assessment and preoperative ICD-10 diagnoses from the SNPR. Similarly, the SHOCKED, VALID-CRT, ScREEN, EAARN scoring systems and the number of comorbidities as described by Zeitler et. al were calculated for all patients with sufficient data. Only complete cases were included in analyses. [134, 175–177, 198]

Separate Kaplan-Meier curves were plotted for all scoring systems, stratified by score. The scores' performances were assessed with univariable proportional hazards regression and Har-

rell's C. Also, ROC analysis with AUC calculation was performed for mortality at five and ten years. All criteria included in CHA_2DS_2-VASc were assessed with univariate Cox regression. A multivariate analysis was performed, including the total CHA_2DS_2-VASc score and other factors known for predicting CRT outcome. All Cox analyses were performed with the mortality endpoint as well as the secondary composite endpoint of time to death or hospitalization for heart failure. Furthermore, logistic regression was used to assess whether CHA_2DS_2-VASc correlated to the dichotomous early subjective improvement post-implant variable described in Paper I. Interaction analysis was performed between the CHA_2DS_2-VASc variable and the early subjective improvement, sex and atrial fibrillation variables.

Results

Study population

A total of 796 patients were included in the 'base' cohort. 16.1% of the patients were female, the mean age at implantation was 69.4 years. A total of 348 (43.7%) patients received a CRT-D device. At baseline, mean QRS duration was 168 ms and 63.9% had LBBB. The majority of patients (69%) were in NYHA class III, and the mean LVEF was 24%. The main etiology was ischemic (63%). 20.3% of the patients were upgraded to CRT from a previous conventional pacemaker. The usage of beta-blockers and ACEi/ARB was high (83.7% and 91.2%, respectively), as was the usage of loop diuretics (87.2%). Aldosterone antagonists were not as widely used (54.6%).

The variables distributions are largely equal across the four studies, except the variables used for patient selection (e.g. no CRT-D in study I). The full baseline characteristics of the population stratified by substudy are presented in Table 7.

Table 7: Table describing baseline characteristics for papers I-IV. Note that some variables include missing values, percentages are of variable total.

Variable	Paper I	Paper II	Paper III	Paper IV
n	446	705	401	796
Age in years, mean (SD)	72.1 (9.7)	69.6 (10.3)	69.8 (9.7)	69.4 (10.1)
Female gender, *n* (%)	76 (17)	116 (16.5)	76 (19.0)	128 (16.1)
CRT-D, *n* (%)	0 (-)	257 (36.4)	169 (42.1)	348 (43.7)
QRS duration (ms), mean (SD)	169.9 (27.4)	168 (27.9)	169.8 (19.7)	168 (28)
LBBB, *n* (%)	280 (63.2)	459 (65.5)	401 (100)	509 (63.9)
'True' LBBB *n* (%)	232 (58.6)	362 (59.3)	401 (100)	401 (57.8)
NYHA class *n* (%)				
I	4 (1.0)	15 (2.3)	9 (2.5)	18 (2.5)
II	54 (13.6)	131 (20.1)	77 (21.0)	149 (20.7)
III	304 (76.4)	453 (69.6)	253 (69.1)	497 (69.0)
IV	36 (9.0)	52 (8.0)	27 (7.4)	56 (7.8)
LVEF (%), mean (SD)	24.4 (7.0)	24.3 (6.5)	23.21 (5.9)	24 (6.5)
History of atrial fibrillation *n* (%)	269 (60.3)	331 (47.1)	175 (43.6)	416 (52.3)
Diabetes *n* (%)	152 (34.1)	224 (31.8)	116 (28.9)	258 (32.4)
Ischemic etiology *n* (%)	262 (67.4)	394 (63)	218 (58)	451 (63)
Previous pacemaker *n* (%)	96 (21.5)	128 (19)	11 (2.8)	158 (20.3)
β-blocker use *n* (%)	328 (78.3)	565 (82.6)	325 (83.1)	649 (83.7)
ACEi or ARB use *n* (%)	370 (89.8)	602 (91.1)	355 (93.2)	684 (91.2)
Aldosterone antagonist use *n* (%)	231 (55.3)	361 (54)	217 (56.8)	412 (54.6)
Anticoagulant use *n* (%)	216 (50.8)	344 (51.0)	184 (47.3)	389 (50.9)
Digoxin use *n* (%)	118 (29.6)	172 (28.2)	97 (27.1)	198 (28.5)
Loop diuretic use *n* (%)	359 (89.1)	548 (87.3)	325 (88.2)	622 (87.2)

Paper I

Of 446 CRT-P patients, 309 had available data on subjective improvement after implantation. During follow-up, 236 patients died. 48% died from heart failure, 18% from cardiac arrest, and 12% died from AMI.

When comparing baseline characteristics between patients who experienced an early subjective improvement (the 'yes' group) and those who did not (the 'no' group), we found that patients in the 'yes' group had slightly fewer symptoms (lower NYHA class), wider QRS complex, and received ACEi or ARB treatment to a higher extent. Among these 'yes' group patients (the early subjective responders), mortality by heart failure was significantly lower (41% vs. 59% among non-responders).

In univariable Cox regression analysis, greater age, ischemic etiology (vs. non-ischemic), higher NYHA class (III-IV vs. I-II), previous AMI, previous CABG, low LVEF, beta-blocker use, aldosterone inhibitor use, loop diuretic use, anticoagulant use, early subjective improvement and a history of atrial fibrillation were associated with long-term mortality. In multivariate analysis, greater age (HR 1.057, 95% CI 1.04-1.08, $P = 0.009$), NYHA class (HR 2.020, 95% CI 1.16-3.50, $P = 0.013$), LVEF (HR 0.975, 95% CI 0.95-1.005, $P = 0.014$), ACEi or

