# Non-invasive Prediction of Cardiac Resynchronization Therapy. Focus on the role of atrial fibrillation, device-diagnostics and ECG-based risk markers

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LUND
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**Title and subtitle**

Non-invasive Prediction of Cardiac Resynchronization Therapy: Focus on the role of atrial fibrillation, device-diagnostics and ECG-based risk markers


**Abstract**

Heart failure (HF) is a common condition with high morbidity and mortality rates. In spite of many advancements and new available treatment opportunities during the last decades the prognosis remains poor and is even worse among patients with concominant comorbidities such as atrial fibrillation (AF). Cardiac resynchronization therapy (CRT) has among patients with reduced ejection fraction and signs of dyssynchrony been proven to reduce morbidity and mortality but many patients do not benefit from the treatment and patients with AF have a higher risk of becoming non-responders. Risk-stratification needs to be improved among patients with advanced HF. This thesis sought to assess the prognostic impact of AF in CRT recipients and to find non-invasive tools for risk-stratification. All papers were based on a retrospective material of almost 900 consecutive patients with CRT device implanted in Lund, Sweden between the years 1999 and 2012.

The thesis included four papers:

**Paper I** assessed the prognostic importance of device-detected ventricular high rate episodes, reflecting non-sustained ventricular tachycardias and found that such episodes during the first year of CRT treatment were associated to a higher risk of overall 5-year mortality but not death in cardiac arrhythmias.

**Paper II** evaluated the prognostic importance of AF before CRT implantation as well as AF during CRT treatment and found that AF history was associated to a worse prognosis but did not independently predict worse outcome in 10 years from CRT implantation whereas a higher burden of AF during first year of treatment independently predicted a worse outcome.

**Paper III** studied the importance of achieved biventricular pacing (BivP) percentage in patients with AF and found that AF and low BivP was independently predictive of death or heart transplant in 10 years from CRT implantation. Patients with AF and high BivP (>98% of all ventricular beats) did not have an inferior outcome compared to patients with no AF history.

**Paper IV** evaluated the electrocardiographic P wave abnormalities of interatrial block (IAB) and abnormal P-wave terminal force in lead $V_1$ ($PTFV_1$) among patients with no AF history before CRT implantation. The study found that IAB independently predicted a higher risk of new-onset AF, death or heart transplantation as well as death or heart transplantation alone in 5 years from CRT implantation but abnormal $PTFV_1$ was not associated to an inferior prognosis.



**Key words** Cardiac resynchronization therapy, heart failure, atrial fibrillation, risk-prediction, device-diagnostics, electrocardiography, interatrial block, abnormal P-wave terminal force in lead $V_1$

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*a smooth sea never made a skilled sailor*

**Franklin D. Roosevelt**

# Contents

# Populärvetenskaplig sammanfattning på svenska

Ungefär 1–2% av alla människor i västvärlden lider idag av hjärtsvikt som är ett syndrom som ofta innefattar ett stort lidande med orkeslöshet, andnöd och bensvullnad som vanliga symtom. Trots flertalet medicinska framgångar under de senaste decennierna är dödligheten i svår hjärtsvikt fortsatt hög och jämförbar med flera cancerdiagnoser.

Den bakomliggande etiologin till hjärtsvikt varierar men vanliga orsaker är hjärtinfarkt och högt blodtryck. Vid en hjärtinfarkt drabbas en del av hjärtmuskeln av syrebrist och efter redan relativt kort tid dör då muskeln och hjärtat blir därefter en mindre effektiv pump. Då hjärtat inte klarar av att tillföra blodflöde till kroppens olika vävnader i den utsträckning som krävs drabbas patienten av hjärtsvikt.

Läkare upptäcker oftast hjärtsvikt i samband med ett besök där typiska symtom framkommer och eventuella kliniska tecken som exempelvis bensvullnad och nedsatta andningsljud föreligger. Diagnosen kan sedan bekräftas med hjälp av exempelvis blodprov, elektrokardiografi (EKG) och ultraljud av hjärtat.

Idag talar man om flera olika typer av hjärtsvikt som utgår från kamrarnas förmåga att pumpa blod. Man talar om så kallad ejektionsfraktion (EF), en EF på exempelvis 50% innebär att hjärtmuskeln under varje hjärtslag klarar av att pumpa ut hälften av blodmängden i kammaren. En EF under 50% definieras som ”hjärtsvikt med nedsatt EF” och det är framförallt för dessa patienter man lyckats framställa mediciner och terapier som signifikant minskar dödligheten.

Bland patienter med låg EF och samtidiga tecken till så kallad dyssynkroni, dvs. att de olika hjärtrummen pumpar ”ojämnt/osynkroniserat” har så kallad CRT pacemakerbehandling (även kallad sviktpacemaker och biventrikulär pacemaker) visat sig vara gynnsam. Sådan terapi kan för rätt patient minska symtomen från hjärtsvikten såväl som dödligheten. CRT är en förkortning för Cardiac Resynchronization Therapy (kardiell resynkroniseringsterapi) och som namnet antyder syftar behandlingen till att, med hjälp av pacing (elektrisk stimulering) av hjärtmuskeln, återställa en synkron sammandragning av hjärtmuskeln. Till skillnad från en konventionell pacemaker har CRT pacemakern, i tillägg till elektroder i höger förmak och höger kammare, ytterligare en elektrod i den vänstra kammaren och med hjälp av densamma kan ”resynkronisering” uppnås. Nuvarande indikationskriterier för terapin är EF under 35% i kombination med EKG kriterier som förlängt så kallat QRS komplex och helst vänstergrenblock vilka båda speglar störningar av hjärtats retledningssystem som bidrar till dyssynkronin.

Även om behandlingen hjälper många är det fortfarande omkring en tredjedel av patienterna med CRT som inte har någon nytta av behandlingen trots att de uppfyllt alla indikationskriterier. Problemet är än större bland patienter som samtidigt lider av förmaksflimmer (FF), en oregelbunden ofta snabb hjärtrytm. FF försvårar

exempelvis för pacemakern att adekvat stimulera hjärtmuskeln och vid avsaknad av stimulering uteblir effekten av behandlingen. Studier har visat att patienter får bäst nytta av behandlingen om pacemakern lyckas stimulera hjärtmuskeln vid åtminstone 98% av alla hjärtslag, något som ofta är svårt att uppnå bland patienter med FF.

Det är idag välkänt att patienter med FF har en sämre prognos. Däremot är det ännu inte helt klarlagt varför det är så. Man vet exempelvis inte om det är förmaksflimret i sig som orsakar detta. Europeiska riktlinjer efterfrågar fler studier kring FF och inte minst bland patienter med CRT där ett problem är att de flesta stora studierna valt att exkludera patienter med FF.

Förutsatt att pacemakern klarar av att stimulera hjärtmuskeln adekvat menar emellertid nuvarande europeiska riktlinjer att patienter med FF har samma indikation för behandlingen som patienter utan. Omkring 3% av den vuxna befolkningen i västvärlden har FF och förekomsten av FF är starkt kopplad till graden av hjärtsvikt. Bland patienter med svår hjärtsvikt har man sett att upp emot hälften av alla också lider av FF vilket alltså innebär att många patienter där man överväger CRT också har FF. Hittills har de flesta studier inte funnit någon prognostisk nytta av att med hjälp av läkemedel eller andra terapier bryta förmaksflimret och återställa en normal hjärtrytm. Det är dock inte utvärderat ännu bland patienter med CRT.

En CRT pacemaker kan vara utrustad med en så kallad defibrillator (omnämns ofta ICD). En sådan kan upptäcka hjärtstopp och vid händelse av sådant ge en kraftig elektrisk stöt och på så vis starta hjärtat på nytt. Defibrillatorterapi är alltså potentiellt sätt livräddande men det kan vara svårt att förutsäga ifall patienten har hög risk för hjärtstopp. Det finns flera anledningar till att man inte ger defibrillatorer till alla, några är att sådana är associerade till en ökad risk för komplikationer som exempelvis att defibrillatorn avger en kraftig elektrisk stöt trots att hjärtstopp inte föreligger, något som självklart är mycket obehagligt och smärtsamt för patienten. Därtill innebär tillägg av defibrillatorterapi ingen ökad livskvalité och kostnaden blir mycket högre varför Socialstyrelsen anser att behandlingen bör prioriteras relativt lågt och i Sverige har vi som tradition valt att ge en stor andel av patienterna CRT utan defibrillator.

CRT pacemakrar har en god förmåga att samla in och spara information kring exempelvis hjärtats rytm och uppnådd pacing. Dessa data omnämns ”device-diagnostik”. Det finns flertalet surrogatmarkörer för FF vilka visat sig vara pålitliga och i en klar majoritet av fallen återspegla äkta FF. Information från kamrarnas rytmer finns också att hämta från device-diagnostiken. Idag föreligger stora osäkerheter kring vilken prognostisk betydelse FF upptäckt via device-diagnostiken har. Sådana episoder förekommer ofta utan att patienten känner av dem och kan vara korta eller långa, uppkomma ofta eller mer sällan. Än idag vet vi inte säkert ifall device upptäckt FF, särskilt kortare episoder, bör föranleda någon förändring

avseende patientens behandling eller ifall de är förenade med en sämre prognos. Det är också fortsatt oklart ifall kortare episoder av device upptäckt snabb kammarrytm är förenat med en ökad risk för död och/eller hjärtstopp.

Att i förväg avgöra vem som kommer ha nytta av CRT är alltså än idag en stor och svår utmaning. Dödligheten bland CRT behandlade patienter är fortsatt hög och det är viktigt men svårt att riskstratifiera dessa patienter varför bättre hjälpmedel för sådan efterfrågas. EKG är en billig, icke-invasiv metod som finns på i princip alla vårdinrättningar. Vissa EKG avvikelser har tidigare visat sig kunna förutsäga en ökad risk för framförallt framtida FF men också en ökad risk för död och kan därför tänkas användas som ett hjälpmedel för riskstratifiering. Nyttan av dem är dock inte utvärderade bland patienter med CRT.

Syftet med avhandlingen var att finna icke-invasiva prediktorer för CRT utfall som skulle kunna bidra till en bättre riskstratifiering. Mer specifikt ville vi undersöka den prognostiska betydelsen av FF och se ifall vi kunde bekräfta tidigare fynd av associationen mellan FF innan CRT implantation och en sämre prognos i vårt patientmaterial samt evaluera ifall förmaksflimret i sig hade en betydelse för prognosen. Vi ämnade också utforska varför FF ofta orsakar ett sämre utfall bland patienter med CRT. Därtill ville vi analysera betydelsen av device-diagnosticerade förmaksflimmerepisoder och se ifall sådana var förenade med en ökad risk för död samt ifall den totala mängden FF spelade någon roll. Vi önskade också studera betydelsen av snabba device-diagnosticerade kammarrytmer hos patienter utan defibrillator och se ifall sådana var kopplade till en ökad risk för död i hjärtstopp. Ytterligare ett mål med avhandlingen var att undersöka olika EKG avvikelsers betydelse bland patienter med CRT och se ifall sådana innan CRT skulle innebära en ökad risk för FF och/eller död.

Avhandlingen bygger på ett material om totalt knappt 900 patienter som mellan åren 1999 och 2012 fått CRT vid Skånes Universitetssjukhus i Lund. Efter etiskt godkännande har data kring dessa patienter samlats in från journalgenomgångar och olika register. Nedan ges en kortare beskrivning av avhandlingens olika delarbeten med huvudfynd och slutsatser kring desamma.

Delarbete nummer ett inkluderade endast patienter utan defibrillator och det huvudsakliga fyndet var att korta episoder av snabb kammarrytm upptäckta av CRT pacemakern var förenade med en ökad risk för död men ej död i hjärtstopp. Patienter där man upptäcker sådana anser vi därför bör monitoreras extra omsorgsfullt då de verkar ha en sämre prognos. Våra resultat talar dock inte för att dessa patienter skulle ha nytta av att ”uppgradera” sin CRT till en CRT med defibrillator.

Delarbete nummer två och tre bekräftade associationen mellan förmaksflimmerdiagnos innan CRT och ett sämre utfall men resultaten talade emot att det var förmaksflimret i sig som var orsaken. Det verkar således vara någonting annat som gör att dessa patienter har en sämre prognos. Därtill talar våra resultat

från arbete två och tre inte för att korta device-upptäckta episoder av FF har någon prognostisk betydelse.

I delarbete två fann vi emellertid att en längre total tid med FF första året med CRT signifikant förutspådde en ökad risk för ett sämre utfall oberoende av andra faktorer som vi vet är av prognostisk betydelse. Fyndet kan tala för att patienter med CRT skulle kunna ha nytta av åtgärder som syftar till att minska den totala bördan av FF.

I delarbete tre fann vi att andelen uppnådd adekvat elektrisk stimulering av hjärtmuskeln var av stor betydelse för prognosen bland patienter med FF samt att dessa inte lyckades uppnå en lika hög andel pacing som patienter utan FF. De patienter med FF som under första behandlingsåret uppnådde en simulering över 98% visade sig inte ha en signifikant sämre prognos jämfört med patienter utan FF. Däremot var förmaksflimmer i kombination med stimulering under 98% oberoende prediktivt för en sämre prognos. Resultaten bekräftar tidigare fynd och talar för att en mycket hög andel adekvat stimulering av hjärtmuskeln är viktig samt att en låg sådan kan vara en av anledningarna till att patienter med FF svarar sämre på behandlingen och således har en sämre prognos.

Delarbete fyra utvärderade betydelsen av EKG avvikelser preoperativt och fann att sådana kan prediktera en ökad risk för framtida FF såväl som död. Sådana avvikelser verkar alltså vara av betydelse även för patienter med CRT och vi menar därför att dessa kan vara till hjälp för kliniker när det kommer till riskstratifiering bland patienter med CRT behandling och svår hjärtsvikt.

