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Doctoral dissertation

Cardiac resynchronization therapy and implantable cardioverter defibrillators –

Patient selection, pharmacological considerations, and ICD programming to improve outcomes

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Preface

The studies included in this dissertation were carried out in the period 2012-2021. They are the summation of a personal scientific journey after finishing my PhD thesis. In 2012, my wife and I were fortunate to be offered and funded* for two-year research positions at the University of Rochester, NY, US. This opportunity was only possible because of Christian Jøns and we are still very grateful for this chance. In Rochester, Arthur Moss and Wojciech Zareba provided excellent research opportunities working with the data from the large clinical trials MADIT-CRT and MADIT-RIT. Arthur Moss, a fantastic mentor and true pioneer of cardiac research unfortunately passed away in 2018. He is in my memories. Special thanks to Wojciech Zareba and Scott McNitt for exceptional mentorship, friendship, and sharing of statistical skills. Also, thanks to office co-workers and co-authors from the Heart Research Follow-up Program on the many projects. Furthermore, I owe a great deal of gratitude to Gunnar Gislason, who initially took me under his wings on Gentofte Hospital supervising my PhD, but also for his continuous support during the stay abroad and hereafter. I also want to thank the co-authors and collaborators from the Danish Pacemaker and ICD register – but in particular I want to thank Tommi Lindhardt. Tommi mentored a great deal of my clinical arrhythmia training and device implantations and I am grateful for the opportunities given by him. I also want to extend my thanks to the Head of Cardiology at Gentofte and all of my present colleagues in the Gentofte Arrhythmia Group, technicians, and nurses – too many to name them all. Given the research background of the present dissertation I enjoy the challenging scientific and clinical discussions on many of our daily subjects and troubleshootings. I hope to be able to extend the present research even further in many areas of cardiac arrhythmias and look forward to many stimulating and inspiring collaborations in the future. Finally, of course, I want to thank my beautiful wife, Anne Christine, for the unlimited support and patience, but also for her scientific input and assistance with many of the papers in the present thesis. I am forever grateful for your love and understanding but also for giving me four fantastic children (Christoffer, Caroline, Conrad, and Christian).

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1. Ruwald MH, Ruwald AC, Jons C, Alexis J, McNitt S, Zareba W, Moss AJ. Effect of Metoprolol Versus Carvedilol on Outcomes in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy). J Am Coll Cardiol 2013;61:1518-1526[1]
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The papers and the results included in this thesis have not previously been submitted with the purpose of obtaining an academic degree. *The authors contributed equally to this work

Abbreviations and acronyms

ACE – Angiotensin converting enzyme

ADVANCE III - Avoid Delivering Therapies for Nonsustained Arrhythmias in ICD Patients

AF – Atrial fibrillation

AMIOVIRT – Amiodarone Versus Implantable Cardioverter-Defibrillators: Randomized Trial in Patients with Nonischemic Dilated Cardiomyopathy and Asymptomatic Nonsustained Ventricular Tachycardia

APAF - The Ablate and Pace in Atrial Fibrillation

ARB – Angiotensin receptor blocker

ARVC - Arrhythmogenic right ventricular cardiomyopathy

AATAC - Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted Device

APAF-CRT – AV Junction Ablation and Cardiac Resynchronization Therapy for Patients with Permanent Atrial Fibrillation and Narrow QRS

ARTESiA - Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation

AVID – Antiarrhythmics Versus Implantable Defibrillators

BioPace - Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization

BIV – Biventricular

BUDAPEST-CRT - Effect of Biventricular Upgrade on Left Ventricular Reverse Remodeling and Clinical Outcomes in Patient with Left Ventricular Dysfunction and Intermittent or Permanent Apical/Septal Right Ventricular Pacing

CABANA - The Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial

CARE-HF – Cardiac Resynchronization-Heart Failure

CAT – Primary Prevention of Sudden Cardiac Death in Idiopathic Dilated Cardiomyopathy: The Cardiomyopathy Trial

CERTIFY - Cardiac Resynchronization Therapy in Atrial Fibrillation Patients Multinational Registry

CI – Confidence interval

COMPANION - Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure

CRT-D – Cardiac resynchronization therapy with implantable cardioverter defibrillator

CRT-P – Cardiac resynchronization therapy pacemaker

DanICD – A Danish ICD-study in Patients with Coronary Artery Disease Resuscitated from Ventricular Fibrillation

DANISH – Danish ICD study in Patients with Dilated Cardiomyopathy

DANISH-CRT - Does Electric Targeted LV Lead Positioning Improve Outcome in Patients with Heart Failure and Prolonged QRS

DEFINITE - The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation

DCM – Dilated cardiomyopathy

DPIR - Danish Pacemaker and ICD Register

EchoCRT - Echocardiography Guided Cardiac Resynchronization Therapy

EMPIRIC - Comparison of Empiric to Physician-Tailored Programming of Implantable Cardioverter Defibrillators

HCM - Hypertrophic cardiomyopathy

HF – Heart failure

HR – Hazard ratio

ICD – Implantable cardioverter-defibrillator

INTRINSIC-RV - Inhibition of Unnecessary RV Pacing with AVSH in ICDs

IHD – Ischemic heart disease

LBBB – Left bundle branch block

MADIT-CRT – Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy

MADIT-RIT – Multicenter Automatic Defibrillator Implantation Trial- Reduce Inappropriate Therapy

MADIT II - Multicenter Automatic Defibrillator Implantation Trial II

MI – Myocardial infarction

MS - Milliseconds

MIRACLE - Multicenter InSync Randomized Clinical Evaluation

MUSTIC AF – Multisite Stimulation in Cardiomyopathies - Atrial Fibrillation

NYHA – New York Heart Association

PATH-CHF - The Pacing Therapies for Congestive Heart Failure

PainFREE Rx II - Pacing Fast VT Reduces Shock Therapies II

PainFREE SST - Pacing Fast VT Reduces Shock Therapies Smart Shock Technology

Pause-SCD - Pan-Asia United States PrEvention of Sudden Cardiac Death Catheter Ablation Trial

PAVE - Left Ventricular-based Cardiac Stimulation Post AV Nodal Ablation Evaluation

PREPARE – Primary Prevention Parameters Evaluation Study

PROFID-Reduced – Personalized Risk Score for Implantation of Defibrillators in Patients with Reduced LVEF ≤35% and a Low Risk of Sudden Cardiac Death

PROVIDE - The Programming Implantable Cardioverter Defibrillators in Patients with Primary Prevention Indication to Prolong Time to First Shock

PVI – Pulmonary vein isolation

RAFT - Resynchronization-Defibrillation in Ambulatory Heart Failure Trial

RAFT-PermAF - Resynchronization/Defibrillation for Ambulatory Heart Failure Trial in Patients With Permanent Atrial Fibrillation

RESET-CRT - Re-evaluation of Optimal Re-synchronisation Therapy in Patients With Chronic Heart Failure

REVERSE – Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction

SCD – Sudden cardiac death

SCD-HeFT - Sudden Cardiac Death in Heart Failure Trial

SMART-AV - SmartDelay Determined AV optimization

SVT – Supraventricular tachycardia

VF – Ventricular fibrillation

VT – Ventricular tachycardia

VTA – Ventricular tachyarrhythmia

Chapter 1

Introduction

Implantable cardioverter defibrillators

Sudden cardiac death (SCD) is among the leading causes of death in the world, and in the United States alone the annual incidence is estimated to 450,000[11]. Implantable cardioverter defibrillators (ICDs) were developed and emerged as a device-based treatment of SCD caused by malignant ventricular tachyarrhythmias (VTAs)[12-14]. The device was later shown, in major trials, to improve survival for survivors of cardiac arrest caused by VTAs, patients with hemodynamically intolerable VTAs due to non-reversible causes, and patients with syncope and inducible VTA. This indication for ICD implantation is known as a secondary prevention ICD indication[15-17]. Currently, the number of ICD implantations is increasing worldwide[18] with more than 486,000 ICDs implanted over a three-year period alone in the United States[19] and in Denmark up to 1,200 ICDs are implanted yearly (dhreg.dk). Patients with heart failure (HF) have a markedly increased risk of SCD because of increased tendency of the failing heart to produce VTAs. Approximately two percent of the adult population in developed countries has HF with increasing prevalence to more than 10% in patients above 70 years[20,21]. Several randomized trials and register data have shown improved survival, due to reduction in SCD, in patients with HF and reduced left ventricular ejection fraction (LVEF), who were treated with ICDs compared to optimal medical therapy[20,22-25]. This indication for use of ICDs is known as primary prevention indication. Furthermore, an ICD can be utilized in cases, where there is an à priori or suspected high risk of SCD, such as in specific inherited and acquired cardiac diseases[26]. In this latter patient cohort, the efficacy of the ICD has not been examined in major clinical trials as is the case for survivors of SCD and HF patients with reduced LVEF. In general, patients with HF can benefit from improvements such as prevention, pharmacological treatment, technological advances in implantable devices such as ICDs and more; but a continuous stringent evaluation of current guidelines and strategies is of outmost importance. This includes prospective evaluation of patient subgroups in trials to determine the best response to a given treatment and a thorough re-evaluation of “trial-like” real-life patients based on prospective observational or register data. In the first part of the present thesis, the background of pharmacological and selected device-based treatment for HF in terms of both benefit as well as disadvantages is presented to best introduce the clinical issues and views interpreted in the presented papers. The

mainstay of pharmacological treatment for HF during the last two-three decades has been a combined treatment with inhibitors of the renin-angiotensin system, and blockers of the beta-adrenergic and aldosterone receptors, which has reduced morbidity and mortality significantly[20,27-35]. Within recent years this therapy has been even further improved, with the introduction of angiotensin receptor-neprilysin inhibitors and sodium-glucose co-transporter 2 inhibitors[36,37]. Despite this optimal medical management, approximately 10-20% of all HF patients have electrical conduction abnormalities and sustained depressed systolic function[38].

Cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) emerged as a device-based treatment option for HF patients and has improved morbidity and mortality significantly, but the therapy has so far been limited only to patients with depressed LVEF and specific electrical activation disturbances[25,39-49]. These electrical abnormalities and conduction delay in the heart promote interventricular and intraventricular mechanical dyssynchrony of the left ventricle as well as dyssynchrony of the atrial and ventricular contractions. The prevalence of intraventricular conduction delays with QRS duration above 120 milliseconds(ms) among patients with HF and depressed left ventricular function is estimated to be in the range of 25-50% of the patients, and in particular a left bundle branch block (LBBB) is estimated to be present in 15-27% of the patients[50-53]. CRT can resolve or diminish dyssynchrony and resynchronize the inter- and intraventricular delay as well as the atrio-ventricular relationship in patients with HF. This is mechanistically achieved by simultaneous pacing of the right ventricle and lateral wall of the left ventricle with appropriate timing after an atrial activation (if any atrial contractile activity is present). The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT)[41] was one of the major CRT trials and showed a significant 34% reduction in HF hospitalization or death compared to ICD alone for patients with mild HF in New York Heart Association (NYHA) functional class I and II. Table I summarizes landmark clinical CRT trials[54].

Table 1: Overview of landmark clinical CRT trials

Trial (year)	Design	Patients	Mean follow-up, months	NYHA	LVEF criteria, Mean	QRS criteria, ms Mean	Primary end point	Selected secondary End points	Results favoring intervention group
MUSTIC-SR (2001)[55]	CRT-P/Med Crossover	29/29	3	II, III, IV	=35%, 24%	=150, 174	6-MWT	NYHA, QoL, peak VO2, MR, mortality, hosp.	+
PATH-CHF (2002)[56]	RV/LV/CRT-P Crossover	41	12	III, IV	NA, 22%	=150, 175	6-MWT, peak VO2	NYHA, QoL, hosp.	+
MIRACLE (2002)[42]	CRT-P/Med	228/225	6	III, IV	=35%, 22%	=130, 166	NYHA, 6-MWT, QoL	Peak VO2, LVEDD, LVEF, MR, CCR	+
MIRACLE–ICD (2003)[175]	CRT-D/ICD	187/182	6	III, IV	=35%, 25%	=130, 164	NYHA, 6-MWT, QoL	Peak VO2, LVEF, MR, CCR	+
CONTAK-CD (2003)[48]	CRT-D/ICD	245/245	6	II, III, IV	=35%, 22%	=120, 158	NYHA, 6-MWT, QoL	LVEF, CCR	+
COMPANION (2004)[39]	CRT-D/CRT-P/Med	617/595/308	15	III, IV	=35%, 21%	=120, 159	All-cause mortality or hosp.	Cardiac mortality	+/+
MIRACLE–ICD II (2004)[49]	CRT-D/ICD	85/101	6	II	=35%, 25%	=130, 166	Peak VO2	NYHA, QoL, 6-MWT, LVEF, CCR	(+)
CARE-HF (2005)[40]	CRT-P/Med	409/404	29	III, IV	=35%, 25%	=120, 160	All-cause mortality or cardiovascular hosp.	NYHA, QoL, LVEF, LVESV, HF hosp.	+
REVERSE (2008)[57]	CRT-D/ICD*	419/191	12	I, II	=40%, 28%	=130, 153	CCR	LVESVi	(+)
MADIT-CRT (2009)[41]	CRT-D/ICD	1089/731	29	I, II	=30%, 25%	=130, 162	All-cause mortality or HF hosp.	LVESV, LVEDV, LVEF	+
RAFT (2010)[43]	CRT-D/ICD	894/904	40	II, III	=30%, 24%	=120, 158	All-cause mortality or HF hosp.	Cardiac death, non-fatal HF hosp.	+
Echo-CRT (2013)[59]	CRT-D/ICD*	404/405	19	III, IV	=35%, 27%	<130, 105	All-cause mortality or HF hosp.		

*Patients were randomized to CRT on or CRT off. CCR: Clinical composite response. LVEDD: Left ventricular end-diastolic diameter. LVEF: Left ventricular ejection fraction. LVESV: Left ventricular end-systolic volume. LVESVi: Left ventricular end-systolic volume index. HF: Heart failure. Hosp: Hospitalizations. MR: Mitral regurgitation. NYHA: New York Heart Association. QoL: Quality of life. 6-MWT: 6 minutes walking test. Adapted from Ruwald et al. Research Reports in Clinical Cardiology 2014;2014:305-17.

The beneficial effects of CRT have been proven in ischemic and nonischemic cardiomyopathy patients in NYHA class II, III and IV, while an effect for NYHA class I patients has been limited to the small number of ischemic patients enrolled in MADIT-CRT. The MUSTIC[55], COMPANION[39], MIRACLE[42], PATH-CHF[56], and CARE-HF[40] trials aimed to compare optimal medical HF therapy with the effect of CRT in NYHA class III and IV, while newer trials such as RAFT[43] and REVERSE[44,57] and the thesis-relevant MADIT-CRT evaluated the effect of the combined device - CRT with defibrillator (CRT-D) against ICD alone on top of optimal medical therapy for NYHA class I, II and III patients. Most relevant inclusion criteria for the trials involved LVEF <30%-40% and QRS width >120ms – 150ms. It soon became clear that not all patients responded equally well to the treatment, and in the years after publications of the main results followed many sub-analyses and meta-analyses of important aspects such as QRS width, QRS morphology, sex, underlying cardiomyopathy etiology, atrial fibrillation (AF), biventricular (BIV) pacing percentage, and more. Based on these analyses current guidelines recommend CRT for patients in sinus rhythm with LVEF ≤35%, QRS duration ≥150ms with LBBB morphology despite optimal medical therapy[50,51,58]. Additionally, CRT should be considered when QRS ≥150ms for non-LBBB patients and QRS 130-149ms for LBBB patients. In

contrast the ECHO-CRT provided evidence that CRT is not indicated in patients with HF, where QRS <130ms since mortality was higher in the CRT-D group compared to the ICD group[50,59]. For patients with AF the evidence for effect of CRT is much less robust, and indication should be considered in NYHA class III and IV with a planned rhythm strategy to insure high BIV pacing percentage. Based on the above provided evidence of HF therapy combined with protection from SCD most, but not all, CRT patients therefore receive the combined treatment with the ICD, CRT-D[60].

Implantable cardioverter defibrillator programming

The method for reducing and preventing SCD among patients with ICDs is by device-based treatment of the VTA. The ICD can deliver programmed rapid pacing stimuli termed anti-tachycardia pacing (ATP) or a shock to terminate VTA. However, patients with an implanted ICD are also faced with risk of inappropriate ICD therapies[61] (ICD therapy given for other reasons than life-threatening arrhythmias because of a misinterpretation by the device), that have been shown to be associated with negative psychological consequences, impaired quality of life[62], and most importantly, with adverse clinical outcomes[63-66], Table 2.