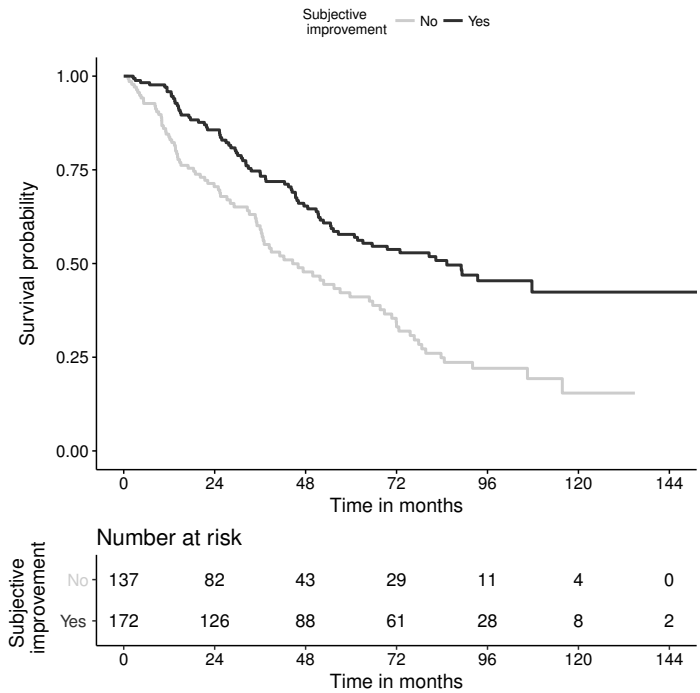

Figure 8: Survival curve stratified by short-time subjective improvement. Adapted from paper I.

ARB use (HR 0.543, 95% CI 0.33-0.9, P = 0.018), loop diuretic use (HR 2.204, 95% CI 1.04-4.6, P = 0.035), anticoagulant use (HR 1.62, 95% CI 1.18-2.20, P = 0.003), non-LBBB ECG morphology (HR 1.39, 95% CI 1.04-1.88, P = 0.029) and subjective improvement (HR 0.558, 95% CI 0.42-0.75, P<0.001) were associated with outcome.

Survival rates were significantly higher for patients who experienced an early subjective improvement (see Figure 8). When testing the male and female subgroups separately, this difference was only seen in the male group (log-rank test P <0.001 and P = 0.63 for males and females, respectively). Although survival rates were better for women, the association between sex and mortality was not significant, HR (univariable) for males was 1.424 (95% CI 0.98-2.07, P = 0.063).

Paper II

705 patients fulfilled the inclusion criteria. 448 (64%) patients had received a CRT-P device, and 257 (36%) received a primary prophylactic CRT-D. Patients with CRT-P were older, had a higher incidence of ischemic etiology, higher NYHA class, higher creatinine and lower hemoglobin levels than the CRT-D group. More patients in the CRT-D group than in the CRT-P group were treated with beta-blockers, and had a higher incidence of hypertension The overall annual mortality was 12.0%: 13.7% for the CRT-P group and 7.5% for the CRT-D group.

In univariable analysis, greater age, ischemic etiology, NYHA class, previous MI, previous CABG, hypertension, LVEF, QRS morphology other than LBBB, history of atrial fibrillation, CRT-P or CRT-D, creatinine levels, hemoglobin levels and use of beta-blockers, ACE inhibitor, ARB or Loop diuretics were associated with outcome. QRS duration greater than 150 ms was not significant, but was included in the multivariate analysis with a P = 0.2. In multivariate analysis, age (HR 1.04, 95% CI 1.01-1.06, P = 0.002), ACE inhibitor or ARB use (HR 0.51, 95% CI 0.27-0.97, P = 0.04) and hemoglobin concentration before implant (HR 0.98, 95% CI 0.97-0.995, P =0.009) were associated with outcome. CRT-D was not associated with significantly better outcome (HR 0.9, 95% CI 0.97-0.995, P = 0.66).

There were fewer female than male patients (n = 116 vs. 589). Males were more likely to suffer from ischemic heart disease. Also, previous AMI, CABG and PCI were all significantly more common in the male subgroup. No other differences were found between males and females. Kaplan-Meier analyses showed better survival rates for females with CRT-P, but no significant difference was found in the CRT-D group (however, the groups were fairly small; females with CRT-D n = 40, males with CRT-D n = 217). See survival curve in Figure 9.

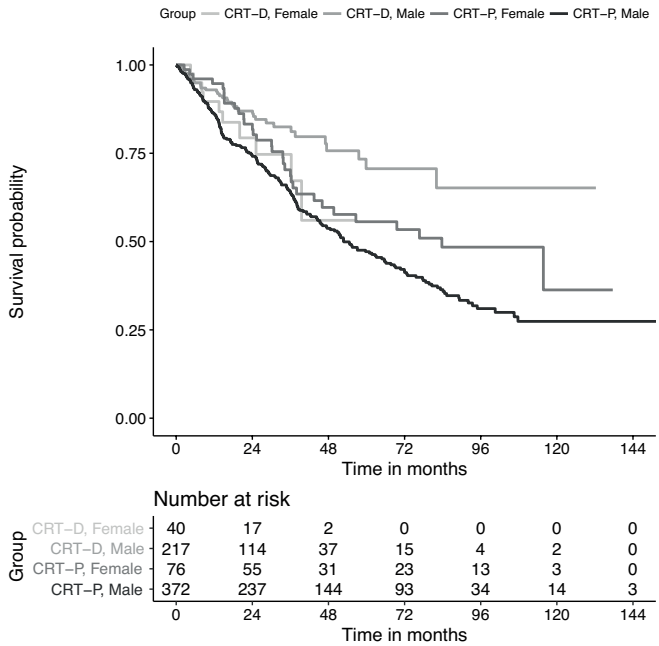

Figure 9: Kaplan-Meier curve showing survival stratified by sex and CRT type. Adapted from paper II.

Paper III

From the base cohort (se Figure 7), we found available preoperative ECGs for 694 patients. Of these, 401 met the LBBB criterion required for analysis in QuaReSs, and Selvester scoring was performed. The median SSc was 6 (IQR 4–8). In a subset of patients, intraclass correlation (average) as a measure of intraindidivual variation was found to be 0.99 (P = 0.001, 95% CI 0.96–1.0). Intraclass correlations for interindividual variation was 0.96 (95% CI 0.88–0.99). The mean age at implantation was 69.8 years (SD 9.7). 19% of the patients were female ($n = 76$), mean NYHA class was 2.8, and the mean LVEF 23.4% (SD 6.0).