# Nomenclature

| | |
|---|---|
| 6MWD | six-Minute Walking Distance |
| ACE | Angiotensin Converting Enzyme |
| AF | Atrial Fibrillation |
| aIAB | advanced InterAtrial Block |
| AMI | Acute Myocardial Infarction |
| ARB | Angiotensin Receptor Blocker |
| ARNI | Angiotensin Receptor Neprilysin Inhibitors |
| AVJ | Atrioventricular Junction |
| CRT | Cardiac Resynchronization Therapy |
| CRT-D | CRT with Defibrillator |
| CRT-P | CRT-Pacemaker |
| ECG | Electrocardiogram |
| Hb | Haemoglobin |
| 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 |
| IAB | InterAtrial Block |
| ICD | Implantable Cardioverter-Defibrillator |
| ICD-10 | International Classification of Diseases, Tenth Revision |
| IHD | Ischemic Heart Disease |
| LBBB | Left Bundle Branch Block |
| LV | Left Ventricle |
| LVEF | Left Ventricle Ejection Fraction |
| MRA | Mineralcorticoid Receptor Antagonist |
| NYHA | New York Heart Association |
| pIAB | partial InterAtrial Block |

| | |
|---|---|
| $PTFV_1$ | P-wave Terminal Force in lead $V_1$ |
| QoL | Quality of Life |
| RAAS | Renin-Angiotensin-Aldosterone System |
| RBBB | Right Bundle Branch Block |
| RCT | Randomized Controlled Trial |
| RV | Right Ventricle |
| SCD | Sudden Cardiac Death |
| STEMI | ST-Elevated Myocardial Infarction |
| VF | Ventricular Fibrillation |
| VT | Ventricular Tachycardia |

# Introduction

> "When the ear is held to the chest, and one listens for some time, it may be heard to see the inside like the boiling of vinegar"

…was written by Hippocrates in the last decades of the 5th century BC and was a description of his bedside clinical examination of a patient with pulmonary oedema, probably due to heart failure (HF). The citation above translated by A. Katz[1] from Hippocrates works, the Hippocratic corpus, also describes a way to drain fluid through a hole drilled in the ribcage, however, by that time there seem to have been no understanding about why the fluid had accumulated. In fact, the general agreement among scientists was for a long time that the primary function of the heart was to distribute air and heat through the body.[2]

The scientific community had to wait until 1628 before a modern understanding of the heart's functions were laid out when the Englishman William Harvey published his book *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus,*[3] and in it described the basis of the systemic circulation. Another turning point occurred in 1918 when Starling described the relationship between end-diastolic volume and stroke volume and provided the basis for the understanding of hemodynamics.[4] Additional historic advances worth mentioning are Willem Einthoven's invention of the electrocardiogram (ECG) in 1924[5] and Inge Edler's and Helmuth Hertz's development of echocardiography.[6] Regarding cardiac medicines, diuretics were first used in the 1920's and thiazide diuretics were introduced in the late 1950's.[2] The CONSENSUS-1 study[7] was an important turning point for the prognosis and life-expectancy of patients suffering from HF as it showed survival benefit of angiotensin converting enzyme inhibitors (ACEi) in patients with severe HF.

Even though the prognosis of HF has improved significantly during the last decades,[8] it is still inferior to many cancer diagnoses. In recent decades, several multivariable prognostic risk scores have been developed for patients with HF but such have in meta-analyses been found to only have moderate accuracy for the prediction of outcomes such as mortality and HF hospitalization.[9] Atrial fibrillation (AF) is one of the most common comorbidities among patients with HF[10] and is associated to an even worse outcome.[11] Cardiac Resynchronization Therapy (CRT) has been available since the early 1990s.[2] Even though CRT significantly reduces morbidity and mortality in most patients with the correct indications, up to around one third of patients do not benefit from the treatment and the number of non-

responders are even higher among patients with AF.[12] Hence, further studies are needed to improve prognosis and risk-stratification in patients with HF.

This thesis evaluates non-invasive risk-stratification instruments and deals with the prognostic impact of AF in CRT recipients. We hope that our results can contribute to a better knowledge and understanding and that they can be of use for clinicians to improve risk-stratification in the context of HF management.

# Heart Failure

## Terminology

Characterized by typical symptoms (e.g. fatigue, loss of breath and ankle swelling) HF is, according to The European Society of Cardiology (ESC)

> "a clinical syndrome that may be accompanied by clinical signs such as elevated jugular venous pressure, peripheral oedema and pulmonary crackles caused by a structural and/or functional cardiac abnormality. This abnormality causes reduced cardiac output and/or elevated cardiac pressures during rest or exercise/stress."[8]

The symptomatic HF syndrome is most often graded as according to the New York Heart Association's (NYHA) functional classification (Table 2) that traditionally has been used to describe the exercise intolerance and severity of symptoms a patient suffers.[13]

| Symptoms | Signs |
|---|---|
| **Typical** | **More specific** |
| Breathlessness<br>Orthopnoea<br>Paroxysmal nocturnal dyspnoea<br>Reduced exercise tolerance<br>Fatigue, tiredness, increased time to recover after exercise<br>Ankle swelling | Elevated jugular venous pressure<br>Hepatojugular reflux<br>Third heart sound (gallop rhythm)<br>Laterally displaced apical impulse |
| **Less typical** | **Less specific** |
| Nocturnal cough<br>Wheezing<br>Bloated feeling<br>Loss of appetite<br>Confusion (especially in the elderly)<br>Depression<br>Palpitations<br>Dizziness<br>Syncope<br>Bendopnea[53] | Weight gain (>2 kg/week)<br>Weight loss (in advanced HF)<br>Tissue wasting (cachexia)<br>Cardiac murmur<br>Peripheral oedema (ankle, sacral, scrotal)<br>Pulmonary crepitations<br>Reduced air entry and dullness to percussion at lung bases (pleural effusion)<br>Tachycardia<br>Irregular pulse<br>Tachypnoea<br>Cheyne Stokes respiration<br>Hepatomegaly<br>Ascites<br>Cold extremities<br>Oliguria<br>Narrow pulse pressure |

***Table 1.*** *Symptoms and signs typical of heart failure. Reprinted with permission from European Heart Journal (2016) 37, pages 2129-2200.*

| NYHA Class | New York Heart Association functional classification |
|---|---|
| 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 |

***Table 2****. New York Heart Association functional classification.*[13]

Most often evaluated by echocardiography, measurements of the left ventricular's ejection fraction (LVEF), have historically been used to describe the different types of HF. The terminology used today compromises a wide range of patients, from those with normal LVEF (≥50%, considered as HF with preserved ejection fraction [HFpEF]) to those with reduced LVEF (<40%, considered as HF with reduced ejection fraction [HFrEF]). In between there is a "gray area" with patients now defined as HF with mildly reduced ejection fraction (HFmrEF).[8]

| Type of heart failure | Left ventricular ejection fraction |
|---|---|
| HFrEF | < 40% |
| HFmEF | 40-49% |
| HFpEF | ≥ 50% |

***Table 3**. Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF).*

In this thesis, mainly patients with HFrEF will be discussed as only this group of HF patients may be considered for CRT.[8,12]

# Epidemiology

Approximately 1-2% of the adult population in developed countries suffer from HF.[14] The prevalence rises with age, is higher among men, and the overall lifetime risk for HF, at age 45 through age 95 years, has in developed countries been found to be 20-45%.[15] As the western population is ageing and as HF rises with age, the prevalence is likely to increase.[8]

In Sweden though a quite recent publication[10] found that the prevalence of HF remained unchanged from 2006 to 2010 and that the incidence decreased by 24% and mortality by 19%. The decreased incidence was believed to be explained by a better control of risk factors for HF. The total prevalence of HF was 2,2% in 2010 with more than 90% of the patients 60 years or older. The authors also found that the prevalence as well as the incidence was higher among men and that the mean age by the first recorded diagnosis of incident patients was 74 years among men and 80 years among women.

The most common cardiovascular comorbidity was hypertension (73% and 69% among women and men respectively) followed by ischemic heart disease, atrial fibrillation/flutter, diabetes mellitus, cerebrovascular disease and chronic obstructive pulmonary disease. Atrial fibrillation/flutter, was significantly more often found in men (in 48% and in 43% of women). The total 5-year survival rate from the first recorded HF diagnosis was 48% and the mortality was higher among males.

# Etiology and pathophysiology

Patients have different pathologies that contribute to HF. Data has indicated that coronary heart disease, hypertension, diabetes mellitus, obesity and smoking are responsible for 52% of incident HF cases in the population.[15] One may summarize most of the aetiologies into three categories; diseased myocardium (e.g. ischemic heart disease, toxic damage, immune-mediated and inflammatory damage, infiltration, metabolic derangements and genetic abnormalities), abnormal loading conditions (e.g. hypertension, valve and myocardium structural defects, pericardial and endomyocardial pathologies, high output states and volume overload) and arrhythmias (e.g. atrial or ventricular tachycardias and bradycardias). As identification of the specific pathology leading to HF may offer certain therapeutic opportunities, the etiology of HF should be included in the diagnostic workup according to current European guidelines.[8] Adapted from the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic HF,[8] Table 4 shows different etiologies of HF.

| **Diseased myocardium** | |
|---|---|
| Ischemic heart disease | Myocardial scar,<br>Myocardial stunning/hibernation<br>Epicardial coronary artery disease |
| Toxic damage | Substance abuse, medication, heavy metals, radiation |
| Immune mediated and inflammatory damage | Infectious and non-infectious |
| Infiltration | Malignant and non-malignant |
| Metabolic derangements | Hormonal and nutrial. |
| Genetic abnormaliities | Dilated, hypertrophic and arrhythmogenic cardiomyopathies |
| **Abnormal loading conditions** | |
| Hypertension | |
| Valve and myocardial structural defects | |
| High output states | Anemia, sepsis, thyreotoxicosis |
| Volume overload | Renal failure, iatrogenic fluic overload |
| **Arrythmias** | |
| Tachyarrhythias | Atrial and ventricular atthythmias, |
| Bradyarrhytmias | Sinus node dysfunction, concuction disorders |

***Table 4.*** *Examples of etiologies of heart failure.*

# Prognosis

Even though the prognosis of HF has improved due to new treatments and their implementation during the last 30 years,[2,8] the general outcome of HF still remains unsatisfactory. The one-year all-cause mortality rates for hospitalized and stable/ambulatory patients with HF were 17% and 7% respectively according to the most recent European data (ESC-HF pilot study) and the one-year hospitalization rates were 44% and 32% respectively.[16] Most deaths among patients with HF are due to cardiovascular causes and the all-cause mortality is generally higher in HFrEF compared to HFpEF patients.[16,17]

# Treatment of heart failure

As mentioned in the "introduction", the available treatment options for patients with HF have increased during the last decades with some new available options during the last several years (e.g. the combination of angiotensin receptor blockers and neprilysin inhibitors.[18]) As the study population of this thesis is composed of patients studied between the years 1999 and 2017, with high 5-year mortality rates, the treatment options available by the time of CRT implantation, year 1999 to 2012, will be mainly discussed.

## Physiotherapy and lifestyle

The best way to reduce the burden of a disease is to reduce its' incidence. Regarding HF there are several studies at hand that have shown that HF can be delayed or prevented through interventions aimed at modifying risk factors related to lifestyle. Even though smoking cessation has not been shown to reduce the risk of developing HF, there are evident epidemiological associations to cardiovascular diseases,[19] and as cardiovascular disease is a common cause of HF patients should be advised to stop smoking. Regarding alcohol intake and the risk of new-onset HF, there is a U-shaped correlation with the lowest risk among patients with modest consumption (up to 7 drinks per week).[20] Yet, a greater alcohol intake may trigger development of toxic cardiomyopathy and should therefore be avoided. Regular physical activity reduces the risk of HF and should be recommended to most patients,[21] and as obesity is a risk factor for HF,[22] overweight should be avoided. Still, the impact of treatments for obesity on the development of HF is unknown.[8]

### Drug therapy to prevent heart failure

There is a great deal of evidence showing that appropriate control of hypertension will delay the onset of HF and several drugs are available.[23] Statins used to lower cholesterol levels, reduces the rate of cardiovascular events and mortality and there is some evidence at hand proving that they prevent or delay the onset of HF.[24,25] In patients with cardiovascular disease numerous renin-angiotensin-aldosterone-system (RAAS) inhibitors have been able to reduce the rate of hospitalization for HF and mortality and early interventions to reduce the infarct size of acute ST segment elevation myocardial infarctions (STEMIs) decrease the risk of developing HFrEF.[26] Also, after myocardial infarctions, early initiation of RAAS inhibitors and statins reduces the rate of hospitalization for HF and mortality.[26]

### Pharmacological treatment of heart failure with reduced ejection fraction

Several drugs have been shown to be able to improve clinical status, functional capacity, quality of life (QoL), prevent hospitalization and to reduce mortality in HFrEF patients. Unless contraindicated or not tolerated, neurohormonal antagonists are recommended for the treatment of all of these patients.[8] ACEIs, Mineralcorticoid/Aldosteron receptor antagonists (MRAs) and beta-blockers are examples of such antagonists that inhibits the RAAS and they have all Class 1A recommendation according to the ESC guidelines[8] as they in several randomized controlled studies[7,27,28] have been able to reduce morbidity as well as mortality.

As a common symptom of HF is dyspnea on account of fluid congestion in the lungs, diuretics such as furosemide may be used to relieve such but as no randomized trials have studied diuretics' effects of mortality and morbidity, diuretics should be carefully considered and the aim of the therapy should be to achieve euvolemia with the lowest achievable dose.[8]

## Device therapy

### Implantable cardioverter-defibrillator therapy

In HF patients, especially among those with milder symptoms, a high proportion of deaths occur suddenly and unexpectedly.[29] Some due to malignant ventricular arrhythmias, bradycardias and asystole. Implantable cardioverter-defibrillators (ICDs) are effective in preventing bradycardia and correcting ventricular arrhythmias that are potentially lethal.[30,31] There are different indications for ICD-implantation for primary- and secondary prevention of such cardiac deaths.[30]

### Secondary prevention of sudden cardiac death

An ICD is recommended in patients that have survived a cardiac arrest or experienced an episode of sustained symptomatic ventricular arrhythmia when the intent is to increase survival[8,30] Yet, recommendations according to guidelines clearly stipulate that the patient's view and QoL should be taken into account before a decision is made. Also, survival benefit is uncertain in patients with LVEF > 35% and especially among patients with a high comorbidity burden with other diseases likely to cause a nearby death, ICD-implantation should be considered extra carefully.[30,32]

### Primary prevention of sudden cardiac death

For the primary prevention of sudden cardiac death, guidelines are not as clear and the evidence is less robust.[30] Generally, ICD-implantation should be considered only after optimal medical treatment of HF during at least three months has failed to increase the LVEF > 35%.[8,30] In patients with LVEF > 30%, the evidence is lower as few patients have been included in the randomized studies at hand. The evidence is greater in patients with ischemic etiology of HF compared to patients with a dilated cardiomyopathy and patients with widened QRS-complexes (>130ms) should instead be considered for an ICD with CRT (CRT-D), see below.