Table 2. Rates of inappropriate ICD therapy in selected registers and clinical trials of ICD and CRT-D patients

Data (Year)	*Inappropriate ICD therapy (%)*	*Registered therapy*	*Follow-up, months*	*Patients, number*	*Type of prevention, primary (P) or secondary (S)*
AVID (2003)[244]	9% (of the patients), 21% (of any therapy)	ATP or shock	22	449	S
Pain Free II (2005)[62]	15% (of the patients)	ATP or shock	11	582	P,S
Miracle ICD A (2004)[245]	14% (of any therapy)	ATP or shock	10	415	P
Miracle ICD B (2004)[245]	30% (of any therapy)	ATP or shock	10	563	S
MADIT-II (2008)[65]	12% (of the patients)	Shock only	20	719	P
SCD-HeFT (2008)[64]	17% (of the patients), 32% (of any therapy)	Shock only	46	811	P
ALTITUDE ICD (2010)[222]	16% (of the patients), 30% (of any therapy)	Shock only	28	39,396	P,S
ALTITUDE CRT-D (2010)	17% (of the patients)	Shock only	28	29,904	P,S
Desai et al. (2010)[208]	13% (of the patients)	Shock only	41	549	P
Van Rees et al. (2011)[213]	13% (of the patients)	Shock only	41	1,544	P,S
Yang et al. (2012)[66]	23% (of the patients)	Shock only	29	148	P,S
Weeke et al.(2013)[249]	3% (of the patients)	Shock only	23	1,609	P
MADIT-CRT (2013)[2,61]	7% (of the patients)	Shock only	41	1,790	P
Wijers et al. (2013)[188]	3% (of the patients)	Shock only	31	1,075	P
DANISH (2016)[140]	0-3 per 100 person-years	ATP or shock	68	556	P

This enigma initiated successful larger trials targeting unnecessary and inappropriate ICD therapies through better ICD programming, among which was the Multicenter Automatic Defibrillator Implantation Trial – Reduce Inappropriate Therapy (MADIT-RIT)[67]. MADIT-RIT randomized HF patients with a primary prevention indication for ICD to one of three different ICD programming arms. The main results were that programmed high-rate ICD therapy or delayed ICD therapy led to a significant decrease in inappropriate ICD therapies and mortality, when compared with conventional ICD programming, without an increase in adverse events such as syncope. The second part of the present thesis has focused on evaluation of ICD programming in patient subgroups and delivered ICD therapies in patient subgroups, and therapies over time. For optimal treatment benefit it is important continuously to evaluate subgroups of patients within trials in order to identify those who might have reduced or improved response to a given treatment. Collected data further allow for exploration of pathophysiological mechanisms and hypotheses of potential use in future designs of trials. Collectively, these two randomized controlled device-based trials, MADIT-CRT and MADIT-RIT allowed for investigations of clinically pressing questions in the context of treatment with CRT and ICDs. Finally, following guideline-changing randomized studies, it is imperative to continuously further evaluate device treatment, effect of medical therapy, ICD therapies and prognosis among “real-life” patients with ICDs and CRT-Ds. This thesis undertakes the effort to evaluate multiple hypotheses using three different datasets in order to elucidate several clinical important questions related to ICD patients through 10 years of research. The first five studies were conducted on the data from the MADIT-CRT trial from 2009, the next three studies were conducted on data from the MADIT-RIT trial from 2012 and the final two studies were based on combined real-life patient data from the nationwide Danish ICD Register and Danish Patient Register. The thesis and following review were designed by introducing specific aims and hypotheses, the overall methods and statistics, presentation of results of conducted studies, which is then discussed and interpreted in context to present knowledge in separate chapters and finally put into future perspectives and conclusions.

Chapter 2

Aims and hypotheses

The overall aim of this thesis was to evaluate the prognosis of HF patients with CRT-D or ICD devices and the effect of various modifiable (risk) factors for optimal patient selection, device programming, device utilization and outcomes both for patients enrolled in clinical controlled trials and for real-life patients.

The aim in Paper I was to compare the effects of the two most widely used beta-blockers metoprolol and carvedilol, on clinical outcomes of HF hospitalizations or all-cause mortality. The hypothesis was that carvedilol was associated with improved outcomes due to drug-specific ancillary properties. The aim of Paper II was to evaluate the use of beta-blockers and clinical risk of inappropriate ICD therapy with a subanalysis of the arrhythmic causes of inappropriate ICD therapy. The hypothesis was that carvedilol was associated with reduced inappropriate ICD therapy because of possible greater antiadrenergic and antiarrhythmic activity and effect. The prognosis in CRT-D patients and the influence of ventricular and atrial premature ectopic beats and likelihood of low BIV pacing percentage was evaluated in Paper III. We hypothesized that increasing number of ectopic beats was associated with higher likelihood of low BIV pacing (<97%) percentage and consequently associated adverse outcomes. In paper IV we investigated the risk of VTA and outcomes by clinically relevant categories of LVEF determined at 12-month follow-up echocardiogram. The hypothesis was that patients with a normalization of LVEF (>50%) had very low risk of VTAs and further that these patients have significantly improved outcomes as determined by the LVEF recovery. In Paper V the aim was to describe the circadian distribution of VTA and to evaluate the importance of time of VTA on subsequent outcome. The hypothesis was that VTA would show a pattern of increased incidence in morning periods, which potentially could be related to increased mortality. Paper VI used the MADIT-RIT database and sought to evaluate incidence of syncopal events in HF patients with ICD and CRT-D devices and relate the cause of syncope to subsequent outcome. The primary aim was to determine syncope etiology and the risk of arrhythmogenic syncope by randomized setting of ICD therapy parameters. The hypothesis was that high-rate cut-off or prolonged delay before ICD therapy did not increase risk of arrhythmogenic syncope as compared to conventional programming. In Paper VII and Paper VIII, we sought to evaluate the risk of inappropriate ICD therapy, appropriate ICD therapy and

mortality and the influence of randomized ICD therapy programming settings in two major patient subgroups of ischemic and nonischemic cardiomyopathy and diabetes mellitus (DM). In Paper VII and VIII the hypothesis was that ischemic cardiomyopathy and DM, respectively, would have increased risk of inappropriate and appropriate ICD therapy, and of mortality, and thus could have a relatively larger benefit of ICD therapy parameters set to high-rate cut-off or delayed therapy. In Paper IX the aim was to investigate the incidence of appropriate ICD therapy after elective generator replacement. The hypothesis was that patients without appropriate ICD therapy in the first generator period were at very low risk for appropriate ICD therapy in the second generator period. In Paper X the aim was to estimate the temporal development in rates of appropriate and inappropriate ICD therapies by cardiac diagnosis in secondary prevention ICD patients. The hypothesis was that there would be a decline in both appropriate and inappropriate ICD therapies over time, and that the risk varied by the underlying cardiac etiology.

Chapter 3

Methodological aspects

Main study designs and data

Data from two randomized controlled clinical trials and a real-life prospective register were used in the present thesis as described below.

MADIT-CRT

In 2005 and 2009 the protocol and primary article of the MADIT-CRT trial were published[41,68]. The trial included 1,820 mild HF patients in NYHA class I or II, who had LVEF ≤ 30 % and QRS duration ≥ 130ms. The study was conducted in the period from December 22nd 2004 through June 24th 2009 and a total of 110 centers in Europe, Canada and USA enrolled patients, who were then randomized in a 3:2 fashion for CRT-D or ICD. The study was designed to address a preventive indication for CRT-D in mild HF patients and showed a 34% reduction in HF or death compared to ICD. Patients had to be on optimal pharmacotherapy in accordance with available HF guidelines at that time[69]. Patients were excluded if they had AF at enrollment or had a recent myocardial infarction (MI) or revascularization procedure (within three months) along with other exclusion criteria noted in the protocol[68]. One month after randomization a device interrogation and clinical

evaluation were scheduled and hereafter at three-months intervals until trial termination. Treating physicians were not blinded. The study was approved by the institutional review committees and patients provided written consent. The study was sponsored by Boston Scientific and registered at http://clinicaltrials.gov (NCT00180271).

MADIT-RIT

In 2012 the protocol and primary article of the MADIT-RIT study were published[67,70]. The trial enrolled 1,500 HF patients from September 15th 2009 to October 10th 2011 from 98 hospital centers in Europe, Canada and USA. Enrolled patients, who had a primary prevention guideline indication for ICD or CRT-D, were randomly assigned to one of three ICD programming configurations termed "conventional" (A), "high-rate" (B) and "delayed therapy" (C) for detection and subsequent initiation of ICD therapy for ventricular tachycardia (VT) or ventricular fibrillation (VF). MADIT-RIT was designed to determine if ICD or CRT-Ds with high-rate cut-off/and or prolonged delay was associated with reduction in inappropriate ICD therapies compared to conventional programming. Patients were excluded if they had permanent AF or had a recent MI or revascularization procedure (within three months) along with other exclusion criteria noted in the protocol[70]. A clinical evaluation and device interrogation was conducted at three-months intervals for the first year and then at six-months intervals. Treating physicians were not blinded. The study was approved by the institutional review committees and all patients provided a written consent. The study was funded by Boston Scientific and registered here http://clinicaltrials.gov with number NCT00947310.

Danish register data

The Danish Pacemaker and ICD Register (DPIR) contains prospectively collected data on Danish ICD and pacemaker patients and captures clinical data at time of implantation, i.e., device indication, NYHA class, LVEF, lead data, device type and clinical and remote follow-up data from device interrogations including complications, generator replacement indications, appropriate and inappropriate ICD therapies. Data from the National Danish Patient Register, the Civil Persons Register, and the Danish Register of Medicinal Products Statistics were available through Statistics Denmark servers. The unique CPR number used in Denmark allowed for encrypted linkage

between these registers. Patient data on vital status, comorbidities as determined by discharge diagnoses and medications as determined by redeemed prescriptions were used for the dataset as described in detail later. Approval for use of the encrypted and anonymized data was given by the DPIR and the Danish Data Protection (authorization approval number: Capital Region Denmark P-2019-398).

Study populations, definitions and outcomes

Paper I, II, III, IV and V were based on data from the MADIT-CRT study. Paper VI, VII and VIII were based on data from the MADIT-RIT study and Paper IX and X were based on data from the Danish DPIR and national registers. The study populations in Paper I, II and V consisted of 1,790 patients from the MADIT-CRT study. Of these 1,790 patients 1,072 had CRT-D implanted and 718 had an ICD implanted. The study population in Paper III consisted of 801 patients randomized to implantation with CRT-D who had both available pre-implantation Holter monitor recording and an average BIV pacing percentage reading. An echocardiographic subanalysis in Paper III consisted of 609 patients, who in addition had a paired baseline and 12-months echocardiogram. The study population in Paper IV consisted of 752 CRT-D patients with paired baseline and 12-months echocardiograms.

Papers VI, VII, and VIII all utilized data from MADIT-RIT thereby consisting of 1,500 patients of which 514 had conventional ICD therapy settings (A), 500 had high-rate cut-off ICD therapy settings (B), and 486 had delayed ICD therapy settings (C).

The study populations in Paper IX and X were identified through the DPIR in the period from January 1st, 2007 to December 31st, 2016. In Paper IX the study population consisted of 670 primary prevention ICD and CRT-D patients, who lived to receive an elective ICD generator replacement (second generator). Baseline data were determined on the date of generator replacement using the CPR number for linkage of register data as described above. Exclusion criteria were cardiomyopathies not clearly defined as ischemic or nonischemic cardiomyopathy such as hypertrophic cardiomyopathy (HCM), congenital heart disease, arrhythmogenic right ventricular cardiomyopathy (ARVC), channelopathies, idiopathic ventricular fibrillation or other causes. Also excluded were those, who received a non-elective generator replacement due to infections, technical issues such as pace or sense failures, heart transplant or device recalls. In

Paper X the study population consisted of 4,587 patients implanted with a first-time ICD or CRT-D for secondary prevention and baseline data were acquired on the date of implantation in same fashion as Paper IX. Exclusion criteria were age younger than 18 years, no valid CPR number, inaccurate implantation information, emigration before implantation date, congenital heart disease or if the cause of implantation was unknown.

Medications in MADIT-CRT

Patients had to be on optimal pharmacotherapy in accordance with HF guidelines prior to enrollment in the trial as previously mentioned under presentation of the trial[69]. Optimal HF therapy at that point in time consisted of beta-blockers, angiotensin-converting enzyme inhibitors (ACE) or angiotensin receptor blockers (ARB) and statins (for ischemic patients) in a stable regime for at least one month prior to enrollment. Beta-blockers furthermore had to have been prescribed for three months in a therapeutic dose. The choice of beta-blockers and other HF therapies was left to the discretion of the implanting physician. All medication, including type of beta-blocker, and the doses were recorded at baseline and during clinical follow-up at one month and at three-month clinical intervals. This allowed for continuous registration of type and doses of HF medication throughout the trial.

Device implantation, programming, and interrogation in MADIT-CRT

Boston Scientific devices, commercially available, were used in MADIT-CRT and were implanted by standard transvenous implantation methods. Programming mode was DDD for CRT-D, VVI for single-chamber ICDs, and DDI for dual-chamber ICDs with a lower rate of 40. Details on AV delay, sensitivity, pacing output and RV-LV timing were given in the protocol. Protocol recommendations included programming a VT zone at 180 beats per minute (bpm) with 2.5 second (s) detection and a VF zone at 250 bpm with 1 s detection. VT zone therapy was burst-type ATP first, then shock; second therapy should be shock at defibrillation threshold plus at least 10 Joules. The remaining therapies was maximal energy shocks. Time (date, hour, second) and total number of any given ICD therapy was captured in the device memory and on printouts. BIV pacing percentage was determined as the average delivery of BIV pacing percentage throughout the follow-up time at the last available device interrogation. All device interrogation were sent to the independent

electrogram analysis core laboratory at Stanford University Medical Center, Stanford, CA, for categorization and final blinded evaluation of detected arrhythmias/therapies.

Echocardiographic methods in MADIT-CRT

Echocardiograms were performed before device implantation and at 12-months follow-up[68]. Paired echocardiograms from baseline and at 12-months were available in 752 patients in the CRT-D group. Echocardiography investigators and sonographers at the centers were qualified to perform echocardiography according to the protocol. Echocardiograms were sent on videotape or digital storage media to the independent echocardiographic core laboratory at Brigham and Women's Hospital, Boston, MA, where they were screened for quality and then analyzed offline blinded to intervention type and outcome. The ventricular and atrial diameters were measured according to standard methods. Apical 4- and 2-chamber views and Simpson's disk method was used to measure left ventricular and atrial volumes. The LVEF was calculated according to the established American Society of Echocardiography protocols[71]. The coefficients of variation for end-diastolic volume, end-systolic volume, and LVEF were 5.2%, 6.2%, and 5.5%[72].

Holter monitoring methods in MADIT-CRT

Patients assigned to CRT-D underwent 24-hour 12-lead Holter monitoring prior to implantation and at 12-months follow-up. Mortara H12 recorders were utilized, and data were analyzed by the noninvasive ECG core laboratory located at the University of Rochester Medical Center, NY, using Mortara H-Scribe scanning system (Mortara Instruments, Inc, Milvaukee, WI). The automatically derived annotation of beats was verified for quality by experienced ECG technicians blinded to outcome and data was further used to quantify monitoring period, total beats during monitoring period, total atrial and ventricular ectopic beats, runs of atrial tachycardia and runs of VT.

Adjudications and outcomes definitions in MADIT-CRT

An adjudication as a HF event required symptoms consistent with congestive HF and response to intravenous decongestive therapy for outpatients and either oral or intravenous decongestive therapy for in-hospital stays. The diagnosis of a HF event was adjudicated by a HF committee blinded to treatment assignment using the clinical documentation from hospital or outpatient

settings[68]. Death was for all analyses based on all-cause mortality with specific classification of deaths as SCDs, other cardiac, non-cardiac and uncertain death used in Paper IV based on the Hinkle-Thaler criteria; adjudicated by a mortality committee[73]. Adjudication of electrograms was performed by an independent arrhythmia adjudication committee blinded to treatment assignment and outcomes. An appropriate ICD therapy for VT or VF delivered as either ATP or shock defined the term "VTA" used in Paper III, IV and V, while the term appropriate ICD therapy was used in Paper I. In Paper IV VTA was further grouped as slow VTA<200 bpm and fast VTA≥200 bpm. In supplement to the core lab adjudication of electrogram; VT was defined as ventricular rate up to 250 bpm with V>A, if 1:1 A:V relationship on the EGM, changes in V-V interval would drive changes in A interval. VF was defined as ventricular rates faster than 250 bpm with disorganized electrograms.

Inappropriate ICD therapy used in Paper II and IV was defined as occurrence of ICD therapy delivered as ATP or shock, without the presence of VT or VF as by adjudication above. Inappropriate ICD therapy was grouped by arrhythmic type in atrial tachyarrhythmias, AF and/or atrial flutter, non-arrhythmic events, and other arrhythmic events.

ICD programming in MADIT-RIT

As noted, patients were randomized 1:1:1 ratio to conventional (A), high-rate (B) and delayed (C) ICD programming. Details of ICD programming was further described in the protocol[70]. In all three treatment arms, ICD therapy was ATP first, followed by shock therapy, when ATP was not successful in termination of the detected VTA. Conventional programming had two zones: One zone 170-199 bpm (detection delay of 2.5 s) and a second zone ≥ 200 bpm (detection delay 1 s). High-rate cut-off programming also had two zones and comprised a monitor-only zone in 170-199 bpm range and a second zone ≥ 200 bpm (detection delay 2.5 s). Delayed programming comprised three zones: one zone 170-199 bpm (detection delay 60 s), a second zone 200-249 bpm (detection delay 12 s), and a third zone ≥ 250 bpm (detection delay 2.5 s). For all detection delay time periods the devices allowed for monitoring and recording of the arrhythmia. Anti-bradycardia pacing was DDD mode with lower rate of 40 and recommended to avoid unnecessary right ventricular pacing in ICD devices and to use of SMARTDelay algorithm and BIV trigger ON to enable maximum BIV

pacing in CRT-D devices. For all settings the built-in Rhythm ID detection enhancements was ON and details were provided in the protocol of the trial[70].