178 patients reached the endpoint during follow-up; the median time to endpoint (death, heart transplant or follow-up) was 36.7 months (IQR 15.0–65.7). Five-year survival was found to be 44.1%. When comparing the ischemic and the non-ischemic subgroups, the ischemic patients were older at implant (72 vs. 66 years P = 0.001), and there were fewer females in that group (14% vs. 24%, P = .01). They also had a higher mean SSc (mean 6.9 vs. 5.8, P = 0.001, corresponding to an estimated 17% and 21% scar, respectively), a higher prevalence of diabetes mellitus (33% vs. 24%, P = .05), and a higher mean NYHA class (2.9 vs. 2.7, P = 0.02).

The SSc variable was dichotomized in a high- and a low score group by the fourth quartile

(SSc 9 and above), based on the Kaplan-Meier curve (Figure 10) and a spline analysis (see the original article in the Appendix).

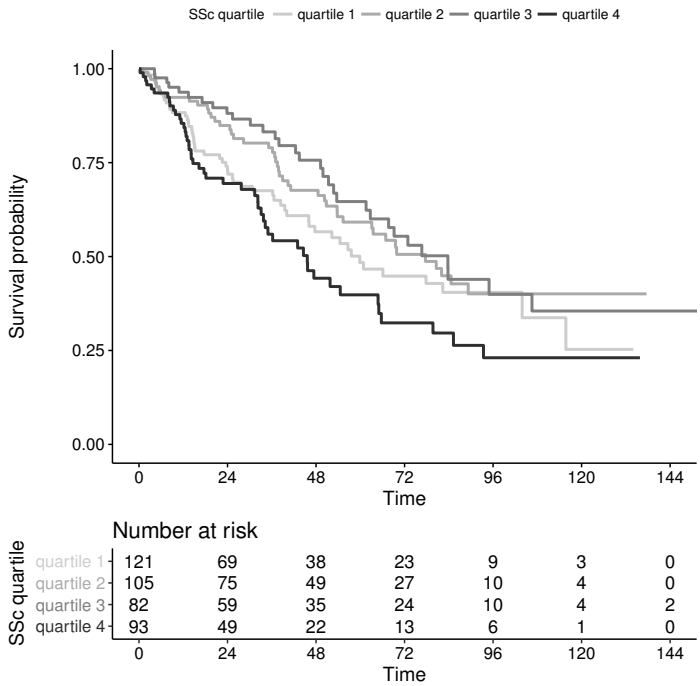

Figure 10: Kaplan-Meier curve showing survival stratified by SSc quartile. Adapted from paper III.

The patients in the high-score group were found to have significantly higher mortality (HR 1.63, 95% CI 1.17–2.28, $P = 0.0038$) than patients in the low-score group. Significant variables in univariable analysis were: Selvester score, ischemic heart disease, age, history of atrial fibrillation, NYHA class, and hypertension. In multivariate analysis, the following variables were associated with outcome: Selvester score ≥ 8 (HR 1.472, 95% CI 1.05–2.06, $P = 0.025$), age (HR 1.035, 95% CI 1.01–1.06, $P = 0.001$), NYHA class (HR 1.56, 95% CI 1.14–2.14, $P = 0.006$) and hypertension (HR 0.64, 95% CI 0.45–0.9, $P = 0.012$). Selvester score did not achieve significance when entered as an integral variable (HR 1.05, 95% CI 0.995–1.11, $P = 0.075$).

When individual criteria were assessed, five criteria were significantly associated with the endpoint in univariable analysis. R $<$ 0.2 mV in lead I, Q $\geq$40 ms in aVL, R/Q $\geq$0.5 in aVF, R $\leq$20 ms in V1 and R/S $\leq$2 in V6. R/S $\leq$0.5 in aVF was associated with better outcome. In multivariate analysis, four criteria achieved significance: Q $\geq$40 ms in aVL, R/Q $\leq$0.5 in aVF, and R/S $\leq$2 in V6 were associated with worse outcome, and R/S $\leq$0.5 in aVF was associated with better outcome.

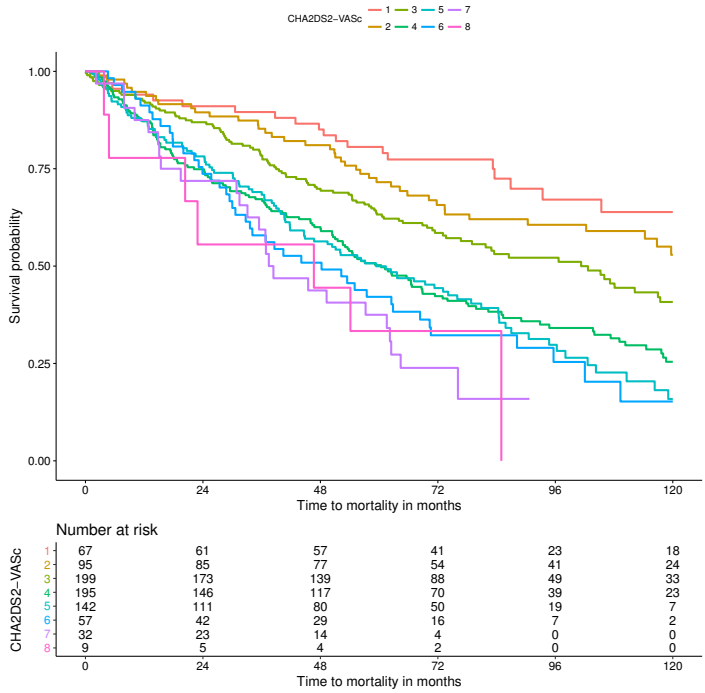

Figure 11: Kaplan-Meier curve showing survival for the cohort, stratified by CHA_2DS_2-VASc score.

Paper IV

796 patients were included in the study. Median age at CRT implantation was 71 years, 16% of the patients were female. 44% received CRT-D. The median time to death or follow-up was 64 months (IQR 33-90). 58% patients died during follow-up, 573 (72%) reached the secondary endpoint. Full baseline characteristics are presented in Table 7 on page 36.