## Cardiac Resynchronization Therapy

Signs of a poorly synchronized contraction of the myocardium have been identified as a potential therapy target from the early 1990s. In 1996 Cazeau et. al. published the first report that discussed biventricular pacing in detail. In a small number of patients with severe HF and widened QRS complexes they found that multisite pacing was associated to a rapid and sustained hemodynamic improvement.[33] After initial exploratory studies, such as Cazeau's, a number of prospective multicenter studies on the effect of biventricular pacing have been performed. The design and main findings of a selection the major CRT trials are presented in Table 5.

| Trial (year) | Design | Patients | NYHA Class | QRS ms-inclusion, mean | Primary endpoint | Main findings |
|---|---|---|---|---|---|---|
| MUSTIC-SR (2001)[34] | CRT/OMT | 29/29 | II-IV | ≥150, 174 | 6MWD | CRT improved 6MWD |
| PATH-CHF (2002)[35] | RV/LV/CRT-P | 41 | III-IV | ≥120, 175 | 6MWD, peak V02 | CRT improved 6MWD |
| MIRACLE (2002)[36] | CRT-P/OMT | 228/225 | III-IV | ≥130, 166 | NYHA, 6MWD, QoL | CRT impproved NYHA, 6MWD, QoL |
| MIRACLE-ICD (2003)[37] | CRT-D/ICD | 187/182 | III-IV | ≥130, 164 | NYHA, 6MWD, QoL | CRT improved NYHA, 6MWD, QoL |
| CONTAK-CD (2003)[38] | CRT-D/ICD | 245/245 | II-IV | ≥120, 158 | NYHA, 6MWD, QoL | CRT-D improved NYHA, 6MWD, QoL |
| COMPANION (2004)[39] | CRT-P/CRT-D/OMT | 617/595/308 | III-IV | ≥120, 159 | All-cause mortality or hosp. | CRT-P and CRT-D reduced all-cause mortality and hosp. |
| MIRACLE-ICD II (2004)[40] | CRT-D/ICD | 187/182 | II | ≥130, 166 | NYHA, 6MWD, QoL | CRT-D improved NYHA and QoL |
| CARE-HF (2005)[41] | CRT-P/OMT | 409/404 | III-IV | ≥120, 160 | All-cause mortality or hosp. | CRT-P reduced all-cause mortality and hosp. |
| REVERSE (2008)[42] | CRT-P or D/OMT | 419/191 | I-II | ≥120, 160 | HF clinical response | CRT improved ventricular structure and, NYHA and reduced HF hosp. |
| MADIT-CRT (2009)[43] | CRT-D/ICD | 1089/731 | I-II | ≥130, 162 | All-cause mortality or HF hosp. | CRT-D reduced all-cause mortality or HF hosp. but not all-cause mortality alone |
| RAFT (2010)[44] | CRT-D/ICD | 894/904 | II-III | ≥120, 158 | All-cause mortality or HF hosp. | CRT-D reduced all-cause mortality or HF hosp. |

***Table 5**. A selection of the major CRT trials.*

These trials constitute the foundation of the current ESC guidelines on CRT treatment[12] and the guidelines conclude that

> "There is strong evidence that CRT reduces mortality and hospitalization, improves cardiac function and structure in symptomatic chronic HF patients with optimal medical therapy or ICD alone. In these patients, further research is very unlikely to change our confidence in the estimate of effect".

The ESC indications for CRT in patients with sinus rhythm (SR) are illustrated in Table 6.

| Recommendations | Class [a] | Level [b] |
|---|---|---|
| **1) LBBB with QRS duration >150 ms.** CRT is recommended in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment. [d] | I | A |
| **2) LBBB with QRS duration 120–150 ms.** CRT is recommended in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment. [d] | I | B |
| **3) Non-LBBB with QRS duration >150 ms.** CRT should be considered in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment. [d] | IIa | B |
| **4) Non-LBBB with QRS duration 120–150 ms.** CRT may be considered in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment. [d] | IIb | B |
| **5)** CRT in patients with chronic HF with QRS duration <120 ms is not recommended. | III | B |

***Table 6.*** *Indications for CRT in patients with sinus rhythm according to the ESC. Reprinted and modified with permission from European Heart Journal (2013), 34, pages 2281-329.*

As the name itself implies, CRT is a therapy with the main purpose to restore mechanical synchrony by electrically activating the myocardia in a synchronized manner to achieve resynchronization. In addition to a conventional right ventricle (RV) lead (with or without a right atrial [RA] lead) the CRT pacemaker also has a coronary sinus lead placed for left ventricular (LV) pacing. This allows for simultaneous pacing of the LV and the RV, thereby improving mechanical functioning of the LV.

According to the annual statistic report from the Swedish pacemaker registry, 60 CRT-P and 59 CRT-D implants per million population were performed in 2018[45] and most likely many more patients are eligible for CRT treatment and would benefit from the therapy.[46] In a Swedish registry study from 2014 only 6% out of 30% of patients that had indication for CRT actually received the treatment[47] and underutilization of CRT was also found more recently in another study where the prevalence of CRT was 7% in patients with HF, whereas the prevalence of CRT indication in those without CRT was two to almost four times higher.[48] The cost of a CRT-P is today around 27 000 SEK and of a CRT-D around 50 000 SEK. As a CRT-D compared to a CRT-P does not provide any benefits regarding QoL,[39] the treatment has a low priority according to the Swedish National board of Health and Welfare.[49]

## CRT in patients with atrial fibrillation

According to ESC guidelines, there is a lack of evidence from randomized and controlled trials (RCTs) on patients with AF and CRT.[12] Few patients with permanent AF have been included in such studies[50-52] and the only subgroup of patients with AF in which beneficial benefits have been proven by RCTs are patients with concomitant indications for RV pacing. During the last decades a number of meta-analyses have been performed on CRT recipients with AF[53-55] and European guidelines[12] now stipulate that:

> "Despite the weak evidence – due to lack of large randomized trials – the prevailing opinion of experts is in favour of the usefulness of CRT in AF patients with the same indications as for patients in SR, provided that AV junction ablation is added in those patients with incomplete (<99%) biventricular capture. There are no data regarding NYHA Class II patients."

Yet, patients with AF seem to benefit less from the treatment[53,55,56] and inadequate biventricular pacing (BivP) percentage capture has in several studies been identified as one of the main explanations to the lower effect of CRT in AF patients.[57-60] As mentioned above, current guidelines conclude that a BivP of as near as 100% as possible should be achieved[12] and studies have found that the greatest magnitude of reduction in mortality has been observed among patients with a BivP in excess of 98% of all ventricular beats.[59]

## CRT pacemaker with or without defibrillator

The choice between implanting a CRT with (CRT-D) or without (CRT-P) a defibrillator is difficult and current European guidelines do not provide any strict recommendations due to a lack of proven superiority by trials of CRT-D over CRT-P.[12] No randomized controlled trials have been designed to compare CRT-D and CRT-P with regards to survival benefits. Yet, in asymptomatic or mildly symptomatic patients (NYHA Class I-II) guidelines speculate that there may be reasons to choose a CRT-D. These patients have fewer comorbidities and a higher proportion of sudden- versus non-sudden cardiac deaths[8] and may therefore benefit more of a defibrillator. In a recent meta-analysis of a large number of published CRT trials it was found that the mortality benefit of CRT was mainly driven by a reduction of HF-related death.[61] The CRT and control group did not differ in the risk for sudden cardiac death and current European guidelines conclude that CRT-D is beneficial in all disease states but the benefit appears to be relatively small in end-stage HF.[12] Adapted from the 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy, Table 7 shows the clinical guidance to the choice of a CRT-P or CRT-D in primary prevention.

| Factors favouring CRT-P | Factors favouring CRT-D |
|---|---|
| Advanced heart failure | Life expectancy >1 year |
| Severe renal insufficiency or dialysis | Stable heart failure, NYHA II |
| Other major co-morbidities | Ischaemic heart disease (low and intermediate MADIT risk score) |
| Frailty | Lack of comorbidities |
| Cachexia | |

***Table 7.*** *Clinical guidance to the choice of CRT-P or CRT-D in primary prevention according to the ESC guidelines. Reprinted with permission from the European Heart Journal (2013) 34, pages 2281-329.*

In light of the uncertainties stated above, recent publications have highlighted the need for active risk-stratification in CRT recipients when it comes to the choice between a CRT-D or CRT-P.[62-64] As CRT-P treatment is more cost-effective and associated to a lesser burden of complications[12] there may be a reason to implant a higher proportion of CRT-P. However, if so a critically important consideration will be to accurately determine if a patient with CRT-P has developed an increased risk for malignant arrhythmias during the treatment and therefore is in need of an upgrade to a CRT-D. Studies have recently suggested that diagnostic data from ICD device carry diagnostic information that can be helpful in the management and clinical outcomes in HF patients[65] and such data may therefore be useful in the risk-stratification context of CRT-P recipients.

# Atrial fibrillation

Characterized by disorganized atrial depolarizations that result in an absence of effective contraction of the atria and a rapid, irregular rhythm, AF can cause symptoms of dyspnea, palpitations and angina. Yet, up to 25% experience no symptoms.[66] The AF diagnosis is based on ECG showing irregular ventricular rhythm without consistent P waves. Illustrations of AF and SR with are found in Figure 1 and 2. AF is initially often presented as short self-terminating episodes that over time lasts longer and eventually ends up in more permanent forms of AF.[67]

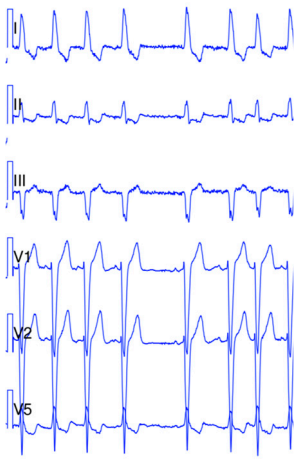


***Figure 1.*** *ECG from a patient with atrial fibrillation.*

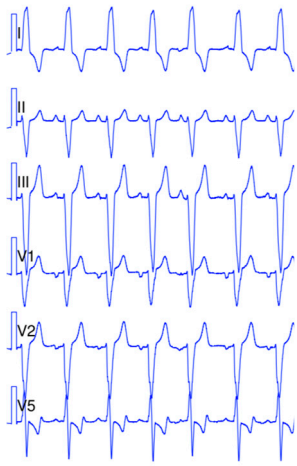


***Figure 2****. ECG from a patient with sinus rhythm.*

## Epidemiology and etiology

In Europe and the USA, one in four middle-aged adults will develop AF[68-70] and current estimations suggest an AF prevalence of 3% in adults.[71,72] AF is the most common heart rhythm disorder and it is more common among older persons[73] and among patients with certain comorbidities such as HF.[74] The prevalence of AF is increasing due to increasing age and conditions predisposing to AF[75] but also due to better detection of silent AF.[76]

Apart from older age and HF there are several other conditions associated with AF. Hypertension,[75] valvular heart disease,[77] coronary artery disease,[75] thyroid dysfunction[78] obesity,[75] diabetes mellitus,[75] chronic obstructive pulmonary disease,[79] sleep apnea,[80] chronic kidney disease,[81] smoking,[82] alcohol consumption,[83] and habitual vigorous exercise many days a week[84] are examples of such.

As HF and AF are linked by similar risk-factors, the prevalence of AF is directly linked to the severity of HF and in HF trials and registries the prevalence of AF ranges from 13-41%. In a European clinical practice registry 23% of patients who received CRT were in AF[85] but higher numbers of up to 50% of patients have been found in other studies of CRT recipients.[55]

# Pathophysiology

## Atrial remodelling

Due to the various etiological factors discussed above, remodelling of the atrial structure is one important mechanism that leads to AF. Enhanced connective tissue deposition and fibrosis because of activation of fibroblasts are important mechanisms of the complex remodelling process.[86-88] Inflammatory infiltrates, fatty infiltrations, myocyte hypertrophy, necrosis and amyloidosis in the atria have been found in patients with AF.[89,90] The structural remodelling causes electrical dissociations between muscle bundles and local conduction heterogeneities.[91] Such may be found on surface ECG[92] and favour re-entry and perpetuation of AF.[93] AF is also associated with atrial dilatation that increases the amount of available atrial tissue leading to more substrate that can accommodate re-entry circuits.[94,95] The structural remodelling occurs before the onset of AF in many patients,[87] and such may therefore indicate that the patient has a higher risk of developing AF. The remodelling may be irreversible[96] and early initiation of treatment is desirable.

Especially in the left atrial appendage, functional and structural changes in the atrial myocardium may cause stasis of blood thereby generating a prothrombotic mileau. Even short episodes of AF lead to atrial damage and expression of prothrombotic factors on the atrial endothelial surface along with activation of platelets and inflammatory cells that contribute to a generalized prothrombotic environment.[97,98]

### Electrophysiological mechanisms of atrial fibrillation

Largely due to downregulation of $Ca^{2+}$-inward current and upregulation of inward rectifier $K^+$ currents,[99,100] AF can provoke shortening of the atrial refractory period and AF cycle length. Yet, structural heart disease tends to prolong the atrial refractory period[101] which illustrates the heterogeneous nature of mechanisms that cause AF in different patients.