Adjudications and outcomes definitions in MADIT-RIT

Episodes and therapies from device interrogations were reviewed independently by the interrogation adjudication committee blinded to the programming arm and broadly categorized into inappropriate ICD therapy and appropriate ICD therapy with specific definitions listed below. The present thesis utilized below definitions in Paper VI, VII and VIII. The definition of inappropriate ICD therapy was based on ICD therapy delivered (ATP or shock) for anything else than VT or VF. The inappropriate ICD therapy was then interpreted and classified as sinus tachycardia, regular supraventricular tachycardia (SVT), AF or flutter or other entities such as noise, T-wave over-sensing, electromechanical interferences and myopotentials. AF was identified as an episode with rapid, irregular atrial activity with disorganized atrial electrograms and with irregular ventricular rhythm. Atrial flutter was defined as fast atrial rhythms with stable cycle length, and often with a 2:1 AV-conduction. Sinus tachycardia was defined as a rapid atrial and ventricular activity with 1:1 AV-conduction. Regular supraventricular tachycardia (SVT) included atrial tachycardias, atrioventricular nodal reentry tachycardia, and atrioventricular reentry tachycardia. Monitored-only, non-treated, SVTs were defined as all SVTs without device therapy at a rate ≥170 bpm for >30 beats. Appropriate ICD therapy was defined as ICD therapy delivered for VT or VF as adjudicated by the interrogation adjudication committee and further categorized by heart rate ranges. Syncope was defined as a transient loss of consciousness with a rapid and spontaneous recovery. All syncopal events were required to be reported as a safety end point and were reviewed by a morbidity and mortality committee using available documentation and ICD interrogations to establish the cause and if possible, a rhythm-symptom correlation. Syncope was categorized as arrhythmogenic if caused by SVT, VT, VF, asystole or other or non-specified arrhythmias. Non-arrhythmogenic syncope comprised vasovagal, orthostatic, neurological or metabolic loss of consciousness. Deaths were reviewed by the morbidity and mortality committee that appraised all available information on lethal events during the study from clinical charts and ICD recordings and agreed upon classification of individual deaths as cardiac (sudden or non-sudden) or non-cardiac, according to a modified Hinkle-Thaler definition[73]. Only all-cause mortality was used in the analysis of the present thesis.

Comorbidity, procedures, and medications in Danish register data

Comorbidity definitions for baseline variables in Paper IX and X were based on ICD-8 and ICD-10 discharge diagnose, procedural codes and ATC codes as listed in Table 3.

Table 3. ICD-codes, procedure codes and ATC-codes for defining baseline comorbidities in Paper IX and X.

Comorbidity	Details	ICD-8, ICD-10 and ATC-codes used
Myocardial infarction	An admittance ever, under the diagnosis of myocardial infarction.	ICD-8: 410. ICD-10: I21-23, I252.
Ischemic heart disease	An admittance ever, under the diagnosis of ischemic heart disease, coronary bypass surgery, or percutaneous intervention.	ICD-8: 410-414. ICD-10: I20-25, T822, Z951, KFNA, KFNB, KFNC, KFND, KFNE, KFNH20, KFNG.
Atrial fibrillation	An admittance or ambulatory visit within the last 5 years under the diagnosis of atrial fibrillation or radiofrequency ablation for atrial fibrillation.	ICD-8: 4274. ICD-10: I48, BFFB03, BFFB04
Diabetes	An admittance or ambulatory visit within the last year under the diagnosis of diabetes with or without complications. Redeemed prescription glucose lowering medication within 180 days prior to baseline.	ICD-10: E10, E11, E13, E14. ATC: A10
Chronic obstructive pulmonary disease	An admittance or ambulatory visit within the last 5 years under the diagnosis of chronic disease of the lower airway. Redeemed prescription of medication for obstructive pulmonary disease within 180 days prior to baseline.	ICD-8: 490-493. ICD-10: J40-47. ATC: R03.
Chronic kidney disease	An admittance or ambulatory visit within the last 5 years under the diagnosis of chronic renal failure disease	ICD-8: 581, 582. ICD-10: I12-13, N18, T861, Z940, Z992.
Percutaneous coronary intervention	Procedure codes of percutaneous coronary intervention.	KFNG00, KFNG02, KFNG05, KFNG10, KFNG12 KFNG96
Coronary artery bypass grafting	Procedure codes of coronary artery bypass grafting.	KFNA, KFNB, KFNC, KFND, KFNE, KFNH20
Amiodarone	Prescription redeemed within 180 days prior to baseline.	C01BD01
Digoxin	Prescription redeemed within 180 days prior to baseline.	C01AA
Beta blockers	Prescription redeemed within 180 days prior to baseline.	C07AB02, C07AA05, C07AB03, C07AB07, C07AG02, C07
Calcium channel blockers	Prescription redeemed within 180 days prior to baseline.	C08, C09BB, C09DB
Diuretics	Prescription redeemed within 180 days prior to baseline.	C07B, C07D, C03A, C03EA, C03C, C03EB
Renin angiotensin system inhibitors	Prescription redeemed within 180 days prior to baseline.	C09AA, C09BA, C09BB, C09CA, C09DA, C09D C09XA02, C09XA52
Statins	Prescription redeemed within 180 days prior to baseline.	C10AA

Non-cardiac comorbidity definitions used in Paper IX included ICD-8 and ICD-10 discharge diagnoses for dementia, stroke, psychiatric diseases, rheumatic diseases, liver disease, peripheral vascular disease, cancer, chronic obstructive pulmonary disease, chronic renal disease and DM. For DM and chronic obstructive pulmonary disease, the definition included any redeemed prescription of glucose lowering medications or medications for obstructive pulmonary disease, respectively. Procedure codes for percutaneous coronary intervention and coronary artery bypass grafting were also used to supplement the definition of ischemic heart disease (IHD) and as baseline procedural data, Table 3. ATC codes on redeemed prescriptions up to 180 days prior to generator replacement (Paper IX) or ICD implantation (Paper X) were used to define concomitant medications at baseline. Specific data on doses were not available for the two studies. For Paper X the assumed underlying cardiac etiology as well as rhythm indication for a secondary preventive ICD at time of ICD implantation was registered by the implanting electrophysiologist in the

database. The data were stratified on the following groups; IHD, dilated cardiomyopathy (DCM), HCM, other cardiomyopathies (including prior myocarditis, cardiac sarcoidosis, amyloidosis and noncompaction), idiopathic VF, ARVC, long QT syndrome and Brugada syndrome (last two as one entity termed channelopathies). LVEF and NYHA functional class was registered in the DPIR based on clinical information and most recent echocardiogram available at time of implant. For Paper IX, updated NYHA functional class and LVEF were only available for a limited number of patients at time of generator replacement, since it was not a requirement to register this data for the procedure.

Adjudications, programming, and outcomes in register data

Device programming was not registered in DPIR and no information was available, but was typically set in accordance with current manufacturer specifications and consensus documents for primary prevention patients and programming. For secondary prevention the programming was typically set in an individualized manner depending on presenting arrhythmia documentation, cardiac diagnosis and/or age. Outcomes in Paper IX and X included first appropriate ICD therapy and all-cause mortality. First inappropriate ICD therapy was included in Paper X only. Appropriate ICD therapy was defined as a device activation of either ATP or shock for VT or VF and the definition of inappropriate ICD therapy was a device activation as either ATP or shock for rhythms not considered to be VT or VF.

Device activations were registered in DPIR at either remote follow-ups through remote ICD transmissions or through scheduled or unscheduled clinic visits or hospitalizations. The outcomes were prospectively collected, evaluated and recorded in the DPIR by the device technicians and treating physicians and was not based on the device-based interpretation of the episode. Death and date of death defined all-cause mortality and were available through the Danish Civil Person Register.

General statistics

Throughout the present thesis from Paper I through X, continuous covariates were expressed as mean ± Standard deviation (SD) or medians with 25^{th} and 75^{th} percentiles. Categorical data were summarized as frequencies and percentages. Baseline clinical characteristics were compared between various grouped patients in the thesis papers using Wilcoxon ranked sum test or Kruskal-

Wallis test for continuous covariates and Chi-square test or Fisher's exact test for categorical covariates, as appropriate. In Paper III, the echocardiographic measurements and evaluation from baseline to 12-month follow-up was compared using ANOVA or Kruskal-Wallis test for continuous covariates, while a chi-square test was used for the categorical covariates. In Paper III and IV multivariate logistic regression models were used to select covariates with a significant (p-value <0.05) association with low BIV pacing (as 1/0 covariate) in Paper III and LVEF normalization (as 1/0 covariate) in Paper IV. These covariates were selected from the pool of available clinically parameters and measurements collected at enrollment in the two trials. Cumulative probability of given outcome in Papers I through VIII was displayed by Kaplan-Meier method as survival analysis with comparisons of cumulative event rates in patient subgroups by the log-rank test. For Paper IX and X, the outcomes of appropriate and inappropriate ICD therapy were displayed using cumulative incidence curves that accounted for competing risk of death and by Kaplan-Meier for all-cause mortality. Multivariate Cox proportional hazards regression analyses[74] were used to identify and evaluate the impact of covariates on the effect of subsequent outcomes used in Paper I through X. The multivariate Cox models were adjusted for relevant clinical covariates found by either best subset regression or stepwise selection always including those that are predictive of the outcome at a p-value of <0.05. These methods for covariate selections were used after an initial rational and clinical pre-selection of relevant covariates. Therefore, throughout the thesis the covariates that were adjusted for varied with the specific outcome as well as with the sample sizes in order also to uphold robust models with approximately one covariate per 10 events. Time-dependent covariates were utilized in Paper I and II, V, VI and VIII and were incorporated in the multivariate Cox regression models and specifically in Paper I and II with identification of patient follow-up time either "on" or "off" specific beta-blockers. For Paper V, VI and VIII time-dependent covariates of in-trial events, such as syncope, inappropriate and appropriate ICD therapy were incorporated in multivariate Cox regression models on outcomes of all-cause mortality adjusting for relevant covariates found as described above; thus, allowing specific risk time to be calculated and analyzed from the in-trial event to the time of reaching the outcome or censoring of the data. Interactions of covariates and investigated outcomes were tested systematically through Paper I-X and reported if significant. In Paper I, III and V the known interaction in MADIT-CRT of LBBB and CRT-D treatment on HF or death outcome was taken into account and, where possible, effects

were shown for LBBB patients and CRT-D patients versus non-LBBB and ICD patients separately. The assumption of proportionality was assessed by examining log-negative-log survival curves as well as testing interactions of the main effects with the log of follow-up time in multivariate models and checked whether hazard ratios (HR) for examined covariates were time-varying. For Paper X, we estimated temporal annual rates of outcomes from events by individual risk time in person-years. The trend of event rates over time was evaluated by the Kendall tau-b correlation test. Throughout this thesis, all statistical tests were two-sided and a p-value of <0.05 was considered statistically significant. Odds ratios (OR) and HR with their 95 % confidence intervals (CI) and two-sided p-values were reported for multivariate logistic regression analyses and multivariate Cox regression analyses, respectively. For this thesis summarized results was provided using the following standard, i.e., HR 1.00, CI 1.00-1.00, p=1.00 or HR 1.00, p=1.00. Analyses were carried out with SAS software (version 9.3, SAS institute, Cary, North Carolina).

Methodological considerations

Overall, both MADIT-CRT and MADIT-RIT were multicenter randomized clinical trials with blinded adjudications of events and rigorous follow-up and data management ensured by major expert core laboratories and statistical facilities. However, in the present thesis several methodological considerations and limitations should be acknowledged. In MADIT-CRT several of the available covariates such as lab measurements of NT-pro BNP, clinical six-minute walking test, and annotation of patients who had NYHA class III symptoms prior to enrollment had more than 5% missing values and were not evaluated in the multivariate Cox regression models. Further in Paper IV, a 12-months follow-up echocardiogram was used to evaluate risk of various outcomes. Such an approach used a selected cohort of likely healthier surviving patients, who survived until the 12-month mark and follow-up echocardiogram, an issue termed *survival bias*. Also, in Paper IV not all patients (although maybe randomly picked) had paired echocardiograms from baseline to 12-months follow-up. This could potentially lead to a selection of a certain group of patients, an issue termed *selection bias*. In MADIT-RIT baseline ECG was missing in >50% and echocardiograms were evaluated based on measurements from enrolling center rather than echocardiogram core-lab measurements (as in MADIT-CRT). This method is particularly prone to include patients with higher LVEF than enrollment criteria; this issue is known as *inclusion bias*. This issue was detected

in MADIT-CRT and it was shown that 38% of patients enrolled had LVEF above the inclusion criteria if LVEF was evaluated by the echocardiogram core-lab rather than the enrolling center[75]. All Papers in this thesis violated original trial randomization and used multivariate Cox regression and (in Paper I and II) supplementary propensity score analyses to adjust for potential confounders. This approach cannot take into account potential confounders that are not measured or included in the trial. This bias is typically referred to as *unmeasured confounding bias*. Throughout the papers the various biases were sought handled by combinations of using several statistical covariate selection methods, by only including covariates that were biologically plausible to influence effect/outcome, by rational discussion of which covariate though to be clinically relevant and by using several different statistical methods to reach the same result such as propensity score matching and Cox proportional hazard regression analyses. Furthermore, whenever results from the papers should or could not be generalized or when complementary supporting studies were needed this was pointed out in limitation sections or worded conservatively. Specifically, in MADIT-RIT the follow-up time was relatively short particularly when considering death event rates and death power analysis. A total of 71 deaths occurred during an average of 1.4 years of follow-up. This was a considerable limitation in Paper VI, VII, and VIII and needed to be pointed out in the papers. Likewise, the quite small number of syncopal events in Paper VI results in limited statistical power to differentiate between the three randomized arms. In general, the objectives in the papers of the present thesis were not pre-specified and the outcome of inappropriate ICD therapy was not a pre-specified outcome in MADIT-CRT. However, one pre-specified objective in MADIT-CRT was to evaluate whether Holter-recorded noninvasive electrocardiographic parameters could identify subjects with increased hemodynamic benefit in CRT-D group. This objective was considered and analyzed in Paper III. In MADIT-RIT, syncope was a pre-specified tertiary outcome and this analysis was expanded to the etiological (adjudicated) cause of and influence of syncope by the randomized arms (Paper VI). Further, the occurrence of events and event rates in ischemic and nonischemic cardiomyopathy was a tertiary planned analysis in MADIT-RIT[70] (Paper VII). Evaluating non-pre-specified outcomes in subanalyses is prone to statistical data dredging ('fishing') and when large numbers of tests are performed, some produce false results; hence 5% of randomly chosen hypotheses turn out to be significant at the 5% level. When enough hypotheses are tested some will falsely appear statistically significant, since most data are likely to

contain random correlations. The papers in this thesis sought to avoid this potential problem by developing hypotheses that were discussed in an academic research group prior to acquiring data and analysis. Subanalysis from clinical trials should in general be interpreted with some caution and further scrutinized in future studies in different datasets/populations. Interaction between covariates is very important in these types of sub-studies and the prognostic information achieved should if possible be reported by covariates. An example from the MADIT-CRT study is LBBB-CRT-D treatment interaction. Overall, the HR for HF or death for CRT-D as compared to ICD was 0.66 indicating an overall effect of CRT-D[41]. A significant interaction for QRS >150 ms was however found and reported in the primary paper[41] but not until secondary data analysis were performed it was clear that the interaction was limited to the LBBB QRS morphology[76] and thus CRT-D benefit was entirely beneficial in LBBB patients and not in non-LBBB patients – no matter the QRS width. This was shown again in the results of the long-term follow-up[77]. Another important consideration in statistical subanalyses is *over-adjustment*. If incorporating clinical covariates that are highly correlated in the multivariate analysis it is possible to underestimate the effect of one or both of these covariates. In all papers of the present thesis, it was sought to avoid over-adjustment and we evaluated and discussed covariates that were highly correlated prior to implementation into a risk model. Several limitations and considerations related specifically to the two papers from the nationwide registers. The data from DPIR were prospectively collected but analyzed retrospectively. The outcomes of appropriate and inappropriate ICD therapy may have been underreported and misinterpreted. The decision only to use time to first event assumed that for patient with multiple therapies, either ATP or shock within a short time span, only one of the therapies would be registered in the DPIR. This is however unknown, and the data have not been validated, which is a major limitation in the use of these outcomes. Validation of these outcomes by either an expert adjudication committee or a core-lab would have increased the validity of these data and increased the chances of correct interpretation. Register-based observational data that are analyzed retrospectively are very prone to bias. *Unmeasured confounding*, as mentioned above, was very likely present in group comparisons for both Paper IX and X. Although the Cox proportional hazard risk regression models were adjusted in the best possible manner, *unmeasured confounding* may have biased the results since the data was not very granular. Information on comorbidity was based on a discharge diagnosis from hospital. This approach

therefore depended on correct registration and coding by a discharging physician and secretary in the National Patient Register. Description and validations of the registers have been published on many occasions[78]. Most often the positive predictive values were reported and with high values, but the sensitivity of many of the diagnoses were unknown since this requires extensive validation work. Therefore, some comorbidities were likely underreported by this coding-based approach on hospitalizations, because COPD, DM and chronic kidney disease do often not require hospitalization, this is termed *misclassification bias.* To limit the underreporting and increase the prevalence we additionally allowed for redeemed prescription of medications specifically related to the diseases. When estimating the prevalence of medications in observational studies, the risk of *confounding-by-indication* is present, but the influence of this likely minimal in the two cohort studies since data on medications were not used as clinical adjustable covariates. The LVEF registration in the DPIR was based on the last performed echocardiogram available to the implanting clinician. Although it may be usual practice to report the LVEF in an echocardiogram with a given range, i.e., 35-40%, the DPIR registration only allow for *one* number. The registration practice of this issue in the DPIR was unknown. Furthermore, there was no requirement to the age of the echocardiogram at time of implant, and the time from echocardiogram to procedure date was unknown. The burden of non-cardiac comorbidities in Paper IX was an oversimplification of the disease "burden" and it was unknown and not further explored if one non-cardiac comorbidity contributed more to mortality and appropriate ICD therapy than the other. Other considerations to account for in the thesis included the limited follow-up time in Paper IX and possible *selection bias* towards the healthiest patients presenting for generator replacement, while those with terminal HF or other terminal comorbid conditions would not be candidates for elective ICD generator replacement.