The median CHA_2DS_2-VASc score was 4 (IQR 3-5). The lowest possible score was 1, as all patients in the cohort were treated for HF, which awards 1 point. Of the individual criteria, age, diabetes and vascular disease were associated with both mortality and the composite secondary endpoint in univariable analysis. Stroke/TIA was only associated with the mortality endpoint (HR 1.51, 95% CI 1.2-1.9, P = 0.001). The hypertension criterion was not associated with the mortality or secondary outcome. Female sex was only significantly associated with the secondary outcome (HR 0.76, 95% CI 0.6-0.96, $P = 0.023$), although there was a trend toward an association with mortality (HR 0.79, 95% CI 0.6-1.03, P = 0.07).

In an unadjusted analysis, the total CHA_2DS_2-VASc score was significantly associated with mortality (HR per incremental score point: 1.28, 95% CI 1.21 - 1.36), as was the case in the adjusted model (HR for primary outcome: 1.23 95% CI 1.14-1.33, $P < 0.001$; HR for second-

ary outcome: 1.13, 95% CI 1.06 - 1.21, $P < 0.001$). A Kaplan-Meier curve showed separation between most groups, see Figure 11. There was no significant interaction between CHA_2DS_2-VASc and history of atrial fibrillation or sex categories. There was no significant association between CHA_2DS_2-VASc score and subjective short-time response. Also, subjective response did not modulate the effect of CHA_2DS_2-VASc in interaction analysis.

Other than CHA_2DS_2-VASc, we identified five other previously validated risk stratification models that were possible to test using available data; number of comorbidities as described by Zeitler et. al. ("Comorbidities"), the VALID-CRT, ScREEN, SHOCKED and EAARN. [134, 175–177, 198] These scores were calculated.

In Cox regression, all scoring systems significantly correlated with both outcomes. All scores displayed a similar Harrell's C at around 0.6, except the EAARN and SHOCKED scores, which performed slightly better at 0.65 and 0.64, respectively. In ROC analysis, SHOCKED and EAARN were best at predicting 5 year survival (AUC = 0.68 for both), while CHA_2DS_2-VASc performed best at predicting 10-year survival (AUC = 0.73). SHOCKED performed best at predicting the secondary outcome at 5 and 10 years (AUC = 0.67 and 0.76, respectively).

Discussion

Early subjective improvement

The main finding of Paper I is that a patient experiencing subjective improvement of exercise capacity early after CRT implantation (two months) is likely to survive longer than a patient who does not experience subjective improvement. Remodeling of the left ventricle may start soon after implantation, but is usually measured after six months. Early CRT studies showed positive acute hemodynamic effects immediately after treatment began. [199] The subjective improvement experienced by 55% of the patients in this cohort could thus be a sign of an acutely improved hemodynamic situation, while "full" remodeling probably does not occur in the first two months. An additional survival curve was plotted with longer observation time (Figure 12).

NYHA class III was more prevalent in the 'yes' group. This finding may indicate that patients with NYHA I or II are not symptomatic enough to notice the immediate effects of cardiac resynchronization, or that therapy has limited effect on these patients. Patients in NYHA

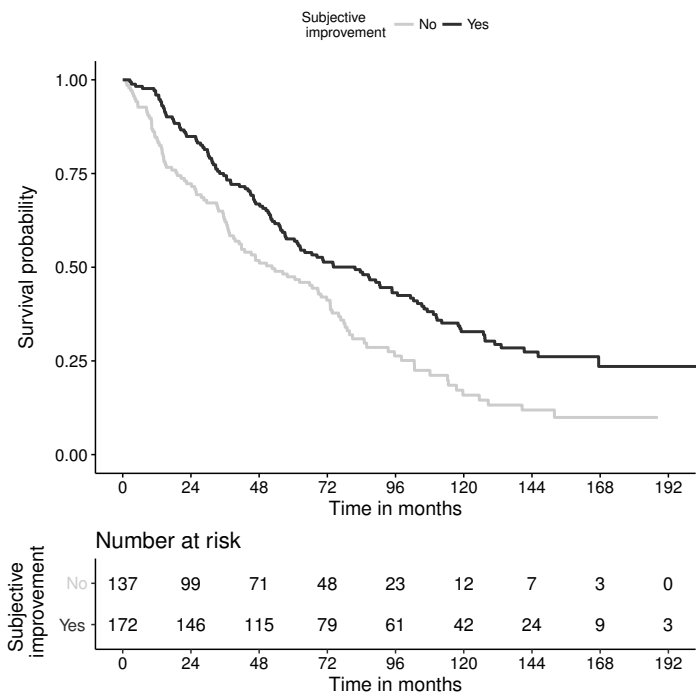

Figure 12: Survival curve stratified by early subjective improvement. The same curve as Figure 8, but with longer observation time. (Exploratory analysis for this thesis only.) $P<0.001$

class IV may be harder to treat with CRT, or the direct effects of CRT may not be as noticeable in a very symptomatic patient. As discussed above, acute hemodynamic improvement has been shown after CRT in NYHA class IV patients, a group that have been shown to benefit from CRT in randomized trials. [75, 82]

The problem with non-responders (definition/identification prior to CRT implantation) was discussed above (page 21). Identifying a non-responder after CRT implantation can be valuable to the treating clinician who can then try to optimize the CRT treatment or consider additional treatment options. Some evidence indicates that some non-responders can be relatively easily converted to responders. [140]

Being identified as a responder or non-responder early on could be of great value to for the patient and his or her treating physician. Both subjective and objective measures of response may be important when evaluating CRT effect. [200] This study shows that even a simple measure of early subjective response may be useful in identifying non-responders.

CRT-P vs. CRT-D

Patients who received CRT-P had a significantly higher burden of comorbidity at time of implantation. This is not surprising, as guidelines typically recommend the addition of ICD to patients with a NYHA class $\neq$ IV and an estimated survival time $>$ 1 year. Therefore, it is also to be expected that the CRT-P group would exhibit a higher mortality rate. When adjusting for other clinical variables, CRT-D was not independently associated with better survival ($P = 0.656$, Paper II).