Within the pulmonary veins, focal clusters that can trigger AF have been observed, and form the basis for the current practice to electrically isolate the pulmonary veins to treat AF.[102] Both localized re-entry and triggered activity can be involved in the mechanisms of the focal activity.[103,104] Ablation of this source is one established surgical treatment option for AF.[11]

The "multiple wavelet hypothesis" proposed by Moe and Abildskov[105] suggests that AF can be maintained by continuous conduction of several independent wavelets propagating through the atrial myocardium in a chaotic manner. Such will be able to sustain the arrhythmia as long as the number of wavelets is above a critical level. The Maze procedure, another established surgical treatment option for AF,[11] supports this theory.[106]

## Atrial fibrillation related mortality and morbidity

AF is correlated to worse outcomes and among patients aged 45-64 years during a follow-up period of 20 years, AF has been found to be associated to a two-fold increase of all-cause mortality in women and a 1,5-fold increase in men.[107,108] Most deaths are due to cardiovascular events such as HF and stroke. Whereas anticoagulation effectively can reduce the numbers of stroke,[109] death due to HF remains common even in patients with optimal medical therapy.[11,110] Adapted from the ESC guidelines for the management of AF, Table 8 shows a number of events associated with AF. From this table it is quite clear that there are needs for interventions beyond anticoagulation reduce the healthcare burden of AF.

| Event | Association with AF |
|---|---|
| Death | Increased mortality, especially cardiovascular mortality due to sudden death, heart failure or stroke. |
| Stroke | 20–30% of all strokes are due to AF. A growing number of patients with stroke are diagnosed with 'silent', paroxysmal AF. |
| Hospitalizations | 10–40% of AF patients are hospitalized every year. |
| Quality of life | Quality of life is impaired in AF patients independent of other cardiovascular conditions. |
| Left ventricular dysfunction and heart failure | Left ventricular dysfunction is found in 20–30% of all AF patients. AF causes or aggravates LV dysfunction in many AF patients, while others have completely preserved LV function despite long-standing AF. |
| Cognitive decline and vascular dementia | Cognitive decline and vascular dementia can develop even in anticoagulated AF patients. Brain white matter lesions are more common in AF patients than in patients without AF. |

***Table 8.*** *Cardiovascular morbidity and mortality associated with atrial fibrillation Adapted with permission from the European Heart Journal (2016) 37, pages 2893-2962.*

# Device-diagnostics

Device-diagnostics includes the detection of atrial as well as ventricular arrhythmias. CRT devices are equipped with reliable and extensive diagnostic features allowing information regarding the number, duration and overall burden of such. In patients with HF and CRT, studies have shown a high frequency of atrial arrhythmias,[111,112] both symptomatic and asymptomatic. For AF, surrogate markers such as Atrial High Rate Episodes (AHREs) and Automatic Mode Switch (AMS) events have been shown to be reliable as they in a great majority of cases reflect true episodes of AF.[113,114] Yet, intermittent under sensing, electromagnetic interference and far-field R wave sensing by the atrial channel are problems and all AHREs and AMS events may not reflect true episodes of AF. Especially short device-detected AF episodes have been found to be more unreliable.[114] By reviewing stored electrograms to confirm AF, such problems can be ruled out.

Ventricular High Rate episodes (VHRs) is another surrogate marker from device-diagnostics. VHRs represents episodes of non-sustained ventricular tachycardias (NsVT). The prognostic impact of episodes of ventricular tachycardias or ventricular fibrillations (VT or VF) and appropriate shocks in patients with ICD is well described[115] but there are many uncertainties regarding the importance of

VHRs in patients with CRT-P. If such episodes are associated to a higher risk of overall mortality or potentially deadly ventricular arrhythmias is not fully established.

CRT device-interrogation also provides estimates of achieved BivP percentage during follow-up. The importance of such episodes has previously been described in this thesis under the headline "CRT in patients with atrial fibrillation".

# ECG-based risk markers

A 12-lead surface ECG can be analysed in a number of ways regarding the rhythm, the frequency and the durations as well as the morphological aspects of the specific components of the ECG. The P wave reflects the activity of the atria whereas the QRS complex reflects the activity of the ventricles of the heart. Today there are a number of automatic, digital analyses at hand, such as the Glasgow algorithm,[116] that can contribute to an accurate and quick analysis of the ECG.

Previously a number of studies have assessed the ECG components reflecting the activity of the ventricles. The QRS complex has been found to be able to provide prognostic information in CRT recipients[117] and attempts to estimate the myocardial scar burden have been performed by automatic analyses of the QRS complex.[118] The QRS complex includes important information regarding the activity of the ventricles of the heart and in current guideline indications for CRT treatment a wide QRS complex is obligate for CRT and reflects electrical as well as mechanical dyssnychrony.[12]

The significance of atria-related markers with regards to prognosis has also been explored and analyses of the P wave have previously been able to provide valuable prognostic information.[92,112,119-125]

In this thesis we evaluate the prognostic importance of interatrial block (IAB) and abnormal P-wave terminal force in lead $V_1$ (abnormal $PTFV_1$) described below.

# Interatrial Block

IAB is an electrocardiographic (ECG) sign of an interatrial conduction abnormality defined as a P-wave duration (PWD) exceeding 120 ms. If, in addition to P-wave prolongation, biphasic (±) P waves are found in inferior leads it is described as an advanced IAB (aIAB). IABs reflect a presence of delay between the right and left atria and can appear with or without atrial enlargement.[126] As in 2/3 of cases, the primary left atrial breakthrough point is in the Bachmann bundle area,[127] it has been considered that when there is a delay of conduction in some part of the Bachmann bundle zone,

IABs appears.[128] The abnormal P-wave morphology in aIABs reflects a retrograde left atrial activation via muscular connections in the vicinity of the coronary sinus.[129,130] Adapted from Bayes de Luna et. al,[126] Figure 3 illustrates the different IAB types.

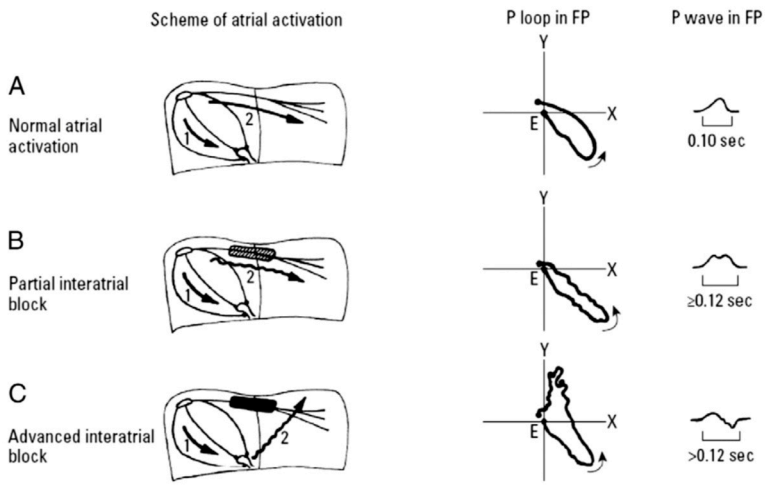


***Figure 3***. *Scheme of the atrial conduction as seen in (A) No IAB, (B) pIAB and (C) aIAB along with an illustration of the P loop and the P wave as seen on ECG in the frontal plane (FP). Reprinted from Interatrial Blocks. A separate entity from left atrial enlargement: a consensus report, Bayes de Luna et. al., Journal of Electrocardiology (2012), 45, pages. 445-51, with permission from Elsevier.*

Previous studies reported that the prevalence of IAB is higher among older patients with more comorbidities and that it is associated with a more severe underlying heart disease. In hospitalized patients, IAB is common and several studies have reported an IAB-prevalence of over 40%.[131,132] Among healthy young men however, IAB was present in only 9% of those younger than 35 years and in 5% of those under 20 years.[133] In patients over 100 years though, IAB was found in 46% of subjects. Advanced IAB is far less common than pIAB[126,134] and the prevalence of aIAB varies greatly depending on the clinical context. It has been reported in around 1% of patients with mitral valve disease,[135] in 14% of patients undergoing coronary bypass graft surgery,[136] in 17% of patients admitted with HF[137] and in 17% of ischemic stroke survivors.[125]

Prolonged PWD (pIAB) as well as morphological abnormalities in inferior ECG leads (aIAB) are associated with structural abnormalities of the atrial wall such as fibrosis due to ageing and cardiovascular comorbidities.[121,138,139] Examples of predisposing factors to IAB are hypertension, coronary artery disease, hypercholesterolemia, diabetes mellitus and hypertrophic cardiomyopathy.[92,126,138,140] All these factors cause inflammation leading to structural abnormalities of the atria that in turn contributes to conduction abnormalities visualised on ECG. In hypertension for example, there is increased

renin-angiotensin-activation with elevated levels of angiotensin II,[140] a mediator known to be associated with atrial remodelling and fibrosis.[141] Conduction velocity through the myocardium is dependent on the conduction of the action potential and from animal studies it has been found that the $Na^+$ channels are affected by the complex remodelling process.[140] As the $Na^+$ channels are important determinants of the voltage-gated ionic conductance, a lower number of $Na^+$ channels or inactivation of $Na^+$ channels due to mentioned predisposing diseases, may cause to a slower conduction velocity.[140]

The association of IAB and atrial arrhythmias such as AF is well known[112,123,142,143] and sometimes referred to as Bayes syndrome.[126] Its ability to predict total mortality is less established and few studies have assessed the diagnostic value of IAB in patients with severe HF. Yet, IAB has been correlated to non-sudden cardiac death in patients with CRT and mild HF[144] and predictive of total mortality in primary care patients.[123] Advanced IAB is most often found among the most severely ill patients and has been associated to worse outcomes compared to pIAB based on the data from mixed or relatively healthy cohorts.[123,126]

# Abnormal P-wave terminal force in lead $V_1$

Abnormal p-wave terminal force in lead $V_1$ ($PTFV_1$), defined as a terminal negative component of the P wave of >0.04 mm·s in lead $V_1$, is another established ECG-abnormality. It has been shown to be predictive of atrial arrhythmias as well as poor outcomes in patients with stroke, in patients with myocardial infarction and in CRT recipients with mild HF and LBBB.[120,145-147] Abnormal $PTFV_1$ was first introduced by Morris et al. and has been proven to be a specific indicator of left atrial enlargement with modest sensitivity compared to echocardiographic measurements.[148] It has also been shown to be correlated to higher left ventricular end-diastolic pressures.[149] During SR in the healthy heart, the main conduction route from the right to the left atrium is often mainly mediated by interatrial connections close to the pulmonary veins of the back side of the heart[150] resulting in a posterior to anterior propagation of the vector and an upright P wave in the right precordial leads. As the connection routes on the back side of the heart has been found to be thinner and less developed compared to the Bachmann bundle[151] it has been suggested that an abnormal $PTFV_1$ seen on ECG is due to that the P wave can no longer propagate on the back side of the heart, leaving Bachmann's bundle as the only remaining interatrial propagation route.[92] The prevalence of abnormal $PTFV_1$ in middle-aged patients without cardiac disease has been found to be 6,4%[119] whereas a higher prevalence of around 18% has been noted in CRT recipients with mild HF.[147]

To our knowledge the prognostic importance of IAB and abnormal $PTFV_1$ has not been studied in CRT recipients with advanced HF.

# Aims

The general purpose of this thesis was to find non-invasive predictors of CRT outcome.

The specific aims of the papers were:

- **Paper I:** To explore if device information regarding occurrence of VHR episodes could add prognostic value in patients with CRT-P and to see if there is a correlation between early post-implant occurrence of such episodes and a higher risk of cardiac arrest within the first 5 years of CRT treatment.
- **Paper II:** To assess the prognostic impact of AF, both pre-procedural and device-detected, in patients with CRT using a composite of death, heart transplant (HTx) and appropriate shock therapy. The study also sought to investigate if a higher cumulative burden of AF during CRT treatment could be associated to a worse outcome.
- **Paper III:** To evaluate the prognostic impact of achieved BivP percentage during the first year of CRT-treatment in patients with AF on the risk of death or HTx at 10 years of follow-up. The secondary objective was to assess the one-year incidence and prognostic importance of new onset device-detected AF.
- **Paper IV:** To analyze the prognostic impact of pre-procedural IAB and abnormal $PTFV_1$, and to assess if there are any correlations between such ECG findings and the risk of new-onset AF or total mortality, or total mortality alone, during a follow-up period of 5 years in patients with HF and CRT.

# Methods

## Study population

All studies in this thesis were based on a patient material gathered from the Arrhythmia Clinic at Skåne University Hospital (SUS) in Lund, Sweden. The local ethics board in Lund approved the project (Dnr 2013/236 and 2016/861).

Consecutive patients that successfully received a functional CRT-device according to the current ESC guidelines between the years 1999 and 2012 were included in the study cohort. General exclusion criteria were age below 18, CRT implantation due to other reasons than HF and explantation within the first two months of CRT treatment. In total the base cohort included 796 cases and an overview of respective study's population is presented in Figure 4.

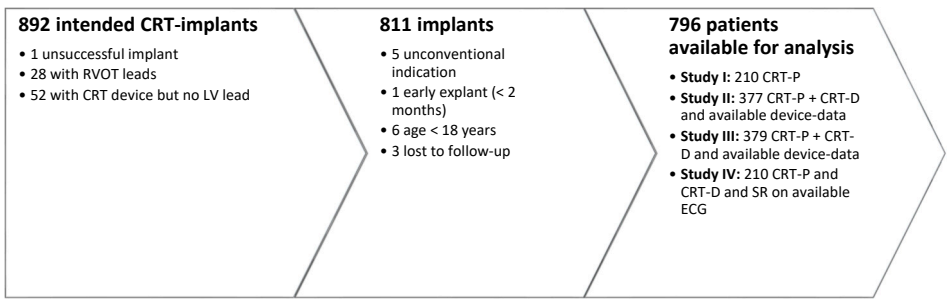


***Figure 4**. Flowchart describing patient selection for the cohort and the four studies.*

With regards to device-detected data, information regarding such was only gathered from patients with a potential CRT follow-up of 5 years to May 2013, the first time data was retrieved from the Swedish Cause-of-Death registry and the Swedish National Patient Registry (SNPR, see below). Paper IV does not include any device-detected data and could therefore also include patients implanted after May 2008. Yet, it only included patients with an available and interpretable ECG showing SR close to the date of CRT-implantation, why many of the 796 patients had to be excluded from that paper as well.