Chapter 4.1

Pharmacological considerations and use of beta-blockers in patients treated with ICD or CRT-D

Optimal, per guideline, evidence-based pharmacological treatment was a requirement for enrollment in most major trials involving HF patients and device-based technologies. In MADIT-CRT, patients were required, per protocol, to be optimally medically treated and accordingly the majority of patients were treated with evidence-based ACE inhibitors or ARBs, beta-blockers and

spironolactone. Paper I and II in this thesis specifically evaluated the use and effect of beta-blockers. Other studies have investigated different aspects of treatment with statins, digoxin, diuretics, ACE inhibitors and ARBs in the same cohort[79-81]. Randomized studies have shown that beta-blockers such as metoprolol, carvedilol and bisoprolol reduce SCD and total mortality in HF patients. However, trials and subsequent meta-analysis have mostly considered symptomatic NYHA class II-IV patients[27,30,35,82-84]. Besides the beneficial effect on mortality, quality of life and cardiac reverse remodeling, beta-blockers were considered first-line therapy for prevention of ICD shocks in ICD/CRT patients[85]. Unanswered questions were, however, whether there was a differential effect with different types of beta-blockers, how beta-blockers affected outcomes in mildly symptomatic patients (NYHA I-II) and how they affected outcome among patients with CRT-D. A possible differing clinical effect within beta-blocker types on both mortality and arrhythmias may be due to a variable sympathomimetic activity and variable binding affinity to both beta-receptors and alpha-receptors. A meta-analysis comparing the different beta-blockers in HF patients from major studies without defibrillators did however not find significant differences in total mortality or cardiac mortality[86]. This finding was disputed in a large observational cohort study of unselected HF patients (n>50,000) from the Danish Patient Register[87], where high-dose carvedilol was associated with significantly lower all-cause hospitalization risk (HR 0.84, p<0.001) and lower all-cause mortality (HR 0.87, p=0.008) than high-dose metoprolol. This study did not investigate, or report use of ICDs or CRT-Ds and could not distinguish metoprolol tartrate from succinate. Other observational studies have shown either that carvedilol was associated with either improved outcome[88] or no significant differences when compared to other beta-blockers[89-91]. The Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) evaluated the dose and impact of beta-blocker therapies in post-MI patients with ICDs on long-term outcomes[92]. The study population included 433 patients on and 258 patients off beta-blockers. Patients receiving the highest quartile of beta-blocker dose had a significant reduction in the risk for appropriate ICD therapies for VTA (HR 0.48, p=0.02), when compared to no beta-blockers. Two hypotheses were investigated in this thesis in Paper I and II within the use of beta-blockers[1,2,93]. The first hypothesis tested if carvedilol was associated with decreased risk of HF hospitalization or death and arrhythmias (as determined by appropriate and inappropriate ICD therapies) as compared to metoprolol. The second hypothesis tested whether the effect was dose-dependent. A total of

1,077 (61%) patients were treated with carvedilol, 438 (25%) patients were treated with metoprolol, 146 (8%) patients were treated with other beta-blockers, while 120 (7%) patients were untreated. Carvedilol therapy was associated with a 30% reduced risk of HF or death as compared to metoprolol (HR 0.70, p=0.001), Figure 1.

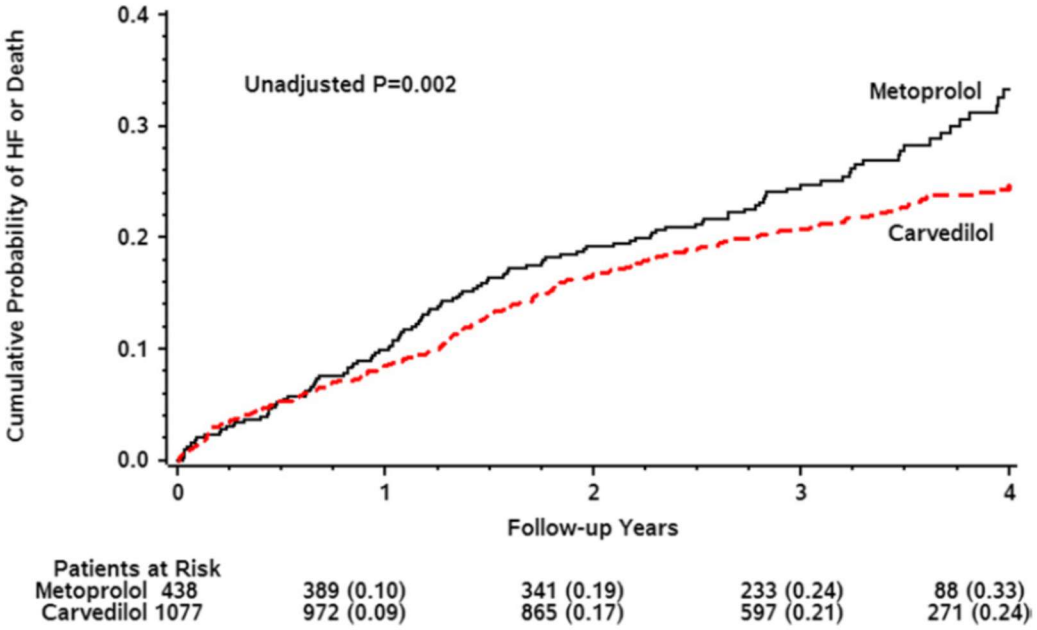


Figure 1 shows the cumulative probability of HF or death according to beta-blocker type, metoprolol and carvedilol. Reproduced with permission. From Paper I.

Further investigation revealed that a subgroup of patients derived pronounced benefit: CRT-D patients on carvedilol (HR 0.61, p<0.001) and CRT-D with LBBB on carvedilol (HR 0.51, p<0.001) when compared to metoprolol. When the risk of appropriately treated VTA was evaluated, similar beneficial effects of carvedilol were observed. Carvedilol was associated with a 20% reduction in VTA (HR 0.80, p=0.05), a non-significant 24% reduction in the CRT-D group (HR 0.76, p=0.069) and 43% significant reduction in the CRT-D LBBB group. In Paper II the influence of beta-blockers on the risk of inappropriate ICD therapy was investigated. Treatment with carvedilol was associated with reduced risk of inappropriate ICD therapy (HR 0.64, p=0.009), reduced risk of inappropriate ICD shocks (HR 0.54, p=0.002) and reduced risk of inappropriate ICD therapy caused specifically by AF (HR 0.50, p=0.004). A significant dose-dependency was observed with a reduction in HF hospitalization or death for patients associated with increasing dose of carvedilol. From baseline to first-change through the study we observed a significant increase in dose for both carvedilol

and metoprolol (from 18 mg±13 to 30 mg±20, p<0.001 and 66 mg±48 to 78mg ±54, p<0.001), but with a relative higher increase in dose for carvedilol. Evidence-based guideline target dose recommendations are currently 25-50 mg for carvedilol and 200 mg for metoprolol[20]. Thus, in MADIT-CRT, on average, patients were generally treated with doses quite below optimal target dose, but in comparable doses to both real-life observational and HF register data[94-96]. The slow release salt succinate used in the MERIT-HF[27] was used in a total of 88% of the patients on metoprolol. Currently (by guideline) the choice of beta-blocker (metoprolol succinate, carvedilol or bisoprolol) for HF patients with ICD or CRT-D devices can be determined by the treating physician. Cautiously interpreted results from Paper I and II, and supported by the reported literature discussed in this thesis, indicated that a choice of carvedilol as a preference beta-blocker aiming for target daily dose of 25-50 mg may be an appropriate consideration for the physician caring for HF patients with implanted devices. The question remains if the observed effect was caused by the type of beta-blocker, by carvedilol-CRT synergistic interaction, by an in-trial relative larger increase in dose closer to recommended target doses for carvedilol than metoprolol facilitated by CRT effect or by a multifactorial general underuse of metoprolol dosage or a combination of the above. Most recently, the beta-blocker type and dose-dependency was however also examined in contemporary Danish ICD patients in 2018 and it was shown that 39% and 26% of the patients were titrated to optimal doses of carvedilol and metoprolol prior to implantation with no differences in outcomes. Further, it was shown that patients on highest doses of beta-blockers were associated with better outcomes in terms of reduced mortality, HF hospitalizations and appropriate ICD therapies underlining the importance of targeting maximal doses[97,98]. Modern HF therapy now may include both angiotensin receptor-neprilysin inhibitors and sodium-glucose co-transporter 2 inhibitors on top of beta-blockers and mineralocorticoid receptor antagonists and it is unknown to what extend the above results can be generalized.

Chapter 4.2

Ectopic beats and biventricular pacing percent in patients treated with CRT

The effectiveness and chance of success associated with implantation of a CRT device relies on the capability to deliver maximal BIV pacing, and even minor reductions in BIV pacing can diminish the beneficial effects of CRT[45,99-103]. Specifically, two studies have looked at this relationship before. A

study by Koplan et al. from 2009[99] used the 1st (lowest) quartile of BIV pacing percentage to set an arbitrary cut-off of <92% BIV pacing in which group the patients had the highest risk of death. The analysis from the ALTITUDE register from 2011 by Hayes et al.[101] from nearly 37,000 patients defined a cut-off of 98.5% of BIV pacing percentage, where the patient population had a maximally different survival pattern. Following these analysis, the MADIT-CRT group analyzed the BIV pacing percentage and associated outcomes and found >97% to be both the mean BIV pacing percentage and the optimal cut-off to separate risk of HF or death in that population, Figure 2[104].

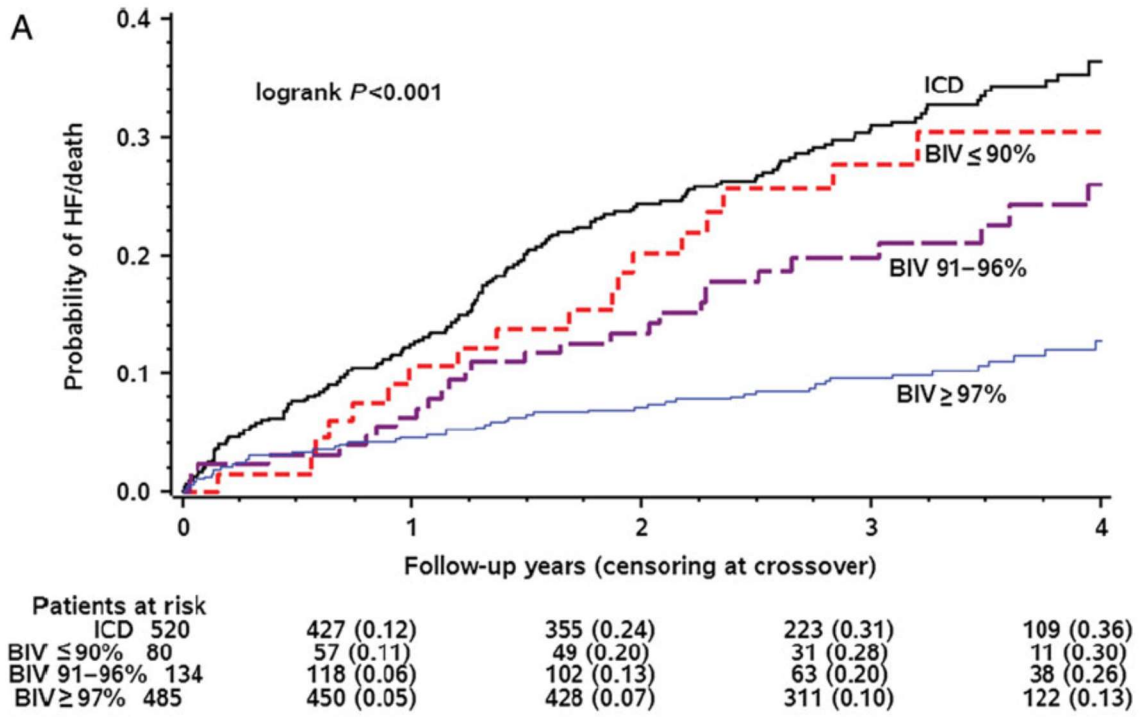


Figure 2 shows the cumulative probability of HF or death according to groups of BIV pacing percentage. Reproduced with permission from Ruwald et al. Eur Heart J 2015;36:440-8. Copyright Oxford University Press.

Several differences existed between these two studies first mentioned and the MADIT-CRT. The study population was primarily NYHA class III (77%) and IV (9%) and up to 34% of the patients had prior atrial arrhythmias with a relative short follow-up of 10 months in the study by Koplan et al. The study by Hayes et al. also included patients with AF and found that mortality was inversely associated with the percentage of BIV pacing and that AF was associated with lower BIV percentages. For comparisons the MADIT-CRT was predominantly NYHA class II (87%) and I (13%),

and 11% had prior atrial arrhythmias (but not within one months prior to enrollment – patients had to be in sinus rhythm) and follow-up was >2.5 years. Thus, the populations were quite different in characteristics and one might expect that sicker, more symptomatic patients, in general would not achieve as high a percentage BIV pacing. With the BIV pacing percentage results from Koplan, Hayes and MADIT-CRT in context we examined the relationship and influence of atrial and ventricular premature complexes (APC & VPC) on BIV pacing percentage in Paper III of this thesis. The aim was to elucidate if such ectopic beats increased the likelihood of low BIV pacing (defined as <97%), as well as reduced the hemodynamic response, and associated with adverse outcomes. The idea was that APCs and VPCs and/or non-sustained VT precluded the delivery of 100% effective BIV pacing and thus compromised symptomatic response and left ventricular reverse remodeling after implantation with a CRT device, Figure 3[105,106].

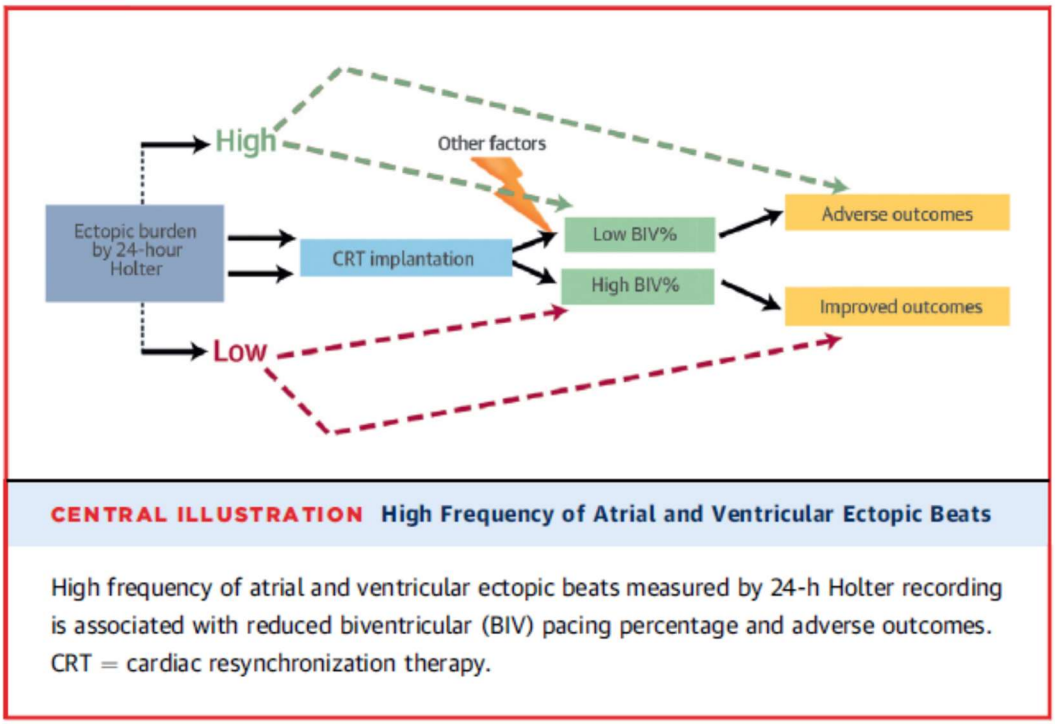


Figure 3 shows a schematic presentation of the influence of ectopic beats on outcomes. Reproduced with permission. From Paper III.

A 24-hour Holter recording is an inexpensive and effective method of acquiring accurate data on the burden and amount of both APCs and VPCs. In Paper III it was shown that a relatively low

frequency (*burden*) of baseline ectopic beats (≥0.1%) increased the likelihood of receiving low BIV pacing (defined as<97%), Figure 4.