The recommendation for primary prophylactic ICD applies to patients with a lowered LVEF due to ischemic or non-ischemic etiology and receives a class IA level of evidence. The finding that CRT-D was not associated with outcome in the adjusted analysis is therefore notable. Paper II was not the first to point this out, and at the time of publication there was an active debate regarding which patients should receive which type of treatment. [201]

Successful CRT treatment may, with reverse remodeling increase LVEF and lower filling pressures. One hypothesis is that if LVEF (or other measures of impaired ventricular function) increases to normal or near-normal levels, the risk for malignant tachyarrhythmia will also decrease. In fact, there is evidence that CRT without ICD reduces the risk for sudden cardiac death. [77] Furthermore, one meta-analysis shows that with reverse remodeling and LVEF approaching normal, the risk for malignant arrhythmia decreases. [202]

Since Paper II was published, several studies of ICD and etiology have also been published. The DANISH trial did not find a mortality benefit for ICD in non-ischemic patients with or without CRT. [21] A retrospective study of propensity score-matched CRT-P and CRT-D stratified by underlying etiology, in which the cohort described in this thesis was included, did

not find any differences in survival between CRT types in the non-ischemic subgroup. [18] Similar results have been published in smaller materials. [203] One study found that non-ischemic CRT patients with left ventricular mid-wall fibrosis detected by GE-MRI derived a mortality benefit from CRT-D as compared to patients who did not have left ventricular mid-wall fibrosis. [166] Future recommendations may take these results into account and recommend the addition of ICD only to patients with ischemic etiology and select patients in the non-ischemic group. (See also discussion about current ICD guidelines in Introduction, page 25)

If ventricular resynchronization alone is sufficient to substantially reduce risk in most patients, it may not be justifiable to use CRT-D as the default therapy. The majority of CRT patients in several published studies received CRT-D, which is in line with guidelines. [204, 205] However, current evidence indicates that it is reasonable to question those guidelines and advocate adding ICD to CRT for select patients only.

Sex differences

It has been widely reported that females respond better to CRT treatment than males. [182, 206, 207] One study (2017) suggested that the more favorable effect seen in females is explained by measurable differences in the female and male characteristics (such as height). [138] Outcome in Paper I was significantly better for females, but not in multivariate analysis. When tested in subgroups according to sex, the discriminatory value of early subjective response seems to lie within the male subgroup only. We proposed that this may imply a more gradual onset of treatment effect in females. Another potential explanation could be a bias in reporting subjective improvement at follow-up between the sexes.

In contrast to Paper I, survival analysis in Paper II did not show better survival for females when adding CRT-D patients to the cohort. It has been reported that male patients may benefit more from primary prophylactic CRT-D and ICD than female patients, which may explain this difference. [144, 181] The number of females was, however, small in both Papers (n = 76 and 116 for Papers I and II, respectively) and conclusions about this subgroup should be drawn with caution, as non-significance may also be (partly, or in whole) a question of low statistical power. There are generally fewer females than males in clinical trials and observational studies for CRT or ICD. [75, 79, 80, 208]

As discussed above, our material likely describes almost the entire population of the uptake area. The low number of female patients may therefore indicate an under-utilization of CRT in females. Several reports indicate that utilization of CRT may be lower in females than in males. [137] We did not have access to data on the general population, and we could therefore not assess whether CRT and ICD were under or over-utilized.

Selvester QRS score

The distribution of SSc in our material is skewed toward higher scores when compared to other CRT populations where Selvester scoring was performed manually. [172, 209] This finding may imply that patients in this study actually had a larger burden of myocardial scarring, or that there is some form of measurement error, either due to the score itself or due to the semi-automated method we used. The semi-automatic method has previously been shown to correlate well with manual scoring, albeit with a tendency to underestimate SSc. If assessed manually, the score in this material could thus be even higher. [173, 210]

Using software for ECG scoring

The QuaReSs software used sped up the scoring process significantly. Manual scoring is a long and tedious process that requires experience and knowledge of the score in particular and of electrophysiology in general. The method we used requires human validation for each point, but in our case the software proposed the individual criteria to be fulfilled, and for the most part the validator only had to confirm that the software identifies notches, slurs and waves of the QRS complex correctly. This made scoring much easier, and made it possible even for a less experienced investigator to perform the scoring. In fact, we found that variation in the resulting scores was low between the main validator (CR), who was a medical intern at the time, and the control (RB), who was a consultant electrophysiologist. A screenshot of the scoring process can be seen in Figure 13. We believe that software-assisted methods for ECG measurements are necessary, especially when it comes to measurements as complex as the SSc. After using the software, we believe that, after some refinement, the algorithms may be able to score automatically, without human intervention, and do so faster and with higher precision than the current version. Another reason to fully automate the process is that a completely computerized tool can be implemented more easily in a clinically-used ECG system or an electronic medical record system, which would make the tool much more accessible in the clinical decision-making process.

Association between SSc and outcome

We found that survival rates were similar among patients in the three lowest SSc quartiles. Patients with SSc greater than 8 were shown to have significantly higher mortality, with an adjusted hazard ratio of 1.59 when compared to patients with scores of 8 or lower. Such an increased risk is comparable to other predictors of outcome in CRT patients such as ischemic etiology, male sex and NYHA class. [206, 211]

Previous studies show that scar present at LV pacing site correlates with a lower chance of left ventricular remodeling. [128] In our study, none of the criteria that has been shown to