## Data sources

All patients' electronic medical records were retrospectively reviewed to gather pre-procedural characteristics including comorbidities, previous medical history, medications, echocardiographic and biochemical data using the hospitals electronic records system (Melior © Cerner Sverige).

From the Swedish Cause-of-Death registry and from the SNPR follow-up data was obtained that included the cause of death as well as pre- and postoperative diagnoses. This data was cross-checked with the data from the medical records and the Swedish Pacemaker Registry. For paper I, II and III data from the Swedish Cause-of-Death registry and the SNPR was collected in May 2013 and for paper IV another four years of follow-up was added as data was obtained once more from the same sources in September 2017.

With regards to AF-diagnosis an extra assessment was made to find any previously undiagnosed cases of AF in paper III and IV. In paper III all available preoperative digital ECGs among patients with no AF-history according to the medical records or the registries specified above were manually reviewed to find any additional pre-procedural AF-cases. In paper IV all available digital pre- and postoperative ECGs, in where the digital analysis interpreted the rhythm as AF, were manually reviewed to confirm the analysis. If AF was confirmed on any pre- or postoperative ECG in a patient with no previous AF-history, that patient was considered to have a pre-procedural diagnosis of non-permanent AF or new-onset AF during CRT follow-up. All ECGs were assessed from the regional electronic ECG databases (MUSE Cardiology Information System v9, GE Healthcare, Chicago, Illinois and Infinity Megacare ECG management system, Dräger, Houston, Texas) that contain all ECGs taken in the hospital catchment area, including primary care facilities, starting from the year 1988.

Follow-up device-data was retrieved from medical records of CRT-interrogations at regular visits at the Arrhythmia Clinic at Skåne University Hospital. These visits contained information regarding device-detected AF, achieved BivP percentage, VHR episodes, antitachycardia pacing (ATP) therapies, appropriate ICD-shocks as well as CRT-complications and upgrades/downgrades from/to CRT with or without defibrillator therapy.

## Erratum

When follow-up data on mortality data was obtained for paper I, an error in the merge process of files received from the Swedish Cause-of-Death registry resulted in erroneous omission of 47 deaths during the entire follow-up period. This was later corrected, and an erratum has been published for the study.[152]

# Outcome measures

Different outcome measures have been used for the different papers in this thesis. Respective paper's outcomes are:

*Paper I:*

Primary outcome: death at 5 years after CRT-implantation.

Secondary outcome: death during the entire follow-up period.

*Paper II:*

Primary outcome: a composite of death, HTx or appropriate ICD-shock therapy (whichever came first) during the entire follow-up period.

*Paper III:*

Primary outcome: death or HTx at 10 years after CRT-implantation.

*Paper IV:*

Primary outcome: new-onset AF, death or HTx at 5 years after CRT-implantation.

Secondary outcome: death or HTx at 5 years after CRT-implantation.

## Study population

*Pre-procedural patient characteristics*

Data was retrospectively obtained from consecutive patients receiving CRT-P or CRT-D device at SUS between the years 1999 and 2012. These patients were identified through a registry. Data regarding demographics, comorbidities, medications and cardiac findings at CRT implantation was assessed by manual review of medical records and this data was cross-linked with the SNPR. Patients fulfilling contemporary ESC guideline indications for CRT[12] were included.

*Data during CRT follow-up*

Data from routine CRT device interrogations after CRT implantation were assessed from medical records. Information regarding AMS events, AHREs, VHRs, achieved BivP percentage, ATP-events and ICD-shocks as well as complications and "upgrades" from CRT-P to CRT-D or inactivation of the ICD was evaluated by reviewing these interrogations. Data regarding AF during CRT follow-up was obtained from the device-diagnostic surrogate variables AMS events and AHREs. The date of the first AMS event and/or the first AHRE was noted. The cumulative burden of AHREs and the achieved BivP percentage was obtained from the first year of CRT follow-up. Episodes of AMS events, AHREs and BivP percentages

were not confirmed by reviewing device electrocardiograms but by clinicians evaluated and if a notation of an inappropriate device-interrogation was found, that was taken into consideration and our evaluation of the device-data relied on the clinician's interrogation.

## Definitions of the ECG abnormalities IAB and abnormal $PTFV_1$

See Table 9 for the definitions of the analyzed ECG abnormalities.

| Parameter | Definition |
|---|---|
| No IAB | PWD<120ms |
| Partial IAB | PWD≥120 ms, positive P waves in leads II and aVF |
| Advanced IAB | PWD≥120 ms and biphasic (±) or negative P waves in leads II or aVF |
| Abnormal $PTFV_1$ | $PTFV_1$> 0.04 mm·s |

***Table 9.*** *Definitions of the ECG abnormalities IAB and abnormal $PTFV_1$.*

The definition of IAB[126] was established on the notion that aIAB diagnosis should primarily be based on leads II and aVF and that isolated abnormal morphologies in lead III is not sufficiently specific for aIAB.[153] Illustrations of the different IAB types are found in Figure 5 and an illustration of an ECG with abnormal $PTFV_1$[154] is found in Figure 6.

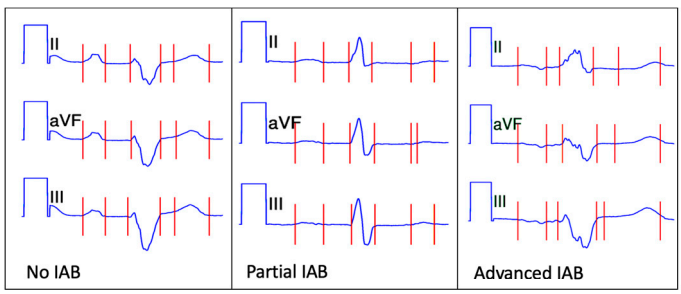


***Figure 5.*** *Illustration of the IAB types.*

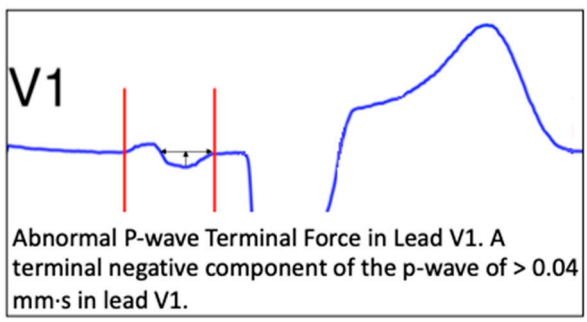


***Figure 6****. Illustration of abnormal $PTFV_1$*

## Statistics

As the project focused on finding non-invasive time-dependent predictors of CRT outcome, Cox regression analysis (proportional hazards modelling) was used in all studies. For binary outcomes, logistic regression modelling was also used. Some papers included univariate Cox regression analyses and all papers included multivariate Cox regression analyses to calculate possible independent predictors. The Kaplan Meier method was used to compare survival over time between groups and the log-rank test to statistically analyze differences between groups.

Histograms and the Kolmogorov-Smirnov test were used to evaluate if continuous data were normally distributed or not. Non-continuous and continuous variables not normally distributed were reported as median ± quartiles (IQR). Continuous, normally distributed variables were reported as mean ± standard deviation (SD). The t-test was used to analyse differences among normally distributed samples, the Mann Whitney u-test to analyse differences among not normally distributed samples and the Pearson chi-square test to compare categorical variables. To evaluate if distributions were the same across groups, the Kruskal–Wallis test was used. In all studies, a two-sided p-value of $< 0.05$ was considered significant. SPSS Statistics for Macintosh, version 22-25 (IBM Corp., Armonk, NY) was used for all data-collection and statistical analyses.

# Results

## Study population

In the base cohort 796 patients were available for analysis but as the inclusion criteria among the different papers varied, the papers' cohorts are different. Yet, as all patients from the base-cohort were implanted according to contemporary guidelines by the time of implantation all papers constitute a 'real-life' CRT population. Except from the fact that paper I only included CRT-P patients and paper IV only patients with CRT-P or CRT-D but no pre-procedural history of AF, there were not many significant differences regarding baseline characteristics between the papers. Yet, the patients included in paper IV had less symptomatic heart disease, more often LBBB and more often received a CRT-D. A selection of the baseline characteristics of the included papers are presented in Table 10.

| Parameter | Paper I | Paper II | Paper III | Paper IV |
|---|---|---|---|---|
| Number of included patients | 210 | 377 | 379 | 210 |
| Median age, years | 72 | 71 | 71 | 67 |
| Male | 81% | 85% | 85% | 80% |
| NYHA Class III or IV | 93% | 90% | 91% | 70% |
| Pre-procedural AF history | 49% | 49% | 54% | 0% |
| Ischemic heart disease | 60% | 57% | 57% | 55% |
| Median LVEF | 22 | 22 | 22 | 25 |
| LBBB | 66% | 62% | 62% | 80% |
| Median QRS duration, ms | 168 | 170 | 170 | 170 |
| CRT-P implanted | 100% | 74% | 74% | 51% |

***Table 10.*** *A selection of baseline characteristics of the included papers.*

# Paper I

In all 220 patients with CRT-P comprised the study cohort of paper I. Occurrence of VHR episodes during the first year of CRT-treatment was noted in almost 14% of patients. Besides from the fact that patients with VHR were significantly older, no other clinically relevant significant differences regarding baseline characteristics could be observed between groups.

The overall 5-year mortality was 52%; 77% for patients with VHR and 48% for patients without VHR (Figure 7). The paper did not find any correlation between VHR episodes and a higher risk of death from cardiac arrest. Any VHR episode within the first year of CRT treatment was associated with higher mortality at 5 years of follow-up with an adjusted OR of almost 10 (p≈0.02). The occurrence of VHR episodes was also associated with a higher mortality rate during the entire follow-up period.

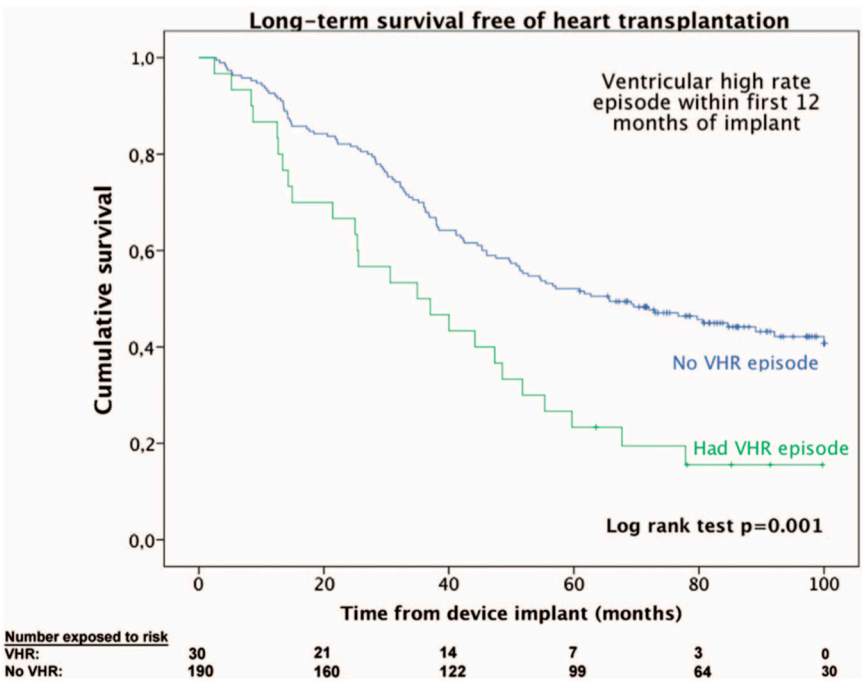


***Figure 7.*** *Kaplan Meier analysis of long-term survival comparing patients with or without VHR episode(s) within the first year post-implant.*

As previously described an erratum[152] has been published for this study and some results therefore changed but as no differences regarding the 5-year outcome was found when comparing the new complete death dates to the older incomplete dates the study's main results remained. However, during the entire follow-up period 182 (83%) instead of 132 patients (60%) died but the association regarding the occurrence of VHR episodes and a higher mortality rate during the entire follow-up period remained.

# Paper II

In paper II, 377 patients with CRT-P or CRT-D treatment were included (median age 71 years, 85% male, 62% LBBB, 170ms median QRS, 22% LVEF, 57% ischemic etiology, 74% CRT-P).

Forty nine percent of patients had a diagnosis of AF prior to CRT-implantation and pre-procedural AF was associated to a worse outcome. No differences in outcome could be observed when comparing patients with non-permanent AF to patients with permanent AF (Figure 8). Among the 194 patients without a preoperative AF diagnosis, 132 patients qualified for the analysis of the new-onset AF in the first-year post-implant. New-onset AF was found in 25% of patients and was not associated to an inferior outcome.