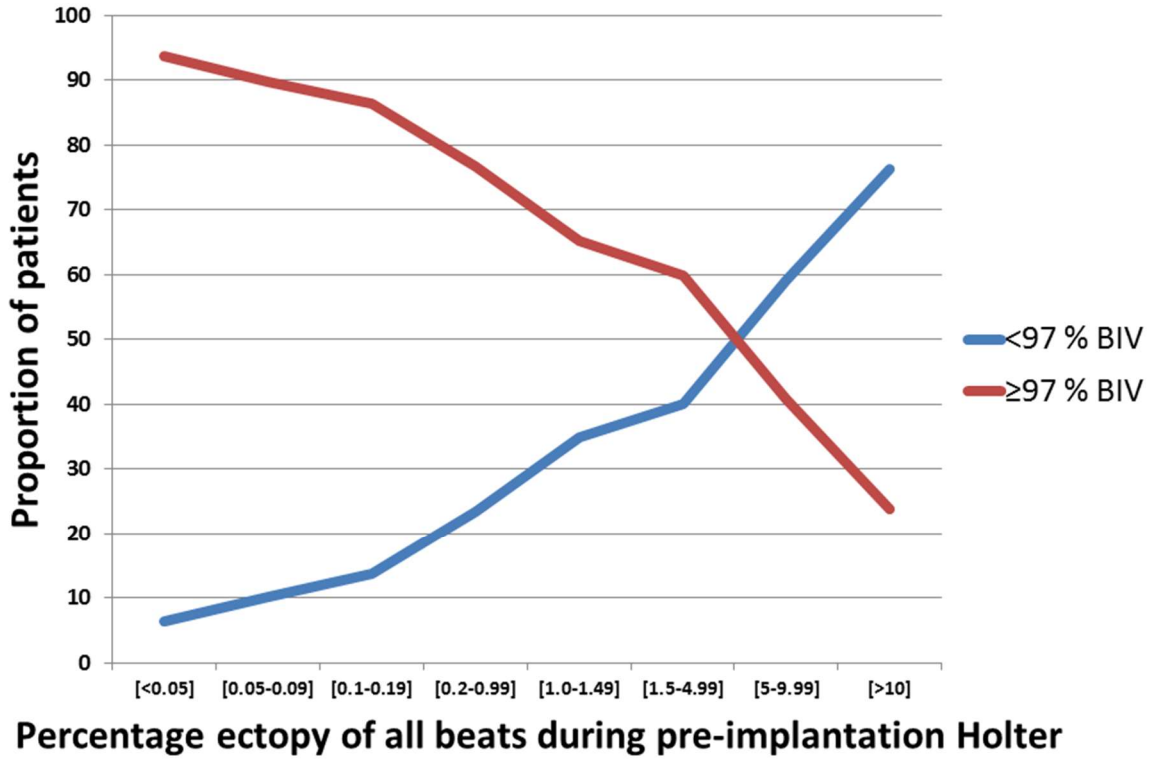


Figure 4 shows the distribution of patients by ectopy burden in percent and stratified by high and low BIV pacing percentage (≥97% and <97%). Reproduced with permission. From paper III.

Further it was shown that the probability of low BIV pacing was increased by 18% per one percent increase in ectopic beats (OR 1.18, p<0.001) or by 16% per 0.1% increase in ectopic beats (OR: 1.16, p<0.001) if estimated by use of an ordinal scale in the range from 0%-1.5% by 0.1% increase and pooling patients above 1.5% ectopy. Reverse remodeling was significantly lower in patients with ≥0.1% ectopic beats compared to patients with <0.1% ectopic beats (% reduction LVESV: 31±15 versus 39±14), p<0.001). The risk of HF or death was significantly increased in those with 0.1-1.5% (HR 3.13, p<0.001) and for >1.5% (HR 2.38, p<0.001). Ectopic beats also significantly predicted future risk of VTA in those with 0.1-1.5% (HR 1.84, p<0.001) and for >1.5% (HR 2.74, p<0.001). The patients who had low prevalence of ectopic beats also had other pre-implantation

characteristics for favorable response in reverse remodeling and clinical outcomes. At baseline these patients had many of the prerequisites already known to result in superior response; female sex, LBBB QRS configuration, lower age and wider QRS configurations[107-109]. The frequency of APC and VPC was comparable to other studies in HF patients[23,110,111,112] suggesting a broader clinical applicability of the results. In HF patients VPCs have been shown to be an independent marker of subsequent malignant VTA and SCD[113-116]. The mechanism by which VPCs and APCs attenuate BIV pacing and worsens outcome is complex and multifactorial. VPCs have a deleterious effect on the clinical course of HF patients in general as they impair cardiac output and may reflect electrical instability in the myocardium or a myocardial arrhythmogenic substrate and thus a marker of impending malignant VTAs[114-116]. APCs (although not as frequent a contributor as VPCs to reduce BIV pacing) may also inhibit optimal BIV pacing through various degrees of fused beats by intrinsic conduction, and probably serve as a marker of later runs of clinically unrecognized AF as has been shown in the general population[117]. For AF this may lead to irregular ventricular responses and increased sympathetic nerve activity, which may promote VTAs and worsen the clinical course. Atrial-ventricular irregularity cause a loss of the atrial contribution to cardiac output, worsening of a mitral regurgitation and exacerbate HF symptoms[118]. Permanent AF has furthermore, as mentioned above, previously been associated with lower rates of high BIV pacing and adverse outcomes[101,119,120]. This observation was important because a significant number of HF patients develop new-onset AF after device implantation and a significant number of patients already have both permanent AF and HF at time of CRT implantation and these patients have not been included in the main trials. More than 20% of CRT recipients in Europe have permanent AF[121] and these patients do currently not achieve optimal benefit. A meta-analysis[122] using 23 observational studies (n=7,495) in which 26% had AF showed that the risk of being a non-responder and death increased by 32% and 50%, respectively in patients with AF. A total of 13% of the patients in the large RAFT[43] trial had permanent AF and did not seem to benefit of CRT-D, compared to those with sinus rhythm or atrial pacing, although the interaction p-value was insignificant. In contrast it was shown in the small MUSTIC AF[123] (n=59) that CRT in permanent slow AF patients was beneficial at least in those achieving >85% BIV pacing. For maintaining sinus rhythm and thereby optimizing BIV efficacy and AV synchronicity, pulmonary vein isolation (PVI) and antiarrhythmic drugs are the mainstay of treatment; while for permanent AF, AV nodal ablation is an option to achieve maximal

BIV pacing. A reduction in hospitalization and an improvement in symptoms using AV nodal ablation and CRT implantation was achieved in the APAF[124] (n=186) and PAVE[125] (n=184) trials. In the observational and retrospective analysis of the CERTIFY register[126] (n=7,384) there was no difference in mortality comparing CRT in AF patients with AV nodal ablation to CRT in sinus rhythm patients, while AF patients treated medically had higher mortality. CRT in conjunction with AV nodal ablation in permanent AF patients (with low BIV pacing) is a class IIa B recommendation in European guidelines[25]. While permanent AF is a major issue it is undetermined how much influence persistent or paroxysmal AF has for outcomes in CRT. Substudies from MADIT-CRT[127] and RAFT[128] showed that in-trial intermittent AF did not attenuate the CRT efficacy or clinical outcomes, suggesting that only permanent AF resulting in low BIV pacing affects the outcomes. With modern day ablation techniques and success rates the role of standard PVI for maintaining and improve BIV efficacy and outcomes, through sinus rhythm, is increasing. The randomized study CASTLE-AF enrolled patients with HF and ICD and symptomatic paroxysmal or persistent AF to PVI versus medical treatment and found significant reductions in HF hospitalizations and mortality[129-131] paving the way for similar studies in CRT patients as well. Along with findings from subgroups in CABANA[132-134] and results of the AATAC trial[135] the sought benefit has now been extrapolated to all HF patients with a recent IIa indication for PVI in AF guidelines 2020[136]. For AV node ablation, again, no large randomized trial has yet shown mortality benefit associated with AV nodal ablation for permanent AF patients. Just published was, however, the APAF-CRT trial (n=133), where AV nodal ablation and CRT was superior to pharmacological rate control of HF patients with recent HF hospitalization and narrow QRS on mortality[137]. An intervention trial targeting VPCs in CRT patients with low BIV pacing percentage is much needed. It is important to select the right patients for CRT implantation who will respond to the therapy, and to identify those who may respond sub-optimally, in order to initiate other treatments or closer follow-up. In Paper III we showed that a relatively low *burden* of baseline ectopic beats increased the likelihood of receiving low BIV pacing and increasing ectopy burden was associated with adverse outcomes. Preimplantation or intermittent Holter recordings may help guide and optimize CRT efficacy.

Chapter 4.3

Left ventricular ejection fraction normalization in CRT

LVEF is an important clinical tool for prognosis as well as for indications of use for both ICD and CRT and this element is a central point in guidelines[20]. A significant improvement in LVEF has been shown consistently for CRT[39-41], but the choice of CRT-D versus CRT-P has not been verified sufficiently with clinical trials. LVEF recovery potentially reduces the need for the defibrillator since the risk of SCD should potentially decline substantially, but this has not been investigated. Other important aspects, although maybe not as pressing in 2021 as earlier, has been increased cost of the ICD, multiple lead fracture issues, inappropriate shocks, infection risks, generator sizes, generator lifetime, and more[138]. In 2013, a document termed "Appropriate Use Criteria for ICD and CRT"[139] was published stating that replacement of CRT-D with CRT-P "may be appropriate" for LVEF 36-49% and LVEF≥50%, which in the era of ICD generator replacements is of considerable interest, but somewhat limited considering the use of DF-4 ICD leads. The use of DF-4 ICD leads makes it impossible, without an adaptor, to downgrade to CRT-P without exchanging/implanting a new RV pace lead. The risk of VTA stratified by clinically relevant LVEF categories at echocardiogram follow-up, where LVEF ≥50% was considered full recovery as well as factors associated with LVEF normalization could be investigated in MADIT-CRT and was explored in Paper IV of this thesis; while the question of efficacy after ICD generator replacement was sought explored in Paper IX. The improvement in LVEF from baseline to 12-month follow-up is shown in Figure 5 stratified by LBBB QRS morphology. The average LVEF increased from 29.5±3.2 at baseline to 40.5±5.9 at 12-months ($p<0.001$).

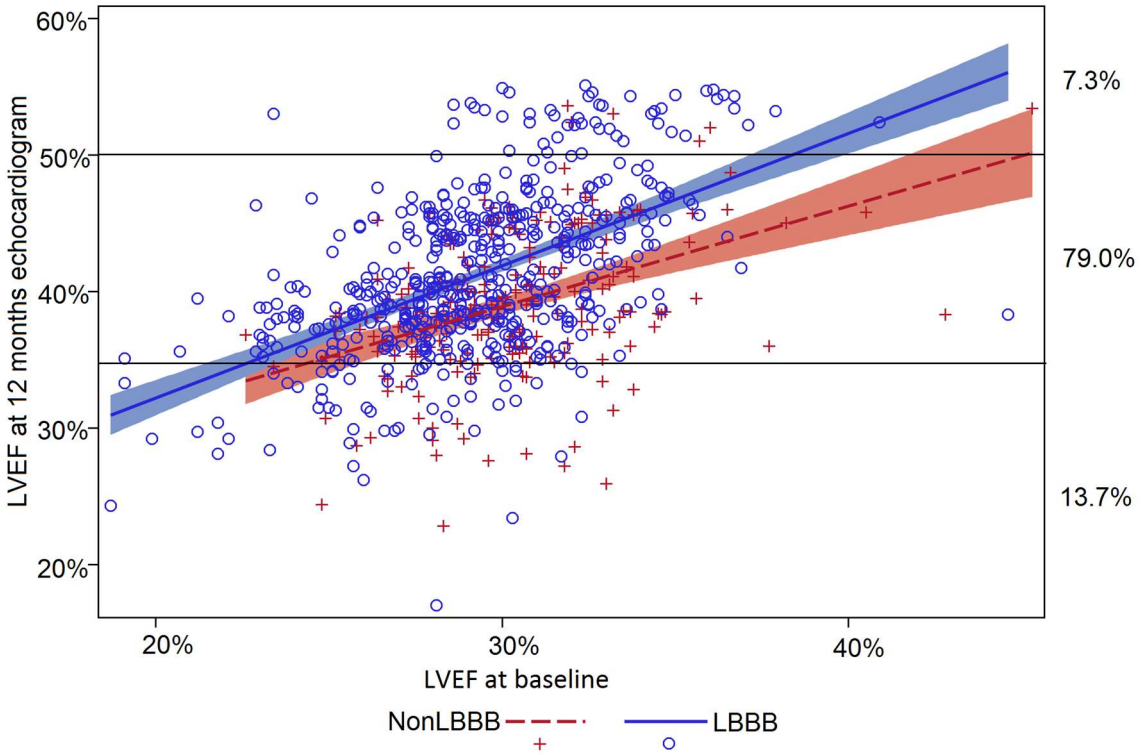


Figure 5 shows the development and improvement in LVEF from baseline to the 12-month echocardiogram by QRS morphology. The clinical groups of LVEF at 12 months and the percentage of patients in these groups are depicted with regression lines and 95% confidence intervals for the regression lines. Reproduced with permission. From Paper IV.

Three groups were defined based on clinical use of LVEF into LVEF ≤35%, LVEF 36-50% and LVEF >50%. A total of 55 (7.3%) patients reached improvement in LVEF >50% (normalization) while 594 (79%) patients improved the LVEF to 36-50% (subnormalization). For LVEF groups of >50%, 36-50% and ≤35% the mean change in LVEF was 19.8±3.5, 11.4 ±3.9 and 4.1±4.2 ($p<0.001$). The primary outcome of appropriate ICD therapy for VTA occurred in 109 (14.5%) of the patients. There was a significant reduction in risk of VTA among both patients with LVEF normalization and LVEF subnormalization, when compared to those with minimal or no LVEF improvement. A total of 3 (5%) patients with LVEF normalization experienced VTAs during follow-up, and of those only one experienced a rate ≥200 bpm and none required a shock for conversion. A total of two patients died of non-cardiac causes in the LVEF normalization group. The LVEF normalization group further experienced very low absolute as well as relative risk of HF or death. In the present Paper IV of this

thesis, important results are summarized here. There was a very low absolute risk of severe VTA (≥200 bm) among patients who had normalized LVEF compared to a significant residual risk of VTA among those with subnormalization of LVEF, Figure 6.

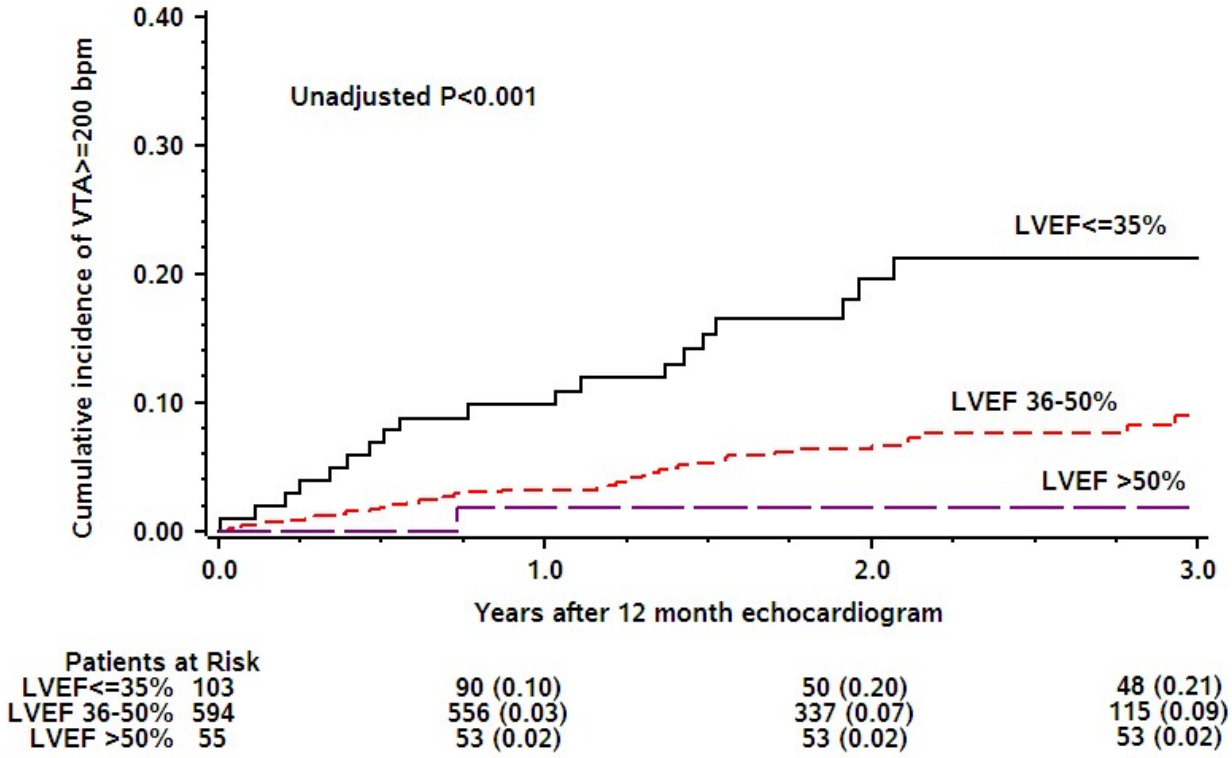


Figure 6 shows the cumulative incidence of VTAs ≥ 200 bpm according to groups of LVEF at the 12 months follow-up echocardiogram. Reproduced with permission. From Paper IV.