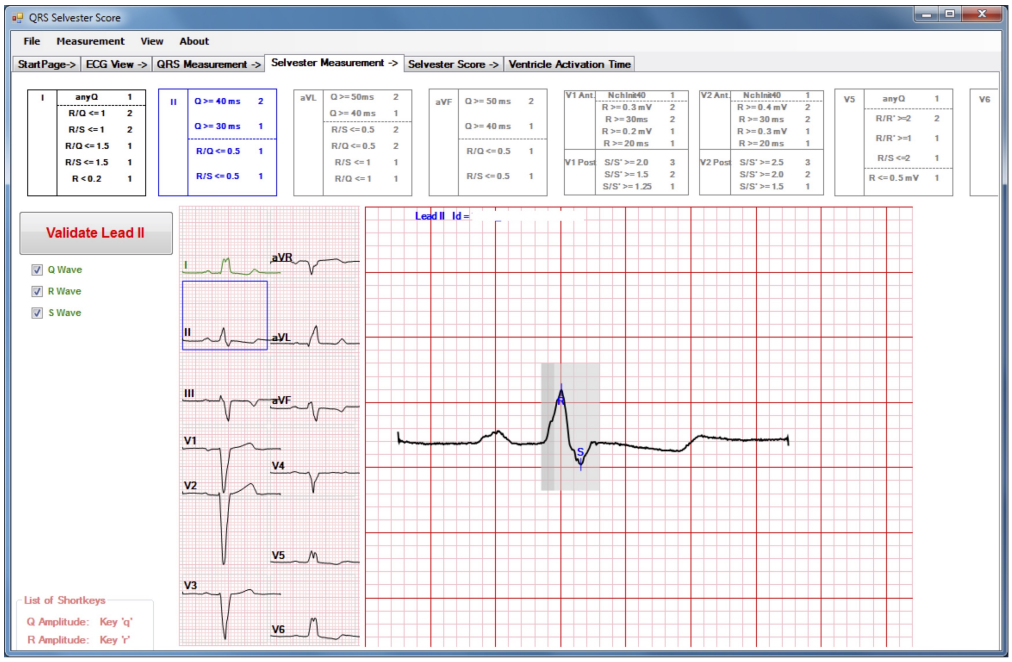

Figure 13: A screenshot from the scoring process in QuaReSs. Here the user is asked to validate whether the software correctly identified the Q, R and S waves of the QRS complex in lead II (there is no Q wave in this particular QRS complex). This validation must be performed for all leads measured in the SSc, and the recorded position of the curves (blue tick marks on the curve) can be adjusted if the software made a wrong measurement. After validating all leads, the user is presented with a report showing which criteria are fulfilled, and displaying the total Selvester score. The individual criteria composing the SSc are presented in the top panel in this screenshot.

correlate to outcome corresponds with scar in the left ventricles lateral wall, where the LV lead is most commonly implanted. [212] Our database did not include data on lead placement or GE-MRI measurements, and therefore we could not directly assess whether pacing at myocardial scar sites was associated with worse outcome at patient level. We found that one criterion was associated with better outcome: $R/S \leq 0.5$ in aVF, indicating inferior scar. In an earlier study, this specific criterion has been associated with a large number of false positives when compared to GE-MRI, which could explain our finding. [213]

Atwater et al. found a correlation between manually scored pre-implantation SSc < 5 and echocardiographic response, defined as a reduction of LVEDV $\geq$15%. That study consisted of 76 patients with strict LBBB and both ischemic and non-ischemic HF etiology. [172] Atwater et al. used LV remodeling as endpoint, whereas in our study we used mortality as endpoint. In ROC analysis, Atwater et al. found that the best discriminatory cutoff value for the (dichotomous) endpoint was SSc ≥ 5.

A substudy of the MADIT-CRT trial investigated SSc in ICD and CRT-D patients with and without LBBB. [209] The study used a pre-specified cutoff at SSc ≥ 5 to divide patients into

high- and low-score groups. It found that association with outcome (death or heart failure event) was equal in the low- and high- SSc groups regardless of CRT, indicating that the score does not predict CRT response. The study did, however, find that, in the LBBB subgroup, SSC was associated with a heart failure event or death as an integral variable, but not when dichotomized. The cutoff used was based on earlier SSc studies conducted before broad usage of CRT. [214, 215]

Ischemic vs. non-ischemic

The mean scores of 5.8 and 6.9 in the non-ischemic and ischemic subgroups of Paper III were higher than we expected, especially for non-ischemic patients. Other studies showed greater differences between the groups, both when assessed with GE-MRI and SSc. [169, 170]. Ischemic HF etiology may correlate to worse outcome in CRT patients. [216] Although present in both ischemic and non-ischemic patients, the underlying causal mechanism and appearance of scar differ between the groups. [166] It is reasonable to hypothesize that these differences may account for some of the variance in CRT and ICD response.

Using the Selvester QRS score

The SSc may be a valuable addition for selecting patients for CRT (and ICD) treatment. The current method has limitations in its correlation to scar in patients with ischemic and non-ischemic HF, and in its correlation to outcomes, as shown in our study and in the two studies cited above. We did not find any patients with SSc = 0, which may indicate a tendency for scar overestimation, especially when comparing the non-ischemic group with other studies. This is in line with previous evidence, and concerns have been raised about the score's performance, especially in non-LBBB populations. [217] SSc thus needs improvement, for instance by constructing a "CRT response prediction-specific" score, or by weighing individual criteria in order to improve sensitivity and specificity.

CHA_2DS_2-VASc in a CRT population

As was expected, the presence of most sub-criteria of the CHA_2DS_2-VASc score correlate to worse outcome in CRT patients (age, diabetes, previous stroke/TIA and vascular disease). However, females did not exhibit higher mortality than males, although there was a non-significant trend toward lower mortality rates in females. This was expected, as several studies reported that females have a better response to CRT treatment. [181, 182] As discussed earlier, there were few females in the present cohort, and the borderline significant result may thus be a question of statistical power. Females had a significantly lower risk for the secondary endpoint compared to males (HR 0.76, 95% CI 0.6-0.96, P = 0.023). The secondary

endpoint may measure CRT response better than crude mortality by incorporating an HF-specific measure. This finding is in line with other studies of CRT in females. The CHA_2DS_2-VASc score awards 1 point for female sex, indicating higher risk for females – however, this goes against the evidence in our study and in other studies. This is a major limitation for CHA_2DS_2-VASc in a CRT setting.

We tested two modified versions of the score – one without the sex variable, and one with it, but reversed (1 point for males instead of 1 point for females). Both adjustments improved the model slightly, but they altered the original score, counteracting the purpose of the study, which was to explore the original CHA_2DS_2-VASc score's potential role in CRT treatment. The main rationale for using the CHA_2DS_2-VASc score outside of its intended setting is that the CHA_2DS_2-VASc score is already widely known and used by clinicians, and this advantage will be lost if there are any modifications made to the scoring system.

Total CHA_2DS_2-VASc score correlates to both the mortality and the composite endpoints in this population. When considering the score alone (univariable regression), as one would in a clinical situation, each score point added a 23% greater risk for mortality and 13% for the secondary endpoint. It is also significant when adjusting for possible confounders. The score did not correlate to short-time subjective positive response after implantation. This, in combination with the fact that CHA_2DS_2-VASc significantly predicts mortality and secondary outcome measures, may suggest that the score indicate the level of overall morbidity rather than the substrate for CRT effect.