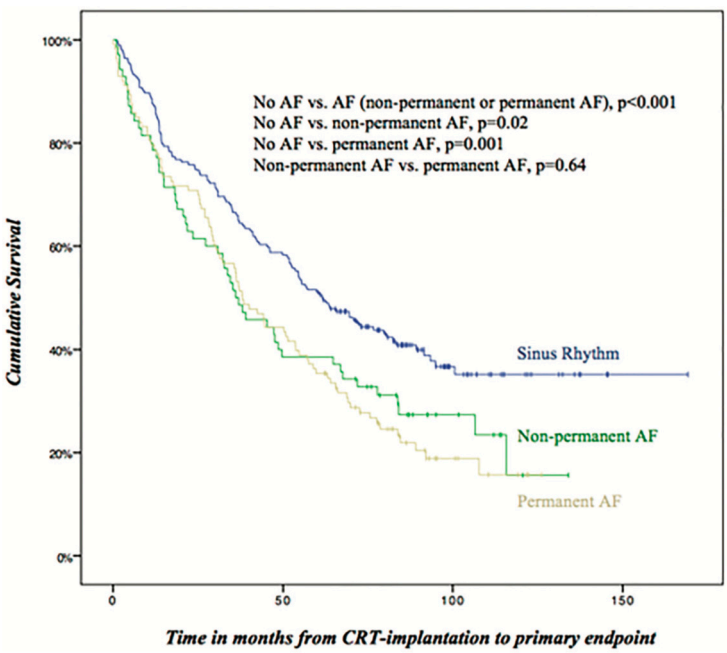


***Figure 8.*** *Kaplan Meier analysis comparing patients with SR, non-permanent AF and permanent AF".*

In adjusted multivariate analysis, the cumulative burden of device-detected AHREs during the first year of CRT treatment was an independent predictor of the composite primary endpoint with a HR of 1.1 for each 10% increased burden of AHREs. Other independent predictors were ischemic etiology of HF and LVEF. Preoperative AF was not significantly associated to the composite endpoint in adjusted analysis.

# Paper III

This study included 379 consecutive patients with CRT-P or CRT-D treatment (median age 71 years, 85% males, 62% LBBB, 170 ms median QRS, 22% LVEF, 57% ischemic etiology, 74% CRT-P). The population was basically identical to paper II but with some differences worth mentioning. Before publication of paper III a more thorough exploration of the medical records was made and the prevalence of pre-procedural AF (according to the combined sources of medical records and the SNPR) was therefore higher compared to the prevalence in paper II. Also, the review of pre-procedural ECGs revealed information about AF-history for another two patients where no information regarding AF-history was found from medical records or the SNPR why these two patients previously had been excluded from paper II.

Furthermore, the manual assessment of all available ECGs prior to CRT implantation among all patients without AF history according to the SNPR or medical records ($n = 190$) revealed further 17 AF-cases and after combining the three sources 54% of patients were found to have pre-procedural AF history.

Patients with AF history were older and achieved less satisfactory BivP compared to patients with no AF. In total, 65% reached the endpoint during follow-up, 73% of patients with AF-history and 54% of patients with no AF-history. No significant differences in outcome were found when patients with non-permanent AF and permanent AF were compared (Figure 9). No significant correlation between the pre-procedural AF history and death from any cause at 10 years of follow-up was observed in a multivariate model adjusted for age, ischemic etiology, LVEF, LBBB and NYHA Class (HR 1.26, 95%CI 0.93–1.70, p-value = 0.133).

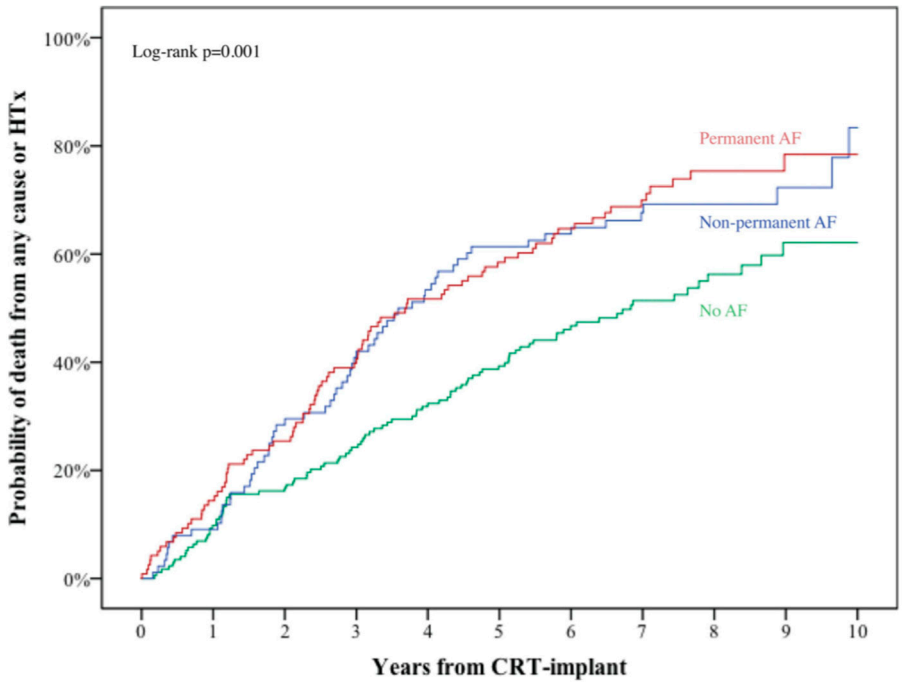


***Figure 9***. *Kaplan Meier analysis, comparing patients with a history of no AF, non-permanent AF and permanent AF before CRT-implant.*

In total, 144 (83%) of patients with no pre-procedural AF history had sufficient data to be included in the analysis regarding new-onset device-detected AF. Of them had 22% device-detected AF during the first year of CRT treatment. New-onset AF during was not significantly associated with the outcome (HR 1.65, 95%CI 0.89-3.09, p=0.12) in multivariate analysis adjusted for age, pre-procedural AF, NYHA Class I/II compared to III/IV, LVEF, LBBB and ischemic etiology of HF at CRT implantation.

Of all patients, 254 (67%) had sufficient follow-up information to be included in the analyses regarding the association of BivP with prognosis. Of those, 35% had BivP ≤98% during the first year of follow-up. Patients with AF had significantly less BivP. There were no significant differences regarding the demographics, medications or clinical characteristics at CRT implantation when patients with AF and BivP ≤98% and patients with AF and BivP >98% were compared. Also, no difference in the heart rate at baseline could be found (p = 0.57).

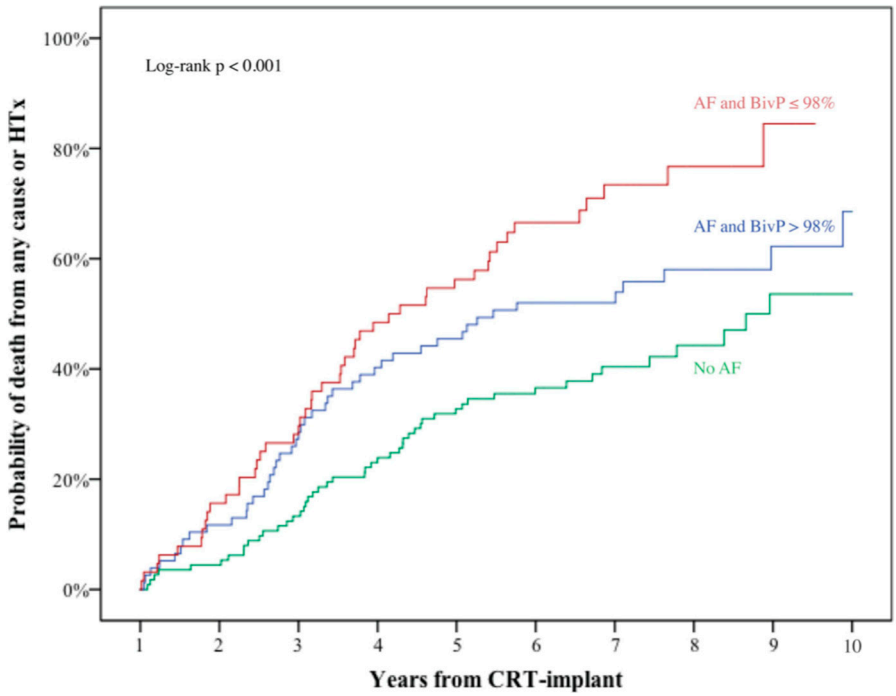


***Figure 10.*** *Kaplan Meier analysis, comparing patients with No AF-history one year after CRT implantation, AF-history one year after CRT implantation and BivP > 98% during first year of follow-up and AF-history one year after CRT implantation and BivP ≤98% during first year of follow-up.*

At one-year of follow-up, BivP ≤98% in patients with either permanent or non-permanent AF was associated with a worse outcome compared to patients with no AF (Figure 10) and was independently associated with the outcome (HR 1.93, 95%CI 1.23-3.03, p=0.005), whereas AF patients with BivP >98% had similar prognosis compared to patients with no AF (HR 1.42, 95%CI 0.89-2.26, p=0.14). These results remained in a sub-analysis of only patients with CRT-P.

# Paper IV

Paper IV included 210 patients who did not have AF history prior to CRT implantation and who had an ECG available for analysis showing SR close to the date of CRT implantation. Partial IAB was found in 34% of patients and aIAB in 11% of patients. Twenty-eight percent of all patients had abnormal $PTFV_1$ and abnormal $PTFV_1$ was more common among patients with IAB.

In 5 years from CRT implantation, 72 patients (34%) died, 47 patients (22%) had new-onset AF and 3 patients (1%) were heart transplanted.

IAB was associated to a higher risk of the primary endpoint of new-onset AF, death or HTx but patients with aIAB did not have an inferior prognosis compared to patients with pIAB (Figure 11). IAB was also associated to a higher risk of death from any cause or HTx. In adjusted analysis, IAB was significantly associated with the risk of the primary as well as the secondary endpoint (Table 11). Separate analyses of pIAB and aIAB alone also revealed significant correlations to both endpoints but no significant outcome differences were observed when comparing patients with pIAB and aIAB (Table 11).

| Parameter | Endpoint AF/death/HTx | | | Endpoint death/HTx | | |
|---|---|---|---|---|---|---|
| | Adjusted HR* | 95% CI | p-value | Adjusted HR* | 95% CI | p-value |
| IAB vs. No IAB (n=182) | 1.88 | 1.22-2.89 | **0.004** | 2.05 | 1.23-3.41 | **0.006** |
| pIAB vs No IAB (n=163) | 1.86 | 1.16-2.97 | **0.010** | 1.88 | 1.08-3.27 | **0.026** |
| aIAB vs. No IAB (n=122) | 2.39 | 1.16-4.92 | **0.018** | 2.44 | 1.08-5.52 | **0.032** |
| aIAB vs. pIAB (n=79) | 0.91 | 0.43-1.94 | 0.804 | 1.07 | 0.45-2.52 | 0.878 |
| Abnormal $PTFV_1$ vs. normal $PTFV_1$ (n=182) | 1.09 | 0.69-1.73 | 0.707 | 1.16 | 0.67-1.99 | 0.598 |

***Table 11.*** *Multivariable Cox-regression analyses. Time from CRT implantation. Follow-up is 5 years.*
**Adjusted for age, NYHA Class, ischemic etiology of HF, LBBB, LVEF, CRT-P vs. CRT-D*

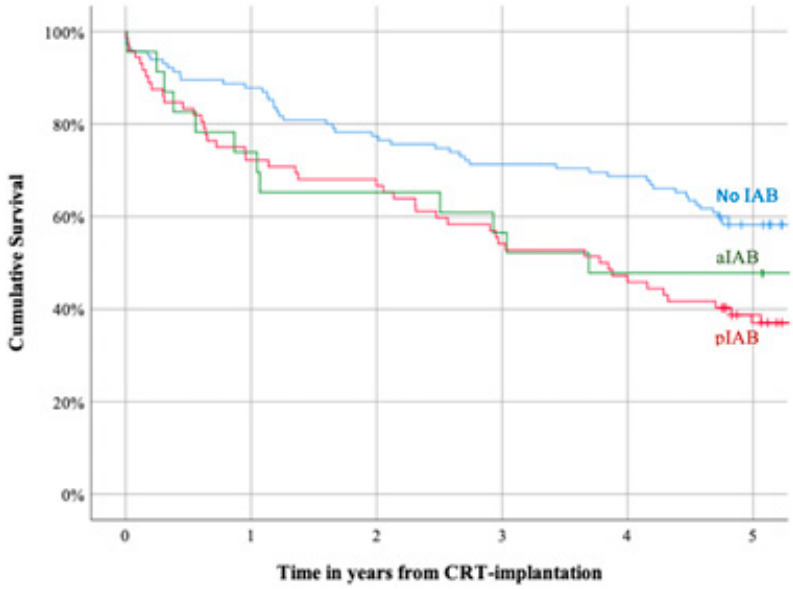


***Figure 11.*** *Kaplan Meier plot comparing patients with No IAB, to patients with either pIAB or aIAB. Endpoint new-onset AF, death or HTx. Log-rank p=0.013.*

Abnormal $PTFV_1$ was not correlated to the primary or the secondary endpoint (Figure 12, Table 11).

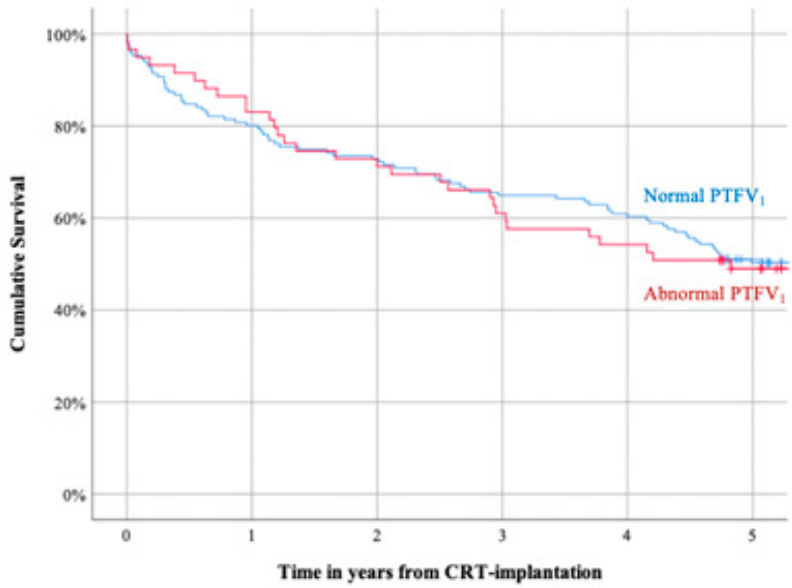


***Figure 12****. Kaplan Meier plot comparing patients with normal $PTFV_1$ to patients with abnormal $PTFV_1$. Endpoint new-onset AF, death or HTx. Log-rank p=0.869.*

A Forest plot of the adjusted multivariate analysis to the primary and secondary endpoint is found in Figure 13.