The same factors associated with LVEF normalization were also related to a reduced risk of VTA, and patients who improved to LVEF normalization had a good prognosis with a three-year cumulative incidence of HF or death of 7%. Finally, despite of LVEF normalization the risk of inappropriate ICD therapy was similar to those with subnormalization of LVEF. A selection of CRT-P at time of first implantation could be considered in patients likely to achieve normalization of LVEF. This could potentially be female patients with LVEF in the 30-35% range, a LBBB and nonischemic cardiomyopathy with no prior ventricular arrhythmias. Further factors to consider involve preimplantation small atrial and ventricular volumes. This postulation is well in concordance with the later published DANISH study were the risk of all-cause mortality and SCD was relatively low. In that study, an “overall” effect of the ICD could not be proven in a

nonischemic cardiomyopathy population and a large proportion (58%) of the patients received a CRT[140] (see also Chapter 4.7). The MADIT study group and others have previously shown similar and comparable factors associated with CRT-responders and CRT-super-response[107-109,141] as seen with LVEF normalization.

There is a global variation in the use of CRT with or without the defibrillator. In Europe, the use of CRT-D ranged from 9% to 92% (median 45%)[142] and in the United States, CRT-D was used in more than 80% of the cases[60]. The choice of ICD backup for patients that are suitable for CRT has significant implications. The decision involves considerations of inappropriate ICD therapies, comorbidities, complications, costs and cost-effectiveness[25,54,138]. Data suggested that SCD accounted for up to one-third of all deaths in CRT-P patients[39,40] and most patients eligible for CRT also have indication for ICD as previously discussed[45,143]. Therefore, in practice, many patients receive the combined device of CRT-D if both ICD and CRT indications are fulfilled. The incremental survival benefit favoring CRT-D to CRT-P is, however, not supported by solid evidence. The COMPANION[39] as well as a later meta-analysis[144] could not establish survival benefit. One of the main reasons for this is a likely CRT-P effect on reverse remodeling with improvement in left ventricular function. As discussed in the results in Paper IV, reverse remodeling is associated with significant reduction in the risk of subsequent SCD mediated by reductions in risk of ventricular arrhythmias[40,145]. In MADIT-II[146] specific risk factors were reported (in ischemic patients) where the benefit of ICD (compared to medical therapy) was reduced or non-present followed by a reduced benefit in NYHA III patients (ischemic and nonischemic) in the SCD-HeFT trial[23]. Overall factors favoring CRT-P, besides lower cost and lower complication rate, is therefore more advanced HF patients, very elderly, severe renal insufficiency or other major comorbidities, life expectancy less than 1 year, no prior ventricular arrhythmias, and further patients, who are very likely to have major reverse remodeling or LVEF normalization and thus protection from ventricular arrhythmias (nonischemic, baseline LVEF>30%, females, LBBB QRS morphology)[107].

Chapter 4.4

Ventricular arrhythmias in patients with ICD and CRT-Ds

A circadian and seasonal variation in VTAs, MI and SCD has previously been shown[147-153]. The mechanism is believed to be a combination of stress-related surge in circulating catecholamines,

changes in physical activity, cold exposure and alterations in autonomic tone. Exploration of this phenomenon is important in terms of pathophysiological mechanisms and pattern of administration of antiarrhythmic medications, beta-blockers, and behavioral activities with the long-term goal of personalizing medications and activity and improving outcomes. The otherwise well accepted pattern of circadian variation was disputed in a report from the SCD-HeFT trial in 811 ICD HF patients, where they found no circadian variation, which may suggest modified and improved medical HF management, when compared to older studies[154]. The MADIT-CRT trial with rigorous expert adjudication of all VTAs as detected by the ICD with time-stamp of every episode allowed for investigation of this phenomenon. These results as well as general presentation of VTAs in patients with mild HF and a CRT-D or ICD are presented in Paper V. A total of 24% of the patients (427/1,790) experienced device activated VTAs during a mean follow-up of 40 months. A total of 3,300 episodes were registered among these 427 patients with a mean number of VTAs per patient of 7.7 ±22.7. Figure 7 presents the circadian distribution of VTAs and showed four phases in a bimodal pattern termed peak 1, plateau, peak 2 and nadir. Peak 1 was defined as a four-hour period from 7.00 am to 10.59 accounting for 23% of the total amount of VTAs, while the seven-hour nadir phase from 00.00 to 06.59 accounted for 9%.

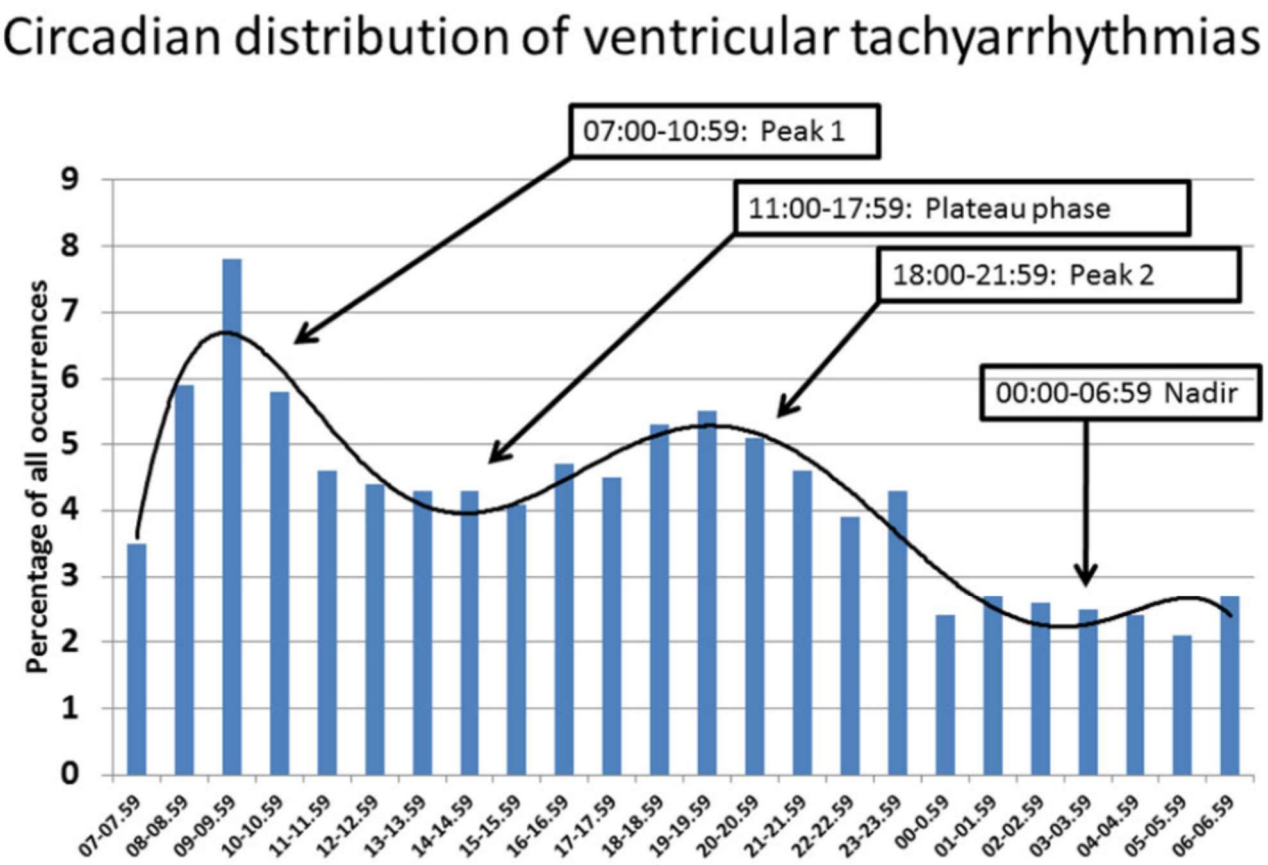


Figure 7 shows the circadian distribution of VTA with 1 peak during morning hours defined as a period of 4 hours from 7 to 10.59, 1 plateau phase from 11 to 17.59, a second smaller peak in the 4 evening hours from 18 to 21.59 and a nadir phase during rest time or potential sleeping hours from 22 to 06.59. Reproduced with permission. From Paper V.

Men accounted for 75% of the population as well as the majority of the proportion of VTAs (90%), thus dominating the trends and phases. When exploring VTAs among the females we found a more heterogenous distribution pattern with lower proportions of VTA in the peak 1 phase (19%), while 32% of the VTAs occurred during the nadir (rest/sleeping) phase, significantly higher than the other phases. Exploring weekdays, there was a steady decline in VTAs from Monday through Sunday ($R2^2 = 0.74$). The time-stamp of the first VTA episode was used as a time-dependent variable in multivariate Cox regression analyses. The results showed that the risk of death was doubled among patients that experienced VTA compared to patients with no VTA (HR 1.96, CI 1.39-2.77, $p<0.001$) and revealed that VTA during morning hours was associated with increased

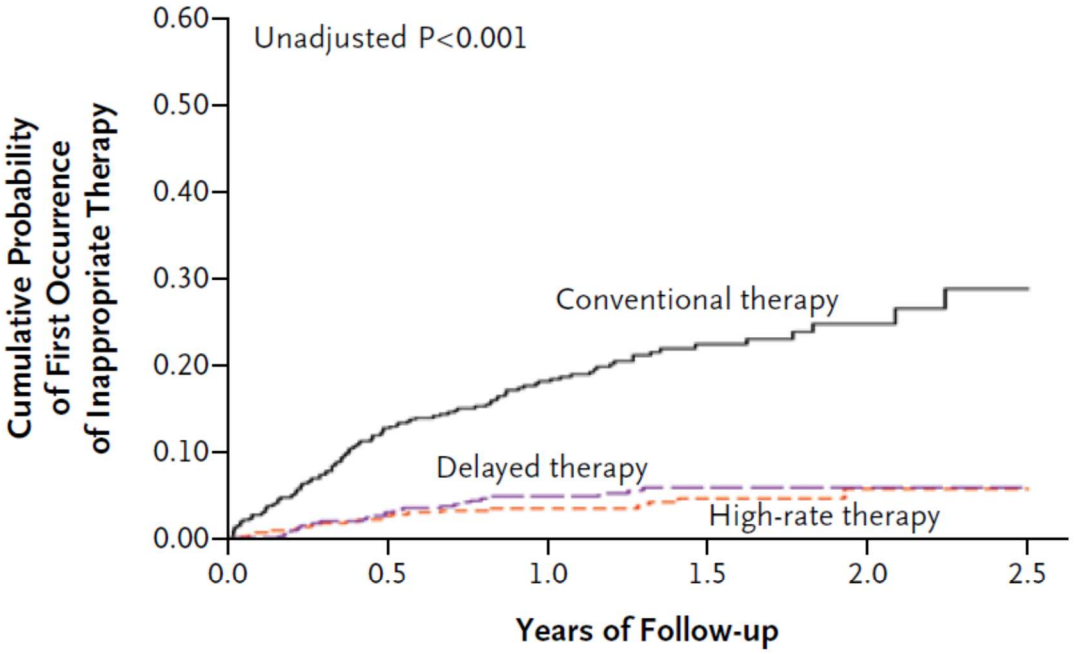
risk of death (HR 2.07, CI 1.14-3.77, p=0.018). The risk of death was highest for females (HR 6.78, CI 1.55-29.86, p=0.011) when compared to males and (HR 1.79, CI 0.92-3.46, p=0.086) with an interaction p value of 0.041. This Paper confirmed the hypothesis of increased VTA during morning and afternoon hours in a very large population of HF patients, as noted in earlier smaller studies cited above, disputing the findings in the report from the SCD-HeFT trial[154]. Most recently a study from 2019 of sudden cardiac arrests in Oregon reproduced the findings of lower incidence of cardiac arrest during nighttime but could not reproduce the morning peak among 1,535 patients[155], while a recent study of 1,559 ICD patients was able to reproduce the bimodal pattern found in MADIT-CRT[156] . The gender interaction displaying a higher risk of death for females with phase-peak 1 associated VTAs was surprising and unexpected and the overall association between phase-peak 1 and subsequent mortality was a novel finding. The proposed mechanisms are multifactorial and involved pathophysiological entities such as myocardial ischemia, abnormal repolarization patterns with variations in hemodynamic properties related to posture, sleep, activity, thrombogenicity, and autonomic tone[157-160]. Another proposed mechanism, most recently shown in 2021, was a variation in the endogenous circadian timekeeping system in cardiomyocytes, but the biophysical mechanisms that should link such molecular circadian clocks to cardiac arrhythmogenesis are not yet understood[161]. In relation to myocardial ischemia and thrombogenicity we were unable to show any difference between patients with ischemic and nonischemic cardiomyopathy. It was unclear why VTAs among females was associated with higher risk of death and this may be a chance finding, as the p-value for interaction was not very strong. However, if the association holds true then the general lower risk of VTAs for females was likely related to a higher chance for females of being CRT responder qua reduction in symptoms, NYHA functional class and improvement in LVEF. Circadian distribution of VTAs may be informative for future guidance of antiarrhythmic medication administration. The proposed suppression of arrhythmogenesis at night-time may be helpful for future studies in mechanisms of protective factors, i.e., increased vagal tone and the relative shift from sympathetic to parasympathetic neuronal dominance, lower blood pressure, reduced myocardial wall stress and myocardial workload.

Chapter 4.5

General ICD programming

Despite the clinical benefit and increased survival with ICD implantation many patients are unfortunately affected by a high frequency of inappropriate ICD therapy. Inappropriate ICD therapy has been shown to be associated with impaired quality of life, unwanted health care resource utilization, and adverse clinical outcome[62-65,162,163]. In addition, a significant proportion of ICD therapies delivered for VTAs may be unnecessary if the rhythm would terminate spontaneously without progression into VF or syncope. These device interventions are known as "unnecessary" ICD therapies. An overview of available data of the rate of inappropriate ICD therapy in both real-life and trial ICD and CRT-D patients was presented in Table 2. The association between increased mortality and inappropriate ICD shocks has been shown in multiple retrospective studies[63-65,164,165], but a direct mechanism has proven to be more difficult to ascertain. Proposed mechanisms include pro-arrhythmic initiation and shock (joules) related myocardial damage leading to progression of HF. Alternatively, inappropriate ICD therapy is simply a surrogate marker for advanced HF and clinical and subclinical AF in more symptomatic (and sick) patients. Same issues and mechanisms have been discussed for unnecessary ICD therapy for VTAs, where an association between adverse outcome and VTAs was also shown[166-170]. Results from a large ICD patient remote monitoring database, The ALTITUDE Survival by Rhythm Study[171], evaluated 3,809 patients who survived a first ICD shock for an appropriate or inappropriate cause and compared to matched control patients, who had not had an ICD shock. A total of 41% of the ICD shocks delivered were inappropriate due to SVT, such as AF/atrial flutter, sinus tachycardia, other SVT, and non-arrhythmic causes including lead noise, artifacts, or oversensing. Mortality was significantly increased for patients with appropriate first shocks for VTAs (HR 1.65-2.10) and for inappropriate first shock for AF (HR 1.61). However, the study did not find increased risk of mortality for those patients with inappropriate first shocks related to lead noise, artifact, or oversensing (HR 0.91) or for rhythms such as sinus tachycardia or SVT (HR 0.97). This observational study thus supported, that the adverse prognosis observed after first shock was related to the underlying arrhythmia rather than an adverse effect of the shock itself. Nevertheless, alternative strategies of ICD programming to reduce the risk of inappropriate and unnecessary ICD therapies and to improve patient outcome were warranted. In the early 2000's, trials were initiated to

overcome the problem of inappropriate and unnecessary ICD therapy. One of the first trials that aimed to reduce unnecessary appropriate ICD shocks was the Pacing Fast VT Reduces Shock Therapies (PainFREE Rx II)[172] trial initiated in 2001, which randomized 582 patients to either ATP or shock as first line therapy for VTAs. It established ATP as safe and effective, when compared to shock for termination of VTAs. In this trial 73% of all VTAs were terminated by ATP and also showed a very low risk of rhythm acceleration associated with use of ATP. In 2006, the Comparison of Empiric to Physician-Tailored Programming of Implantable Cardioverter Defibrillators (EMPIRIC)[173] study (n=900) evaluated physician's custom ICD programming versus empiric ICD programming in three VTA zones (150-200 bpm with 16 beats detection, 200-250 bpm with 18 out of 24 beats detection [number of intervals to detect (NID): 18/24], and >250 bpm). Results were that standardized empiric ICD programming for VTA settings was non-inferior to physician-tailored, patient-specific programming (HR 0.95, CI 0.74-1.23). The Programming of Detection and Therapy Parameters in ICDs Reduces Shock (PREPARE)[174] study from 2008 further demonstrated a reduction in shock frequency by combining the use of ATP for fast VTAs (182-250 bpm), extended detection durations (30 out of 40 beats, NID: 30/40), and the use of SVT discriminators <200 bpm in 700 primary prevention patients. Comparing the PREPARE patients to historic controls from the EMPIRIC and the Multicenter InSync Implantable Cardioversion Defibrillation Randomized Clinical Evaluation (MIRACLE ICD)[175] trial a significant reduction was shown in both appropriate and inappropriate ICD shocks in the first year (9% vs. 17%) and a 56% reduction in morbidity index (comprised of ICD shocks, symptomatic non-treated VTAs and arrhythmic syncope). In 2012 the MADIT-RIT trial[67] (n=1500) as previously mentioned, showed that a relatively simple programming approach involving high-rate cut-off ICD therapy beginning at 200 bpm with a 2.5 s delay resulted in significant 79% reduction in inappropriate ICD therapy and 55% reduction in all-cause mortality for patients receiving ICD or CRT-D devices for primary prevention indications, Figure 8.