The other scores

We were able to calculate five different scores with the available data. Other scores were assessed, but they often required data that was not easily obtained in the retrospective setting.

Of the tested scores, all significantly correlated to both mortality and the secondary endpoint. Harrell's *C* values were similar across scores, and the scores were generally better at predicting mortality than the secondary outcome. Although the correlations were significant, Harrell's *C* was not as high as we expected, especially for CRT-specific scores (EAARN, VALID-CRT and ScREEN). The CHA_2DS_2-VASc scores performance was similar to the most accurate of the other scores, especially in the ROC analysis.

Although not explicitly intended to be used as a CRT risk-stratifying score, the number of comorbidities as defined by Zeitler et al. can be used as a measure of comorbidity in a CRT population. [134] The number of comorbidities does not take into account traditional CRT response predictors such as LVEF or QRS duration. The number of comorbidities still manages to predict outcome, including the composite endpoint of heart failure hospitalization and mortality.

Table 8: The risk stratification scoring systems included in paper IV. AF = Atrial Fibrillation, AVJA = Atriventricular Junction Ablation, CAD = Coronary Artery Disease, eGFR = estimated Glomerular Filtration Rate, COPD = Chronic Obstructive Pulmonary Disease

Score	
CHA_2DS_2-VASc [180]	Presence of: Congestive HF (1p), Hypertension (1p), Age $\geq$75 (2p), Diabetes (1p), Previous stroke/TIA (2p), Vascular disease (1p), Age 65-75 (1p), Sex category (female = 1p).
Comorbidities [134]	1p for each present comorbidity: renal dysfunction, hypertension, diabetes, coronary artery disease, history of atrial arrhythmias, history of ventricular arrhythmias, current smoking, and cerebrovascular accident. Stratified as 0,1,2, $\geq$3 comorbidities.
VALID-CRT [175]	Index = 0.028 × age 66 - 0.044 × LVEF25 + 0.646 × AF1 - 0.154 × AF2 - 0.656 × ICD+0.405 × GENDER + 0.317 × CAD + 0.844 × NYHA34 + 0.167 × diabetes. Stratified by quartiles. (age66 = age - 66 years; LVEF = LVEF - 25; AF1 = 1 if AF without AVJA is present, 0 otherwise (= both sinus rhythm or AF + AVJA); AF2 = 1 if AF with AVJA is present, 0 otherwise (= both sinus rhythm or AF without AVJA); ICD, CAD, NYHA III-IV, diabetes = 1 if present, 0 otherwise; gender = 1 if male, 0 if female)
EAARN [177]	1p for each present criterion: EF $<$ 22%, AF, Age $\geq$70 years, Renal function (GFR $<$60 mL/min/1.73 m^2), and baseline NYHA class IV.
ScREEN [198]	1p for each present criterion: Sex category (females = 1p), NYHA class $\leq$III, LVEF $\geq$25%, QRS duration $\geq$ 150 ms and eGFR $\geq$60 ml/min. A higher score indicates better predicted outcome.
SHOCKED [176]	1p for each present criterion: age $\geq$75, NYHA class III, atrial fibrillation, COPD, LVEF $\leq$20%, diabetes.

The SHOCKED score was derived from a large material of primary prophylactic ICD patients. Recommendations for ICD are very similar to recommendations for CRT, and at the time of writing there are debates as to who should receive which treatment(s). The populations' characteristics are therefore similar, and many patients receive a combination of the two treatments, although the SHOCKED derivation cohort included ICD patients only. [176] The SHOCKED study cohort included many patients with LVEF $<$35%, a wide QRS complex and some form of ventricular conduction delay QRS morphology. The final SHOCKED model includes variables shown to be of importance in CRT treatment and included in guide-lines such as NYHA class, atrial fibrillation and LVEF. The ability of the SHOCKED score to predict outcome in a CRT population is therefore not surprising.

However, the SHOCKED derivation cohort did not receive CRT treatment. The score still performs well in a CRT cohort – indeed, it was one of the most accurate scores tested in this study. The variables included in SHOCKED (many of which are included in the other scores too) may thus not be CRT-specific, but rather may indicate overall prognosis for our population, regardless of CRT.

The scores specifically designed for risk stratification in CRT patients typically include a combination of comorbidity and heart-specific criteria. For instance, the EAARN considers LVEF and atrial fibrillation, while VALID-CRT includes LVEF, coronary artery disease, atrial fibrillation and NYHA class. Arguably, these scores include few "CRT-specific" criteria, i.e. variables that indicate substrate for successful resynchronization therapy or reverse remodeling. One such variable, wide QRS duration, is only included in the ScREEN score despite being widely regarded as an important factor for successful CRT treatment. [48, 218] LBBB was not included in any score, which is a bit surprising since it is one of the strongest predictors of CRT response and is included in the class 1 recommendation in the current guidelines. [9]

Some scores detailed above include advanced echocardiographic measures, and therefore we were not able to test them in our study. Echocardiographic measures (other than LVEF) have been intensely researched for potentially identifying mechanical ventricular dyssynchrony. They have, however, not shown a reproducible ability to identify responders of CRT. [97, 219] To date, no scores include perioperative data such as interelectrode electrical delay or left ventricular lead positioning, in combination with preoperative variables.

Using scores for risk prediction in CRT patients

As discussed in the introduction, the number of patients not responding to CRT treatment is still considered high, even under current updated guidelines. [216, 220] There have been numerous failed efforts to precisely identify patients who will or will not benefit from CRT therapy. [69] Because the exact prerequisites for CRT response are not known, they are not included in the scores. This helps explain why CHA_2DS_2-VASc performed as well as the other scores in this comparison. The scoring tools we tested may to some extent measure the burden of comorbidity or disease severity rather than indicate the substrate for successful CRT treatment. The added morbidity that a higher score of any of the tested scoring systems represents will most probably correlate to a higher incidence of the mortality and the composite endpoint.