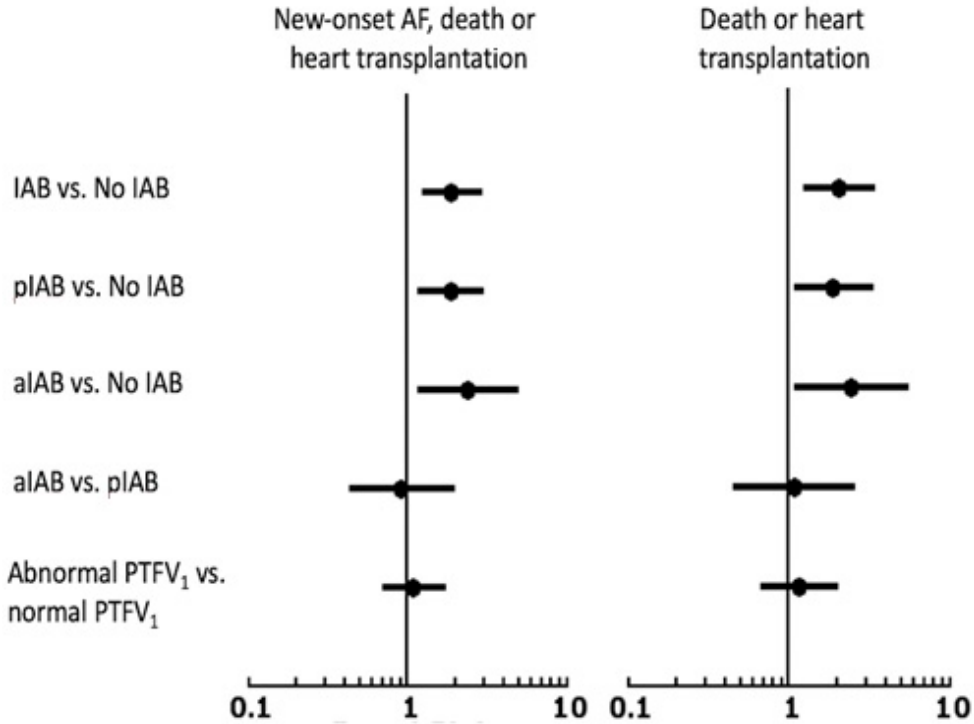


***Figure 13.*** *Forest plot of the adjusted multivariate analysis found in Table 11.*

# Additional analyses and results

To explore if the main results from paper II and III remained if the follow-up period was shortened to 5 years from CRT implantation, additional analyses were performed. It was also explored if the results remained in paper II and III if the multivariate analyses were performed and adjusted for the same variables as in paper IV.

In paper II, the cumulative burden of AHREs during the first year of CRT follow-up remained significantly associated to the combined endpoint of death, HTx or appropriate shock therapy in the univariate analysis (HR 1.1, 95% CI 1.0-1.1, p-value=0.003) but not in the multivariate analysis if the Cox analysis was performed as described in paper II if the follow-up period was shortened to 5 years from CRT implantation. However, when the multivariate analysis was performed as described in paper IV and adjusted for the same parameters as in paper IV, the cumulative burden of AHREs during first year of follow-up turned out as an independent predictor of the combined endpoint with HR 1.05 for each 10% increase in post-implant burden of AHREs (95%CI 1.0-1.1, p=0.032).

In paper III, AF by one year after CRT implantation along with a BivP ≤98% during first year of follow-up remained a significant predictor of the combined endpoint of death or HTx in 5 years follow-up from CRT implantation in the multivariate analysis and was correlated to a worse prognosis compared to patients with no AF by one year of follow up if the Cox analysis was performed as described in paper III (HR 1.9, 95% CI 1.1-3.2, p-value=0.016). AF and BivP >98% first year of CRT treatment was not significantly correlated to a worse prognosis compared to no AF patients by 5 years of follow-up (HR 1.5, 95%CI 0.9-2.5, p=0.155). The multivariate analysis was also performed and adjusted for the same parameters as in paper IV and AF and low BivP remained an independent predictor of death or HTx in that analysis as well (HR 1.9, 95%CI 1.1-3.2, p=0.017) whereas patients with AF and high BivP did not have a worse outcome as compared to no AF patients.

# Discussion

## A history of atrial fibrillation before CRT implantation

### Prevalence

We found a high number of patients with pre-procedural AF, considerably higher compared to most earlier observations of CRT recipients.[12,53,55,85,155] This may be due to our thorough review of medical records cross-linked with the SNPR that previously have been found to be a reliable source of information regarding AF.[156] Furthermore, some additional AF cases were found in paper III after a manual review of a high number of pre-procedural ECGs and it is reasonable to believe that data collection from a number of different sources contributed to higher AF detecting rate. Also, the fact that an additional 17 AF cases was found after the manual ECG review suggest that the prevalence of non-permanent AF history may be underestimated in CRT recipients. In summary. we believe that the AF prevalence reported in our CRT cohort reflects the population's true pre-procedural AF prevalence well and that it is in line with what one would expect in a severely symptomatic cohort of advanced HF patients.

### Prognostic impact

The results from our studies are in agreement with previous findings regarding the association of AF-history and worse clinical outcomes in CRT recipients.[12,53,157,158] It is today well established that patients with AF have an inferior prognosis.[8,11] In paper II and III, AF was strongly associated with worse outcomes in univariate analysis but in multivariate, adjusted analysis, AF did not independently predict poor outcomes. In line with previous studies, our findings indicate that AF should only be regarded as a marker of a more severe underlying heart disease and that there is no causality-link between AF and the poorer outcome observed. Patients with permanent AF do not seem to have an inferior prognosis compared to patients with non-permanent AF. Even though the study may have been underpowered to observe any significant prognostic differences in hard endpoints, the Kaplan Meier curves were crossed with basically no separation, and it is consequently unlikely that any differences would be noted in a higher number of patients. Thus, from our

results it seems as if even patients with a history of only occasional AF episodes before CRT implantation have a higher likelihood of adverse outcome during treatment. Pre-procedural AF is important to identify and carries prognostic information regardless of non-permanent or permanent type.

## New-onset device-detected atrial fibrillation

As the prevalence of AF is highly correlated to the severity of HF,[11,74] a high AF-incidence in our registry-based study cohort is expected. Our results are in agreement with previous observations of CRT recipients[111,112] and indicate that findings of device-detected AF among patients with advanced HF is very common with high incidences during early follow-up. Yet, our results imply that clinicians should not overreact to short such episodes as we in neither study II nor III found any associations with worse outcomes. Our findings are in line with some previous studies were short device-detected AF episodes have not been found to be associated to worse outcomes such as HF, stroke, hospitalization or mortality.[159] However, the results from previous studies are inconclusive but as the definitions of device-detected AF, as well as the monitoring periods have varied, it is difficult to make comparisons and conclusions.[111,160-164] It is also important to recognize that we found a very low cumulative burden of AHREs among our patients and that the study may have been underpowered to find associations of device-detected AF and worse outcomes. Only 9 of the 33 patients with new-onset AF in paper II had clinically recognized AF in medical records. This may suggest that most episodes were asymptomatic and that the physician may not have identified the episode as clinically relevant or that the physician reviewed the intracardiac electrogram of the episode and thereafter concluded that the episode did not reflect true AF. During this time-period, guidelines had no clear recommendations on how to handle short device-detected AF episodes but as our patients had regular follow-up visits at a cardiology clinic, we believe that it is unlikely that episodes of device-detected AF with "clinical relevance" would be ignored and a proper management of such may explain why we were not able to observe any prognostic differences between the groups. Nevertheless, an obvious limitation to our studies was that we did not review any electrograms with regards to device-detected AF, something peer-reviewers have criticized us for. Yet, we can conclude that AHREs and AMS events seldom resulted in a clinical diagnosis of AF in our cohort of patients.

In September 2017 a consensus document regarding device-detected subclinical atrial tachyarrhythmias was published.[165] In summary there are still many uncertainties regarding such episodes but current recommendations suggest that oral anticoagulant (OAC) treatment should be considered in patients with a total duration of AF burden of >5.5 hours on any given day. However, it also stipulates that in patients with extra high risk of stroke, lower durations may merit OAC and the

clinical importance of short device-detected AF episodes remains undetermined. The high degree of uncertainty regarding these frequent episodes further underlines the need of more studies, especially in patients with a high number of comorbidities.

# Atrial fibrillation during treatment with CRT

## The prognostic impact of the cumulative burden of atrial fibrillation

As opposed to short single episodes of device-detected AF, the cumulative burden of AHREs during first year of CRT treatment was an independent predictor of a poorer outcome in our cohort of patients. The results indicate that CRT recipients with severe HF may benefit from a rhythm-control strategy. As CRT recipients represent a special population and as the treatment itself can potentially change hemodynamics, that in turn can result in myocardial remodelling over time,[166] it is particularly difficult to compare CRT recipients to others, especially to the cohorts in the AFFIRM[167] and RACE[168] studies that current European guidelines of AF[11] to a great extent rely on.

Optimum rate-control, maintenance of SR (by cardioversion, lung vein isolation or pharmacotherapy) or atrioventricular junction (AVJ) ablation with permanent pacing constitute some of the management options for patients with AF and HF.[8,11]

A "rhythm-control" in comparison to a "rate-control" strategy has in several studies been evaluated and a recent systematic review with meta-analysis concluded that most patients with AF should be treated with a rate-control strategy as rhythm-control seems to significantly increase the risk of adverse events.[169] The landmark and often cited AFFIRM study concluded that there is no survival benefit for a rhythm- over a rate-control strategy.[167] Yet, only 23% of included patients had HF and six years later, the Rhythm Control versus Rate Control for Atrial Fibrillation and Heart Failure (AF-CHF) study was published. It evaluated the two strategies in patients with NYHA Class III-IV and HFrEF (LVEF <35%) but no reduced cardiovascular mortality was observed in the rhythm-control group among these patients either.[170] The AF-CHF study can be criticized however as the rhythm-control arm relied almost exclusively on amiodarone and that only 73% of patients actually maintained SR at 4-years of follow-up. Moreover, there are some conflicting results regarding the strategies as there have been observations where a higher risk of admission for HF or death have been noted in patients with permanent AF.[171] Maintenance of SR has also been found to be beneficial[168] and the decision between a rate- or rhythm control strategy should be well considered for each patient.

Given the fact that one of the primary barriers to response to CRT is inadequate BivP,[59] and that BivP often is correlated to the burden of AF during CRT treatment,[172] it has been speculated if CRT recipients after all may benefit from rhythm-control.[173] Also, as even transient episodes of AF may cause loss of BivP[60] therapies focused on limiting the risk of AF during treatment with CRT may be beneficial.

To our knowledge there are no randomized clinical trials that have evaluated if rhythm-control can be favourable in CRT recipients. An ongoing trial of 60 patients with CRT will evaluate this but the results are not published as of this date.[174] The results from paper II in this thesis imply that the cumulative burden of AF during early CRT treatment may improve risk-stratification. Similar findings have been observed in CRT recipients not very different from our cohort[111] and we believe that our findings justify further research aimed at assessing the effect of rhythm-control strategies in CRT recipients with advanced HF.

## The prognostic impact of the achieved biventricular pacing percentage

As previously discussed, low BivP has been identified as an important cause to the observed negative effect of AF on the prognosis in CRT recipients. In paper II however, BivP presented and studied as a continuous variable in all patients (with and without pre-procedural AF) did not qualify as a predictor of our composite endpoint of death, HTx or appropriate ICD-shock therapy in either uni- nor multivariate analysis. We did find that the achieved percentage of BivP was lower among patients with pre-procedural AF, also with significant differences observed when comparing patients with non-permanent and permanent AF, in agreement with previous findings[58,172] where an inverse correlation of AF burden and BivP percentage has been observed. Yet, as the percentage of BivP in our study was high in all groups we believe that it should fulfil the requirement for the BivP to be an effective contributor for improving the outcome in HF. However, in paper III we decided to study BivP as a binary variable of over or under the high demand of 98% of all ventricular beats in patients with AF and found that AF history by one year after CRT implantation along with BivP ≤98% independently predicted death or HF progression to HTx. Also, the findings from paper III indicated that patients with AF and adequate BivP did not have an inferior outcome compared to patients with no AF by one year after CRT implantation. Yet, the Kaplan Meier curves were separated and the p-value borderline significant indicating that low BivP is not the only explanation to the inferior outcome observed in patients with AF.

The physiological impact of CRT is postulated to occur through synchronizing ventricular contraction that in turns leads to improved left ventricular filling and pumping efficiency as well as reduced mitral regurgitation.[12,42,43,166] As no atrioventricular synchrony exists in patients with AF and HF, any clinical benefit is predicated on biventricular synchronization. Thus, the impact of achieved BivP

percentage may be even more important in patients with AF and may explain the differences regarding the impact of BivP on prognosis observed between paper II and III.

AF may lead to loss of BivP due to fast and irregular ventricular beats as erratic electric activity of the atria can occasionally penetrate the AV node and override, disturb or interrupt biventricular capture. In several studies strict rate control by medication have not been achieved in around one third of patients with AF.[167,172,175] Inverse correlations of uncontrolled ventricular rates and CRT pacing have been observed and a stricter rate-control strategy have therefore been proposed among CRT recipients [172] as in comparison to the findings of the RACE II trial where strict rate control (< 80 bpm) compared to lenient rate control (< 110 bpm) was not found to be superior among patients with permanent AF affected with less comorbidities compared to a normal CRT population.[175] In our studies we did not analyse any data regarding ventricular rates during follow-up and can therefore not say if the lower observed BivP among our patients with AF was due to uncontrolled ventricular rates. However, as a great majority of AF patients had beta-blocker therapy and as all patients had regular follow-up visits at the arrhythmia clinic, we believe that it is unlikely that many of our patients would have had long-lasting uncontrolled ventricular rates.