No. at Risk

Conventional therapy	514	420 (0.13)	305 (0.18)	149 (0.22)	56 (0.25)	8 (0.29)
High-rate therapy	500	454 (0.03)	339 (0.04)	191 (0.05)	70 (0.06)	17 (0.06)
Delayed therapy	486	445 (0.03)	342 (0.05)	177 (0.06)	82 (0.06)	13 (0.06)

Figure 8 shows cumulative probability of inappropriate ICD therapies according to randomized ICD programming arm. Reproduced with permission from Moss et al. N Engl J Med 2012;367:2275-83, Copyright Massachusetts Medical Society.

The comparison group was termed conventional ICD programming based on MADIT-II[22] ICD settings with ICD therapy for VTA 170-199 bpm with 2.5 second delay and VTA >200 bpm with 1 second delay before ATP or shock. Additionally, MADIT-RIT showed that a more technical approach with delayed therapy ICD programming (60 second delay in range 170-199 bpm and 12 second delay in range 200-250bpm) was associated with 76% reduction in inappropriate ICD therapy and 44% borderline significant reduction in mortality (p=0.06) when compared to conventional programming. The delayed therapy ICD programming resulted, however, in a high number of programming protocol deviations. Both programming settings reduced appropriate ICD therapy significantly 9% and 6% versus 22% for high-rate and delayed therapy versus conventional therapy, respectively. These results were followed by the Avoid Delivering Therapies for Nonsustained Arrhythmias in ICD Patients (ADVANCE III)[176] (n=1,902), which showed a 37%

reduction in inappropriate ICD therapy, but no difference in reduction of appropriate ICD therapy for the intervention group set at increased detection interval (NID: 30/40), when compared to standard setting (NID:18/24 as in the PainFREE II trial). Patients in ADVANCE III were both primary and secondary prevention patients and a recent subanalysis[177] (n=477) showed a significant 25% reduction in overall ICD therapies favoring the long detection setting, when exclusively analyzing the secondary prevention patients.

In both MADIT-RIT and ADVANCE III the reduction in inappropriate and appropriate ICD therapies was dominated by a reduction in delivered ATP. The fact that also appropriate ATP occurred less often in treatment arms set to higher rate cut-offs demonstrated that many VTA episodes terminate spontaneously and do not need ICD therapy. The Programming Implantable Cardioverter Defibrillators in Patients with Primary Prevention Indication to Prolong Time to First Shock (PROVIDE)[178,179] trial (n=1,670) evaluated the effects of randomized longer delay, higher detection rates, and more ATP treatment in the intervention group. Here two VT zones were programmed: a slow VT zone from 180 to 214 bpm (25 beats detection), where two rounds of ATP were attempted prior to shocks, and a fast VT zone from 214 to 250 bpm (18 beats detection), where one round of ATP was attempted prior to shocks. The risk of shock as well as mortality was significantly reduced by 38% and 30% in the intervention group compared to the control group, where ICD programming was set as in the PainFREE Rx II trial. However, in a sense these impressive results were already outdated by the MADIT-RIT and ADVANCE III ICD programming parameters, which utilized more aggressive rate settings in the intervention arms and helped set the standard for use of more ATP prior to shocks in VT zones. The PainFREE SST[180,181] trial published in 2015 further investigated the ability of newer algorithms (SmartShock™ Technology) of increased VTA interval detection to reduce inappropriate shocks in a large sample (>2000 patients) of both primary and secondary prevention and found a two-year inappropriate ICD shock rate of 2.8% for patients with dual chamber ICDs and CRT-Ds and 3.7% for those with single-chamber ICDs. Finally, the Enhanced Device Programming to Reduce Therapies and Improve Quality of Life in Implantable Cardioverter Defibrillator Patients (ENHANCED-ICD)[182,183] showed reduction in unnecessary ICD therapy by prolonging detection duration with an increase in NID to 60/80 without affecting safety or quality of life for the patients. In summary, the ICD programming trend during the last decade has been higher rate cut-offs for VT zones, longer detection times and

more ATP attempts prior to shock, in order to avoid unnecessary treatment of self-terminating VTAs and reduce inappropriate therapies, in particular shocks, without an unacceptable increase in syncopal events as discussed in next chapter. Updated consensus statements from the EP societies were published in 2019 summarizing both that the data and evidence level for ICD programming were strong, consistent and generalizable beyond the specific manufacturers settings and furthermore listed the manufacturer-specific programming settings[184]. Today, there are variations in ICD programming in each ICD-implanting center. For primary prevention patients one approach is four rounds of ATP (burst type in 88% of cycle length) in VT zone 190-240 bpm before shock and ATP during shock charging in a VF zone of >240 bpm. For secondary prevention patients the ICD programming is more physician-tailored depending on presenting rhythm cycle length and factors such as LVEF and knowledge of hemodynamic state at time of VTAs.

Chapter 4.6

ICD programming and syncope

Syncope is a relatively frequent event in HF patients with ICDs. Because of the high-rate cut-off and prolonged delay programming in MADIT-RIT there was a concern for increased risk of syncope among patients randomized to these settings, and thus it was a required safety end point. In Paper VI of this thesis, the specific etiological cause and mechanism of syncope in relation to ICD programming and the impact of both arrhythmogenic syncope and non-arrhythmogenic syncope on death was explored. During the follow-up of 1.4 years, 64 out of 1500 (4.3%) patients had syncope. The incidence of syncope was similar across the three ICD programming treatment arms ($p>0.5$). Prognostic factors of all-cause syncope included the presence of ischemic cardiomyopathy (HR 2.48, $p=0.002$), previous ventricular arrhythmias (HR 2.99, $p=0.021$), LVEF ≤25% (HR 1.65, $p=0.059$), and younger age (by 10-year decrease, HR 1.25, $p=0.046$).

Syncope caused by arrhythmias was responsible for approximately 40% of the syncopal episodes while 60% were caused by non-arrhythmic events such as orthostatic hypotension syncope or vasodepressor reflex syncope. ICD programming to high-rate cut-off or prolonged monitoring algorithms did not increase the risk of syncope caused by VTA and particularly slow VT (in the range from 170-199 bpm) were rare causes of arrhythmogenic syncope with only 1 event (of 34 slow VT episodes). These results indicated that high-risk HF patients with moderate to severe HF

symptoms and reduced LVEF tolerate rather long durations of fast VTs; while slow VTs for practical purposes did not result in a loss of consciousness. In MADIT-RIT both arrhythmogenic and non-arrhythmogenic syncope were significantly associated with increased risk of death irrespective of the etiology (arrhythmogenic syncope: HR 4.51, p=0.012 and non-arrhythmogenic syncope: HR 2.97, p=0.038). Based on these results, syncope in HF patients with ICDs was a significant marker of high risk, independent of the etiological cause of the syncopal event. In perspective this was also reported in a small retrospective study, which found that no patients with slow VT (<187 bpm) experienced syncope[185]. The association between non-arrhythmogenic syncope and increased risk of death found in the present study may indicate that syncope in many HF patients represents an inability to compensate for a hemodynamic collapse rather than an arrhythmic event[186]. Most likely non-arrhythmogenic syncope in HF patients simply identify individuals that are on multiple medications and with reduced cardiovascular reflexes, and based on MADIT-RIT data we cannot postulate that specifically vasovagal syncope is directly related to mortality. A post hoc analysis of SCD-HeFT[187] also indicated that HF patients with syncope had a higher risk of death than those without syncope. The frequency of first-time all-cause syncope in MADIT-RIT was much lower than in SCD-HeFT (4% versus 14%), but with significantly shorter follow-up of 1.4 years versus 3.8 years. It is likely that with a longer follow-up, a similar frequency of all-cause syncope would be found in MADIT-RIT.

Just as in MADIT-RIT, none of the recently reported ICD programming trials have reported increased risk of syncope in the intervention arms. As noted, it was intuitively assumed that prolonging the delay before ICD therapy or increasing the lower rate before ICD therapy could increase syncopal rates. In the PainFREE Rx II[172] increasing detection of NID from 12/16 to 18/24 did not increase syncope. The rate of syncope in PainFREE Rx II was 0.5% for 18/24 versus 2% for 12/16 with no significant difference. In ADVANCE III[176] the incidence of syncope was low in both the long-detection intervention group (NID: 30/40) and in the conventional standard-interval detection group (NID: 18/24). During the study, 34 (2%) patients experienced syncope related to arrhythmic events with 20 and 14 patients (3.1 per 100 person-years and 1.9 per 100 person-years) in each respective group with no significant difference (IRR 1.60, CI 0.76-3.41, p=0.22). In addition, in ADVANCE III the syncopal episodes were not associated with serious injuries. In the

secondary prevention subanalysis[177] from ADVANCE III similar results were reported with syncope in nine patients (2.0 per 100 person/years versus 3.2 per 100 person/years p=0.6) in long-detection versus conventional respectively. In PROVIDE[179], a total of 65 patients (4%) experienced all-cause syncope during an average of 18 months with no significant difference between the intervention group and the conventional group (HR 1.25, CI 0.76 to 2.04, p=0.37). Of these 65 patients, 34% of the patients (n=22) (1.3% of all) had arrhythmic syncope. Numbers very close to those reported in the present thesis. The freedom from arrhythmogenic syncopal events was not significantly different between the two groups (HR 1.64, CI 0.69 to 3.90, p=0.26). Likewise, the calculated arrhythmogenic syncopal event rate was not significantly different between the intervention and control groups (control: 0.012 events/patient vs intervention: 0.017 events/patient, p=0.49). In PREPARE[174], arrhythmic syncope occurred in 1.6% of the patients in a one-year follow-up in the preselected programming (NID: 30/40 beats) group.
In short, ICD programming with either prolonged detection delays or high-rate cut-off before initiation of ICD therapy is safe from a syncope and mortality point of view. Collectively many years of patient follow-up can now be considered, and so far, the acceptable programming threshold for increasing syncope versus reduction in inappropriate and unnecessary ICD therapy has not yet been found. This may be due to the relatively low incidence rate of syncope in the presented studies. However, in the ADVANCE III trial, Gasparini et al. comments that, “when choosing a delayed detection interval protocol, physicians should be aware of the small potential additional risk associated with long-detection intervals”. With much longer follow-up and increasing sample size numerically, it is likely that syncopal rates will increase with higher cut-offs of ICD therapy programming, but so far this has not been shown statistically in the available trials.

Chapter 4.7

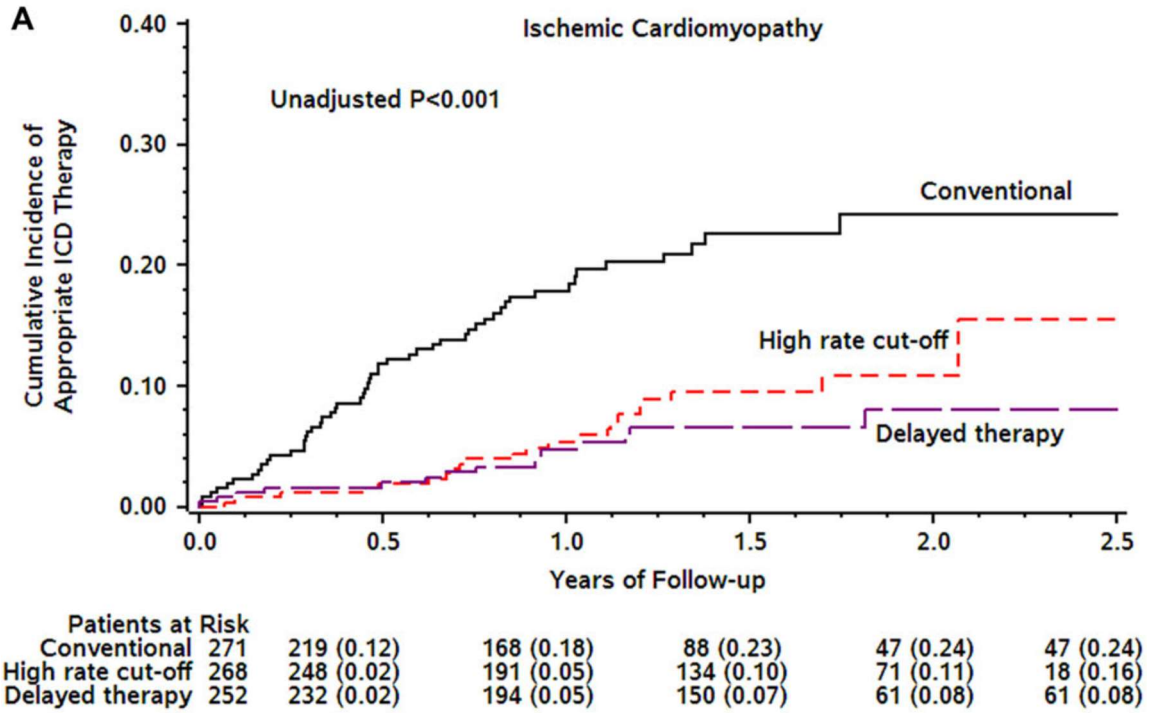
ICD programming and patient subgroups

ICD programming in ischemic and nonischemic cardiomyopathy

The rationale for a differential effect of ICD programming based on type of cardiomyopathy relates to smaller single center studies, which have suggested higher rates of non-sustained VT and higher rates and risk of both appropriate and inappropriate shocks in patients with ischemic cardiomyopathy in comparison to those with nonischemic cardiomyopathy[188]. An à priori higher

rate of both inappropriate and appropriate shocks in this patient group could potentially yield a greater relative benefit of a high-rate cut-off or delayed ICD programming. The VTA rates previously reported have primarily been based upon ICD therapy in VT zone cut-off around 180 bpm and above. Other studies have, in contrast, presented data where rates of both inappropriate and appropriate ICD therapy were similar and thus independent of cardiomyopathy type[189,190]. Given the overall high efficacy of high-rate cut-off and delayed ICD programming compared to conventional ICD programming[67], the hypothesis was that both ischemic and nonischemic cardiomyopathy derive similar significant and clinical benefit of ICD programming interventions, reducing primarily inappropriate ICD therapies but also appropriate ICD therapies.

A total of 791 (53%) of the patients had ischemic cardiomyopathy and in general had more comorbidity, were significantly older and were more often male when compared to patients with nonischemic cardiomyopathy. Less often they were treated with CRT-D (42% versus 60%) to ICD. During a mean follow-up of 17.4 months, there was no difference in risk of inappropriate ICD therapy among ischemic and nonischemic patients (9% vs. 11%, HR 0.96, CI 0.68-1.36, p=0.8), while there was an insignificant trend towards lower risk of appropriate ICD therapy in ischemic patients compared with nonischemic patients (11% vs. 14%, HR 0.75, CI 0.55-1.02, p=0.06). All-cause mortality was 6.1% for ischemic compared to 3.3% for nonischemic cardiomyopathy (HR 1.81, CI 1.07-3.06, p=0.03). The effect of ICD programming was equally pronounced for both ischemic and nonischemic patients: For high-rate cut-off programming the risk of inappropriate ICD therapy was reduced by 81% (HR 0.19, CI 0.09-0.37) for ischemic compared to 89% (HR 0.11, CI 0.05-0.23), [p interaction 0.13] for nonischemic, when compared to conventional programming. Similar results were found when comparing delayed ICD programming to conventional programming and when investigating reduction in appropriate ICD therapy for both programming types (Figure 9).



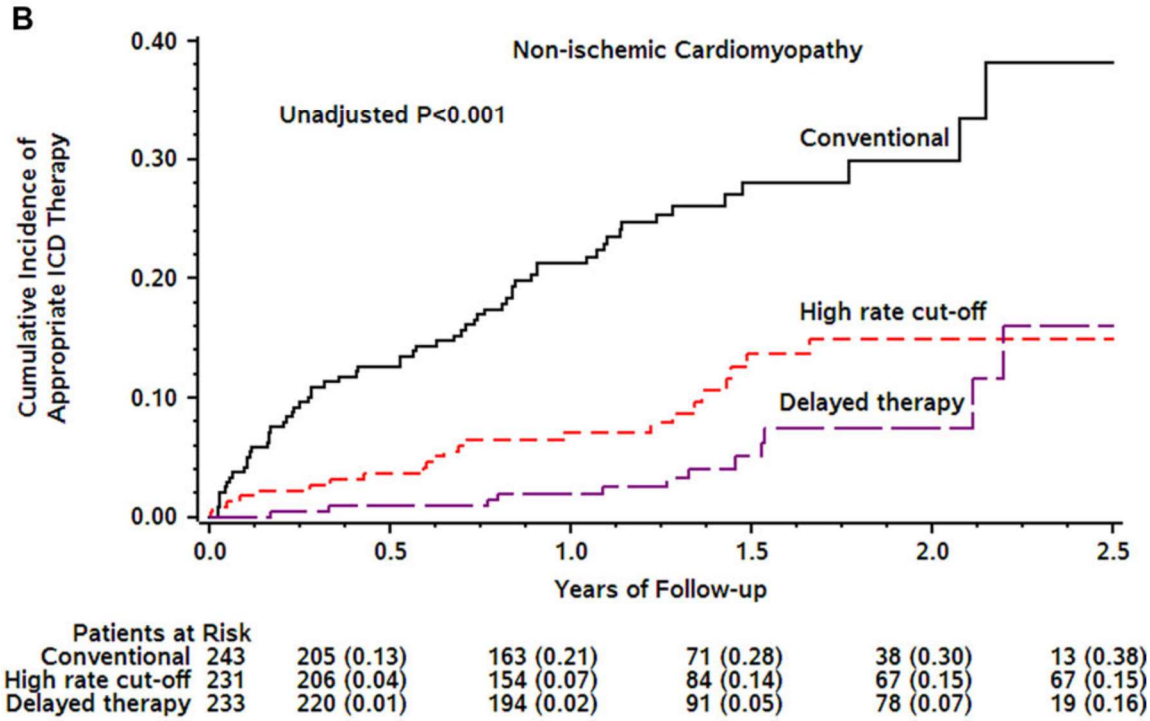


Figure 9 shows the cumulative incidence of first occurrence of appropriate ICD therapy according to treatment group in patients with ischemic (A) and nonischemic (B) cardiomyopathy. Reproduced with permission. From Paper VII.