A common goal when constructing an accurate score for predicting an outcome is to make the model simple in order to be practical to use in clinical practice. However, the interplay between clinical variables may be more complex than a typical scoring system (or even a full regression model) can reflect. A tool such as adding a point to the nominal score for each clinical predictor trades accuracy for simplicity, and may not reflect the relationships between the included variables. The authors of the VALID-CRT score took this into account, and the result is drastically more complex than the other scores, although the VALID-CRT score is arguably harder to use in a clinical situation without a computer-based tool (see Table 8 on page 50.

A problem with risk scores derived from CRT populations and intended for use on CRT patients might be just that the scores are derived from a CRT population. The included patients are largely selected because they have combinations of characteristics known to favor CRT response. The guideline treatment recommendations basically incorporate the evidence we have for CRT response (see guidelines in Table 6 on page 22). What is left is background morbidity that may influence mortality regardless of CRT. This may explain why even the CRT-specific scoring systems (EAARN, ScREEN and VALID-CRT) are mainly composed of factors that are not specific in CRT populations only (such as atrial fibrillation, NYHA class, age, renal function, diabetes, or coronary artery disease). This may also help explain why CHA_2DS_2-VASc performs so well as compared to EAARN, ScREEN and VALID-CRT.

One might argue that it is premature to construct risk stratification tools before fully understanding specific predictors for successful CRT treatment. The optimal score may incorporate preoperative clinical variables and perioperative factors and measures of substrate for resynchronization. The limited accuracy of the presented scores shows that although these scores manage to discriminate fairly well between low-risk and high-risk patients on a group level, these scores should be used with caution on individual patients.

Limitations

This thesis describes a retrospective observational study of consecutive CRT patients. As such, it does not include a non-CRT control group for assessing CRT-specific effects. All patients are recruited from the same hospital and thus reflects that units performance and a potential referral bias, although the database probably reflects close to all patients in the large administrative region that the hospital serves. CRT and HF treatment guidelines have changed during the study period as well CRT technology. The cohort is large for a single-center study, but smaller than many RCTs and published retrospective multi-center studies. Since the study was retrospective, no formal power calculation was performed prior to the analyses, and lack of statistical significance can thus be a result of low statistical power. Furthermore, it does not include follow-up echocardiographic measures, which are commonly used as one measure for therapy response.

A substantial amount of patients did not have data on subjective improvement, and thus limits the statistical power of paper I. The lack of follow-up echocardiography prevented analyzing subjective improvement with echocardiographic measures.

CRT-D was introduced as a therapy later than CRT-P which may bias the selection of the two treatments and follow-up of CRT-D patients is therefore shorter than for patients with CRT-P. Furthermore, the CRT-P and CRT-D groups differed in several characteristics at baseline. Although adjusted for in the multivariate analysis, there may still be residual non-measurable differences that are not accounted for.

Even though the SSc scoring in paper III was software-aided, every measurement still needed to be validated, which was done by a single individual. Only unclear cases were discussed with colleagues and investigator bias cannot be ruled out. No GE-MRI data were available for validation of SSc. No data on lead placement were available, which would have been interesting when assessing individual criteria. As the computer-based method used in study III were only applicable on strict LBBB, a large portion of patients of the base cohort were left out.

With no control group, it was not possible to test for interaction between CRT treatment and the different scores in paper IV. We did not have access to follow-up echocardiographic data, which may be considered a better method to measure specific CRT response. Rather we used endpoints incorporating mortality that may be influenced by overall morbidity. The cohort used in this study was in part used for the original validation of the ScREEN score. Therefore, the results of paper IV do not add to the validation of ScREEN. [198]

Conclusions

- Early subjective improvement of functional capacity is associated with improved long-term survival in CRT-P patients.
- The added value of ICD to CRT can be questioned, and may only be of value to a select subgroup of CRT patients.
- A higher Selvester QRS score is associated with higher mortality in CRT patients with strict LBBB, but the system needs to be refined if it is to be used in clinical practice. SSc is feasible to assess in large materials using a computer-aided method.
- A high CHA_2DS_2-VASc score correlates to higher mortality in CRT patients, and its performance in stratifying patients is comparable to several CRT-specific risk stratification tools.

Perspectives

Substantial research has been conducted on commonly collected clinical variables in order to find the best selection criteria for CRT. Such research has, for the most part, validated findings of major randomized trials and treatment recommendations. Current selection criteria fail to fully characterize the populations' heterogeneity, and future research may focus on individualized diagnostics and treatment.

At the time of writing, a widely discussed topic was whether ischemic and non-ischemic patients should be treated differently with regards to ICD. A growing amount of evidence suggests that the benefit of added ICD functionality to CRT may be either small or restricted to patients with ischemic heart disease, putting paper II of this thesis into a larger context. The question of which patients should receive CRT-D instead of CRT-P warrants prospective evaluation.

As technology advances, previously high-risk or cutting-edge examination modalities may become more widely accessible. ECG-based criteria, such as QRS duration or morphology, do not diagnose resynchronizable dyssynchrony with satisfactory sensitivity and specificity. Therefore, for select patients, it may be feasible to use invasive or non-invasive electrophysiologic mapping methods or computerized simulations of myocardial activation. [221, 222] These and other methods may help refine the patient selection process in order to find subjects with dyssynchrony that can be treated with CRT.

Novel lead technologies may also improve outcomes. LV endocardial pacing has been proposed as an alternative for patients in whom an optimal LV lead placement cannot be achieved, e.g. due to coronary sinus anatomy. The WiSE-CRT system utilizes a wireless lead which theoretically can be placed anywhere in the LV endocardium. [223] Similarly, the ALSYNC trial investigated LV endocardial pacing delivered via a transseptal approach. [224] Multipoint pacing leads with multiple pacing poles are already in use, and are associated with better survival and fewer lead-associated complications. [225] These new methods make it possible to individualize lead placement, perhaps achieving better resynchronization.

Algorithms for identifying and managing nonresponders have shown promise to convert some nonresponders to responders. More programming options and even more versatile hardware make it possible to postoperatively program the devices in an individualized and dynamic manner. Some devices offer monitoring sensors and wireless communication options, enabling the CRT clinic to remotely monitor a patient's CRT system. These factors may improve response rates, morbidity and survival.

Current ongoing prospective trials focus mainly on three subjects: pre-implantation evaluation, device-related information (mainly endocardial and multipoint pacing) and follow-up/optimization strategies.

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