AVJ ablation is performed to isolate the ventricles from the atria, and fast irregular beats can subsequently not be transformed from the atria to the ventricles. The patient consequently becomes life-dependent of permanent pacing but the therapy is attractive as it affords an opportunity to basically guarantee 100% BivP. Only 21 of our patients in paper III had underwent AVJ ablation before CRT implantation. Nine patients were AVJ ablated after CRT implantation, all due to inadequate BivP. The fact that 48% of our patients with AF history had BivP <98% during first year of follow up and that the median BivP in this group was 93% may suggest that AVJ ablation were underutilized in our cohort as several studies have shown survival benefits in AVJ ablated patients with CRT.[176-178] However, there are still uncertainties regarding the effects of AVJ ablation, especially among patients with non-permanent AF and randomized controlled trials have been warranted to confirm the efficiency and safety of the procedure.[179] Yet, current European guidelines are in favour of AVJ ablations, at least in patients with sub-optimal BivP.[12]

To summarize, our results corresponds well to previous findings[58,59] and we strongly believe that a high percentage of BivP is a major determinant of CRT outcome and that low BivP is one of the explanations to why AF deteriorates prognosis and is associated to a higher risk of non-response in CRT recipients. Efforts should be made to increase BivP in patients not achieving a BivP >98%.

# The prognostic impact of VHR episodes

The results from paper I suggest that VHR episodes during early CRT treatment independently predict a higher risk of death within 5 years as well as within a long term of follow-up. The cause of death was HF in 60% of cases which implies that VHR episodes is a marker of a more advanced underlying disease rather than an indicator for increased risk of malignant arrhythmias. Yet, the cause of death was not individually adjudicated by hospital records or pacemaker interrogation post-mortem and we can therefore not rule out that the registered cause of death was inaccurate. The Swedish Cause-of-Death Register is well validated but according to the most recent publication on the quality of the statistics 23% of death causes was incorrect[180] and The Swedish National Board of Health and Welfare concludes in its latest report that the cause of death is more insecure among older patients with a higher number of comorbidities.[181] We do recognize that differentiating between malignant arrhythmia and other cardiac death causes may be difficult or impossible post-mortem without an autopsy and cannot exclude that the higher mortality rate observed in patients with VHR episodes was due to death from malignant arrhythmia. With a low number of patients and large confidence intervals our findings should be regarded as hypothesis generating and further studies are needed to verify the results. As ICD-shock therapy is effective and potentially life-saving but also associated to more complications and more expensive[12] there are many reasons to further investigate what patients may benefit from a CRT with a defibrillator. However, it seems as if device-diagnostics with regards to the ventricular rhythm can be helpful in the complex risk-stratification process of CRT recipients and even short episodes of VHRs should not be ignored as such may indicate a higher risk of adverse events.

# The value of ECG markers of abnormal atrial function

The main findings from paper IV were that IAB adds prognostic value and may therefore be helpful in risk-stratification in the context of HF management, whereas neither abnormal $PTFV_1$ nor aIAB P-wave pattern demonstrated any prognostic value in patients with advanced HF disease.

## The prognostic value of interatrial block

Morphological anomalies of the P wave are associated with structural abnormalities of the atrial wall such as fibrosis due to ageing and cardiovascular comorbidities.[121,138,139] One would therefore expect a high prevalence of IAB as well as abnormal $PTFV_1$ in CRT recipients and could hypothesize that such therefore should be too unspecific and common to contain any additive prognostic information in a cohort of patients such as ours. IAB as well as abnormal $PTFV_1$ were common findings in our cohort but we think it is interesting and inspiring that IAB can contain independent prognostic information irrespective of other clinical parameters well-known to influence CRT outcome. The fact that a surface ECG can contain valuable information that may be used in the risk-stratification process of patents are appealing in a number of ways. First of all, ECGs are available at basically every medical facility and information from such are therefore easily available. Our findings, that are in agreement with previous studies, suggest that IAB should not be ignored as it may reflect an underlying, more severe type of cardiac disease with higher risk of future AF as well as other adverse events. As automated analysis of the P wave is available, IAB is also easy to recognize and would therefore be both cost- and time-effective for physicians to use in the risk-stratification of patients whether the clinician practice in primary care or at a specialized cardiology clinic. Finding patients with high risk of AF within a near future is essential to reduce the burden of the severe outcomes associated with AF, especially as effective and safe treatments are available.[11,182-185]

Our study aimed at exploring the association between ECG markers of abnormal atrial function with new-onset AF and we believe that a special strength in it was that it contained a reliable identification of patients with pre-procedural AF history. This was due to the fact that it combined screening of multiple pre-procedural ECGs along with a meticulous review of medical records cross-linked with the SNPR. We therefore interpret the results as if IAB is predictive of true new-onset AF as opposed to a consequence of AF itself, making it an even more valuable tool.

## The prognostic value of abnormal P-wave terminal force in lead $V_1$

We were not able to reproduce previous findings regarding the correlation between abnormal $PTFV_1$ and worse outcomes.[120,145,146] In our study $PTFV_1$ was also not correlated to the endpoints in patients with LBBB either, as it was in Baturova's study of MADIT-CRT patients.[147] The conflicting results may be explained by the obvious differences between the two populations but our study may also have been underpowered to find any prognostic significance of abnormal $PTFV_1$. However, given the lack of Kaplan Meier curve separation between patients with and without abnormal $PTFV_1$, it is unlikely that the abnormal $PTFV_1$ bears clinically significant meaning in regard to prognosis for patients with severe HF treated with CRT. As few studies have explored the value of abnormal $PTFV_1$ in patients with advanced symptomatic heart disease our results have to be confirmed in future analyses before any conclusions are made.

## Could the underlying pathophysiological differences between IAB and abnormal $PTFV_1$ explain why only IAB had prognostic value?

From our results it does not seem as if abnormal $PTFV_1$ have any prognostic applicability whereas significant associations of IAB and worse outcomes were found. One may speculate why. Both IAB and abnormal $PTFV_1$ are ECG signs of structural atrial abnormalities and although they share common underlying causes their pathogenetic explanations differs.[138] In the right precordial leads, upright P waves have been found to be associated with conduction via interatrial connections in the vicinity of the right pulmonary veins on the back side of the heart and several endocardial mapping studies have demonstrated that conduction via these posterior connections normally dominate during SR.[150] These posterior connections are generally thinner and less developed compared to the Bachmann's bundle.[151] It has therefore been suggested that they are more affected by ageing and thus in elderly leaves only Bachmann's bundle as the interatrial route of connection resulting in an abnormal $PTFV_1$.[138] However, in patients with aIAB, the retrograde activation of the left atrium (visualized as biphasic or negative morphologies in the inferior ECG leads) is induced by the presence of fibrosis of the Bachmann's bundle too,[153] suggesting that aIAB reflects a more abnormal myocardium and thus a more severe underlying heart disease. The different pathogenetic explanations of the different ECG abnormalities may be one explanation why abnormal $PTFV_1$ as compared to IAB (both pIAB and aIAB) did not have any significance in our old patients with advanced heart disease and a great burden of comorbidities. In patients with excessive structural myocardial abnormalities it is expected that interatrial connections such as the posterior less developed ones are affected which may explain why abnormal $PTFV_1$ does not have any additive value in CRT recipients.

# General study design discussion

This thesis focused on finding non-invasive predictors of CRT outcome and even though the endpoints somewhat differed, all papers focused on the overall clinical outcome. The parameters studied differed in each paper but paper II and III had many similarities, especially with regards to the analyses of the prognostic importance of pre-procedural AF history and incidence as well as importance of device-detected AF. However, paper III included a more thorough exploration of pre-procedural AF history, thus rendering the diagnostic value of pre-procedural AF more accurate. Moreover, as paper II used a composite endpoint also including ICD-shocks, we wanted to explore the implications of pre-procedural AF in relation to the more "robust endpoint" of death or HTx in paper III.

In all papers, Kaplan Meier plots and Cox regression analyses were used to compare survival between groups. The chosen follow-up period of the primary endpoints varied between the papers, 5 years in paper I and IV, 10 years in paper III and time to end of follow-up in paper II. As paper I and IV included a lower number of patients we found it reasonable to have a shorter follow-up. Also, as we hypothesized that the parameters studied (VHR episodes, IAB and abnormal $PTFV_1$) would be predictive of endpoints within a near future, we found it more suitable to shorten the follow-up period. Paper I, II and III combined uni- and multivariate analyses, with different inclusion criteria whereas paper IV only included parameters that previously had been found to be significantly correlated to the outcome in CRT recipients, an approach that the Ph.D. student now generally finds more suitable in this material. To explore if the main results from paper II and III remained if the follow-up period was shortened to 5 years from CRT implantation and if the multivariate analyses was performed as in paper IV, additional analyses were performed. As presented in the results section the main findings from paper II and III remained significant. In hindsight one may speculate if it would have been more appropriate to present and perform the multivariate analyses in a similar way in all papers. However, the fact that the results remained further suggest that a higher burden of AF during early CRT treatment as well as low BivP in AF patients, are disadvantageous in CRT recipients.

# Limitations

As all papers in this thesis were retrospective studies, with the inherited risk of bias, our results should mainly be regarded as hypothesis generating and future prospective studies are warranted to confirm our observations. With regards to device-diagnostics, there are some limitations to study I, II and III. AHREs and AMS events most often represent true AF but especially short episodes may be unreliable. With regards to BivP it has been found that the percentage of BivP recorded by the CRT device may be an overestimation of the true biventricular capture.[186,187] Due to inaccurate counting of fusion and pseudo-fusion complexes the device counters are often artificially inflated during AF and clinicians may be misled to believe that adequate BivP has occurred whereas the true capture is far less. Kamath et. al. evaluated the effective versus device-recorded BivP capture in CRT recipients by comparing 12-lead Holter monitoring to device-monitoring. The authors found that pacing counters overestimate the degree of effective BivP capture in patients with permanent AF and that only patients with complete true capture (defined as >90% BivP) responded clinically to CRT.[187] In the small study of only 19 patients, fusion and pseudo-fusion beats constituted as much as 40% of the overall paced beats and it is therefore speculated that clinicians cannot trust the data from CRT counters, especially not in patients with permanent AF.

# Conclusions

- A pre-procedural history of AF is very common in CRT recipients with advanced HF, affecting around 50% of patients. Due to underdetection of AF, the previously reported prevalence may have been an underestimation. AF history is associated to worse outcomes but does not have any independent prognostic impact.
- The results from our study suggest that clinicians should not overreact to short episodes of device-detected AF and these results correspond well to current consensus documents. Yet, more studies are needed to explore the value of short device-detected episodes of AF.
- The cumulative burden of AF during early CRT treatment may improve risk-stratification. Our findings justify further research aimed at assessing the effect of rhythm-control strategies in CRT recipients with advanced HF.
- A high percentage of BivP is a major determinant of CRT outcome and low BivP is one of the explanations to why AF deteriorates prognosis in CRT recipients. Efforts should be made to increase BivP in patients not achieving a BivP of >98%.
- VHR episodes during early CRT treatment independently predicts a higher risk of death within 5 years of follow-up but no evidence was found that this was due to a higher risk of cardiac arrest. Our results imply that VHR episodes should be regarded as a marker of a more advanced HF.
- IAB is an independent predictor of new-onset AF and death in CRT recipients with severe HF. Neither abnormal $PTFV_1$ nor aIAB P-wave pattern have demonstrated prognostic value in patients with advanced HF disease.

# Perspectives

The aim of this thesis was to find non-invasive predictors of CRT outcome that could be of helpful in the risk-stratification process of CRT recipients with advanced HF. As many physicians request easily available tools to improve risk-stratification in CRT recipients and as the numerous prognostic models and risk scores developed so far have only revealed a moderate accuracy in predicting outcomes, new precise and clinically applicable risk stratification tools for patients with HF are needed. The estimation of prognosis is important as it helps the patients, their relatives and the clinicians to decide on the appropriate type and timing of therapies and assists with planning of health and social services and resources.

We focused on the very common comorbidity AF. The results from our studies are in line with previous observations, indicating that AF is a marker of a more severe underlying heart disease and that it does not carry any independent prognostic value itself. Yet, in a very special population such as CRT recipients, where a demand of high BivP percentage seems to be of great importance, efforts to reduce the burden of AF may be beneficial. The results from our studies also indicate an inverse relationship between the cumulative burden of AF and the achieved BivP percentage. Our findings thereof justify further research aimed at assessing the effect of rhythm-control strategies in CRT recipients with advanced HF and underlines the importance of high BivP percentage. The importance of short, device-detected episodes of AF needs further evaluation and it is still not fully established what duration and or what number of such episodes are needed to affect prognosis. As technology advances AF from a number of different sources such as implanted ECG-devices, smartphones and other wearables may detect silent, undiagnosed AF and that further justify more research in this area. Our result imply that short episodes are of lesser importance.

Device-detected VHR episodes during early CRT-P follow-up indicates a higher risk of death in 5 years but as no evidence of a higher risk of cardiac arrhythmias was found, our results do not indicate that CRT-P recipients with VHR episodes would benefit from a defibrillator. Nevertheless, the underlying explanation to the higher mortality rate needs further evaluation and future studies should aim at assessing if there after all may be a correlation of VHR episodes and higher risks of forthcoming cardiac arrests. This could be done by including post-mortem analyses of intracardiac electrograms. The decision between a CRT-P or CRT-D is difficult and complex as it includes many perspectives, not only medical but also ethical and

economical why the indications for each therapy needs to be improved. Our results indicate that VHR episodes can be used in risk-stratification and encourages more studies in this area.

Pre-procedural findings of atrial ECG-abnormalities are of value in CRT recipients with advanced HF. It is appealing that easily available information from a surface ECG can contain valuable data that can be used in the risk-stratification in the context of HF management. IAB was predictive of new-onset AF as well as total mortality. Very few studies have been performed and designed to evaluate the prognostic impact of IAB and abnormal $PTFV_1$ in patients with advanced HF and our results indicate that IAB can be of great value in patients with a high prevalence of comorbidities such as ours as well and more studies of atrial ECG abnormalities in severely ill patients are thereof motivated.

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