Thus, overall, the results were that the incidence of both inappropriate and appropriate therapy was reduced significantly for both high-rate cut-off and delayed ICD therapy when compared to conventional ICD therapy for both ischemic and nonischemic cardiomyopathy with no statistical difference between the two cardiomyopathy subgroups. This was confirmed in supplementary analyses, where the *total* number of therapies in the three treatment arms were considered. Earlier, Poole et al. presented data of patients participating in the SCD-HeFT trial, which enrolled patients with nonischemic and ischemic cardiomyopathy[64]. In that study, 89 out of 391 patients (22.7%) with nonischemic cardiomyopathy experienced ≥1 appropriate ICD shock therapy and 18 patients (4.6%) died during follow-up. A comparable number of patients with ischemic cardiomyopathy received ≥1 appropriate shock therapy during follow-up (93 out of 420 patients, 22.1%), but the proportion of deaths in this patient population was markedly higher (49 out of 420, 11.7%). The study concluded that the occurrence of an appropriate ICD shock was associated with a markedly increased risk of death. The evidence for benefit of an ICD is less strong for nonischemic cardiomyopathy, when compared to ischemic cardiomyopathy. Benefit of an ICD has been well documented for reducing the rate of SCD and total mortality in ischemic cardiomyopathy[22,23,191,192] and the evidence is much stronger than for nonischemic cardiomyopathy. The DEFINITE, CAT and AMIOVIRT trials[193-195] indicated benefit for nonischemic cardiomyopathy, but overall, the evidence was not entirely convincing, mostly due to small sample sizes. The DANISH trial[140] included more than 1000 patients with nonischemic cardiomyopathy and randomized patients to an ICD or medical therapy. The trial had a very long follow-up of 68 months and was unable to show any difference in all-cause mortality for these patients accounting 120 deaths (21.6%) versus 131 deaths (23.4%), (p=0.28) in the control-arm. However, there was a reduction in SCD with 4.3% versus 8.2% (HR 0.50, CI 0.31-0.82, p=0.005) and interaction analyses and later subanalyses showed potential mortality benefit in those less than 68 years of age[196]. Several reviews and meta-analyses have later demonstrated an overall effect of ICD in nonischemic cardiomyopathy supporting the current European and American guidelines[58,197-199]. However, current practice of ICD implantation in nonischemic patients in Denmark is an individualized approach with weighty emphasis on the age interaction found in the DANISH trial. The historically reported incidence of inappropriate shocks (at 10-20%) is no longer valid. Based on contemporary ICD programming and recent trials, including DANISH[140] a more accurate estimate is

2-5% depending on follow-up time. For example, in PREPARE and MADIT-RIT intervention arms, approximately 4% and 3% received inappropriate ICD shocks [67,174], while the rate of inappropriate shocks was one to three per 100 person-years from 2008 to 2013 and less than one per 100 person-years in 2014 in the DANISH trial[140]. The findings of very low rates of inappropriate ICD shocks in the DANISH trial thus confirmed an overall reduction over time consistent with improvements (among others) in medical therapy, lead efficiency, and changes in ICD programming leading to my further explorations in Paper X of the temporal evolvements of ICD therapies during the last decade.

ICD programming and diabetes mellitus

In ICD patients, and HF patients in general, DM is associated with increased risk of hospitalization for HF, SCD, and all-cause mortality, when compared to non-diabetics[200-204]. A substudy from MADIT-CRT[202] showed that patients with DM had more coronary risk factors and experienced significantly more HF or death events than non-DM patients (26.6% versus 18%, P<0.001). It was shown that CRT-D was associated with a significant reduction in risk of HF or death in both DM (HR 0.56, p<0.001) and non-DM patients (HR 0.67, p=0.003) and concluded that patients with DM derive similar benefit from CRT-D compared with patients without DM. From the DANISH trial it was shown in 2019 that there was no difference in benefit of an ICD among patients with DM compared to non-DM, but that DM was associated with higher risk of all-cause death, driven by cardiovascular and SCD[205]. Results from a substudy of the INTRINSIC-RV trial[206] further indicated that DM was associated with reduced risk of inappropriate shocks, particularly in the elderly. Specifically, for ICD patients the association between DM and inappropriate and appropriate ICD therapy has not been investigated thoroughly in the previously mentioned papers of this thesis concerning ICD therapy and risk of mortality. In Paper VIII of this thesis, we used data from MADIT-RIT to evaluate three major objectives. First, we evaluated the effects of the randomized ICD programming settings on inappropriate ICD therapy in patients with or without DM. Second, we estimated the influence of DM on the risk of inappropriate and appropriate ICD therapy throughout the follow-up. Third, we used time-dependent analyses to investigate the impact of (in-trial) inappropriate and appropriate ICD therapy, respectively, on the risk of death for both patients with or without DM. A total of 485 patients enrolled in MADIT-RIT (32% of the total study population) had DM and they were equally distributed in the three randomization arms. The main

results from the paper showed that ICD programming with high-rate cut-off therapy was associated with significantly reduced inappropriate ICD therapy in both DM (HR 0.32, p=0.01) and non-DM patients (HR 0.12, p<0.001). Same and significant effect was seen for patients randomized to delayed therapy with HR 0.39, p=0.02 for DM and HR 0.19, p<0.001 for non-DM patients. Interestingly, there was however, a marked trend toward a more pronounced effect of high-rate cut-off ICD programming in the reduction of inappropriate ICD therapy among the non-DM patients (p-value for interaction 0.06 [testing the difference for HR 0.32 with HR 0.12]). In MADIT-RIT the primary outcome of inappropriate ICD therapy occurred in 34 (7%) patients with DM and in 116 (12%) non-DM patients during the mean follow-up of 17.4 months. In multivariate adjusted Cox analyses, DM was associated with reduced risk of inappropriate ICD therapy (HR 0.54, p=0.002). This effect was entirely due to a decreased risk of inappropriate ATP (HR 0.53, p=0.002) as also seen in the main trial results. There was no significant difference in risk of inappropriate shocks between patients with and without DM (HR 1.25, p=0.44). Specifically, the paper showed an association between DM and a decreased risk of inappropriate ICD therapy caused by regular supraventricular tachycardias including sinus tachycardia (HR 0.57, p=0.016), while we were unable to show an association between DM and increased risk of inappropriate ICD therapy caused by AF or flutter (HR 0.65, p=0.25). DM was associated with a significantly increased risk of appropriate ICD therapy in multivariate analyses (HR 1.58, p=0.003). In this case of appropriately treated VTAs the effect was driven by both an increase in the risk of appropriate ATP (HR 1.60, p=0.003) as well as an increase in the risk of appropriate shocks (HR 1.62, p=0.046) in patients with DM as compared to those with non-DM. The last analysis concerned the relative impact of inappropriate and appropriate ICD therapies on the risk of death. There was a significantly increased risk of all-cause mortality associated with the delivery of inappropriate ICD therapy (HR 4.17, p=0.005) and appropriate ICD therapy (HR 2.49, p=0.04) in patients with DM. Inappropriate shocks were not independently associated with increased risk of death for neither DM nor non-DM patients, which could be explained by few events of inappropriate shocks and relatively short follow-up. In short, the major finding from Paper VIII was that patients with and without DM derived similar beneficial and clinically relevant effect of innovative ICD programming with reduction of inappropriate ICD therapy using high-rate cut-off or delayed therapy when compared to conventional programming. The patient with DM experienced significantly less inappropriate

ICD therapy overall which may be explained by a numeric reduction particularly in supraventricular tachycardia and sinus tachycardia due to possible lower basal heart rates and inability to reach high rates of sinus tachycardia, although this is speculative. Finally, we found that DM was associated with increased risk of appropriate ICD therapy, which was in contrast to results from other large trials such as MADIT-II, MADIT-CRT, COMPANION, REVERSE and CARE-HF[39,40,207-214]. Two smaller earlier studies support our results[206,215], and whether or not DM patients are at higher risk of VTAs and may constitute a special high-risk group is still controversial. An explanation for this finding of increased VTAs in patients with DM involve ischemia and fibrotic scar tissue, reduced autonomic function and reduced coronary circulation[216-219] resulting in a myocardium more prone to produce ventricular arrhythmias. The association between appropriate ICD therapy, particularly shocks, and a subsequent higher risk of death, has been shown previously[64,65,203,207,208,213,220,221] and our study was supportive of these findings for both patients with and without DM. The finding from this paper, in part, initiated the MADIT S-ICD study (www.clinicaltrials.gov, NCT02787785) in 2016 that enrolled patients with DM and LVEF 36-50%. It was designed to show reduction in all-cause mortality and SCD for patients randomized to a subcutaneous ICD when compared to medical therapy, but the study had to be abandoned due to low enrolment. In the SCD-HeFT [64], MADIT-II [65] and The ALTITUDE Survival Study [222] the delivery of inappropriate shocks doubled the risk of death. In Paper VIII, however, through multivariate analysis, there was no significant association between inappropriate shocks and death for patients with or without DM, most likely due to the short follow-up and low death rate. Multifactorial causes such as the underlying rhythm and a potential vulnerable myocardial substrate are likely responsible for the increased mortality and not the shock or device treatment itself. This was also the conclusion from the specific mortality analysis from MADIT-RIT later published[223]. The findings from Paper VIII confirm that DM patients have worse prognosis and may be at higher risk of VTAs. High-rate or delayed ICD programming is safe and efficient for these patients at higher risk and the results underline the importance of an optimized treatment strategy after an appropriate shock to improve clinical outcome.

Chapter 4.8

Appropriate ICD therapy after elective ICD generator replacement

Following the findings from Paper IV indicating very low risk of VTAs among CRT-D patients with normalized LVEF; interest was invested in further understanding the risk of VTA after elective primary prevention ICD generator replacement. Earlier smaller studies have suggested that up to 26% of the patients no longer had ICD indication if the indication was re-evaluated at time of ICD generator replacement, mostly due to improvements in LVEF (and no appropriate therapy in the first generator lifetime)[224]. Other smaller studies found, that LVEF recovery at time of generator replacement could not solely predict future benefit during the second generator lifetime[225-227]. Another clinical aspect of interest was to explore and identify patients, who may no longer need the ICD due to combinations of assumed low arrhythmic risk, advanced age and comorbidity burden and high competing risk of non-cardiac/non-arrhythmic death[228,229]. In Paper IX we used the DPIR and nationwide Danish registers to evaluate the incidence and risk of appropriate ICD therapy after elective ICD generator replacement stratifying the patients by prior versus no prior appropriate ICD therapy. During examination of the databases, it became clear that LVEF at time of ICD generator replacement was unfortunately only available in a limited number of patients. A total of 670 patients underwent ICD generator replacement. Half of the patients had a CRT-D device, and 77% had ischemic cardiomyopathy. The mean time to generator replacements was 5.0 ±2.0 years and the mean age was 69.3 ±9.7 years. LVEF at initial implant was 24 ±7%. Patients with appropriate ICD therapy in the 1st generator period were more often males, they were younger and had more often AF, previous MI and were more often treated with amiodarone (32.5%) at time of generator replacement. The cumulative incidence of appropriate ICD therapy after generator replacement was 4.3% at one year and 16.4% at four years for patients with no ICD therapy in the first generator period compared to 20.3% at one year and 50.6% at four years for patients with ICD therapy in the first generator period. In efforts to tease out the true low risk patients; univariate and multivariate Cox regression models were used and showed that for those with three concomitant factors; LVEF >25% at initial implant, no prior ICD therapy and high age >80 years, a total of *zero* patients had ICD therapy after replacement (0 out of 17 patients). On the other hand, those with initial LVEF ≤25% and with prior ICD therapy 38 out of 138 (27.5%) patients

experienced a new ICD therapy after replacement of the device, see Figure 10 for details.

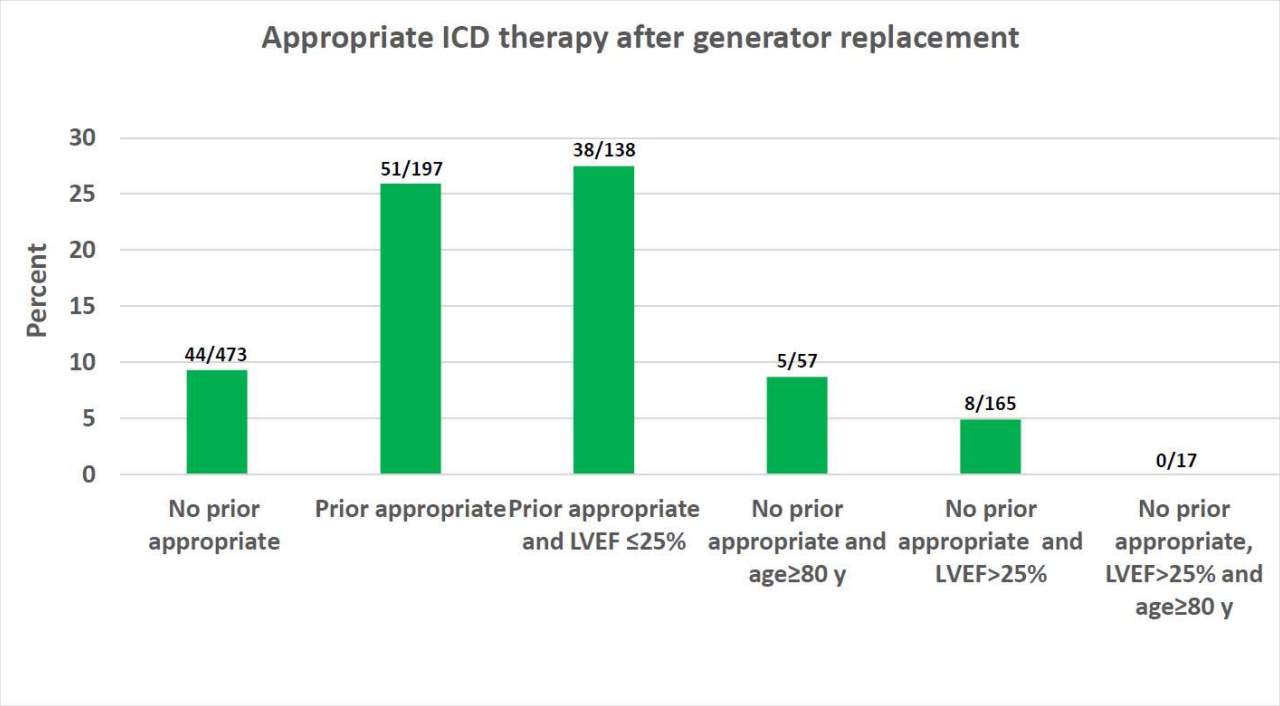


Figure 10 shows appropriate ICD therapy after generator replacement. Bar graph showing percentages of patients with appropriate ICD therapy after generator replacement according to clinical status at time of replacement. Reproduced with permission. From Paper IX.

To further explore and discuss the influence of non-cardiac comorbidities on the need for ICD at time of replacement, an evaluation on mortality was performed. The analysis showed that a total of 76.5% (130/170) of the deaths after replacement had not experienced appropriate ICD therapy and 54.7% of all deaths were without ICD therapy in any of the generator lifetimes and 27% of all deaths were within one year of the replacement. Non-cardiac comorbidity burden highly influenced risk of death as expected, but also reduced device utilization, so that patients with high comorbidity burden had low rates of appropriate therapy. For patients with no prior therapy and more than three non-cardiac comorbidities up to 83% of the deaths were without ever using the device. In perspective, and the clinical reality is, however, that there is no randomized study evaluating cost- or mortality benefit of ICD generator replacement. At time of replacement in patients with advanced age; considerations of appropriate ICD therapy delivered by the first generator, LVEF at time of replacement, influence of comorbidity burden, and thoughts on a competing risk of (non-arhythmic) death are all relevant factors to consider in shared decision-

making with the patient. Smaller retrospective studies evaluated appropriate ICD therapy after generator replacement in patients with improved LVEF [224,225,227,230-232]. Collectively the annual rates of appropriate ICD therapy for these patients were lower, but not neglectable. Most recently, shown in a meta-analysis from 2021 consisting of 29,730 patients from 30 studies, the annual incidence of appropriate ICD therapies was significantly lower in those with improved LVEF, compared with patients with unimproved LVEF: 4.6% versus 10.7% (risk ratio 0.50, CI 0.36–0.68, P<0.0001)[233], with similar results for mortality. When they stratified by appropriate ICD therapy in first generator the rate of appropriate ICD therapy was 3.9% versus 12.5% (risk ratio 0.37, CI 0.33-0.41) with no prior therapy, see Figure 11.

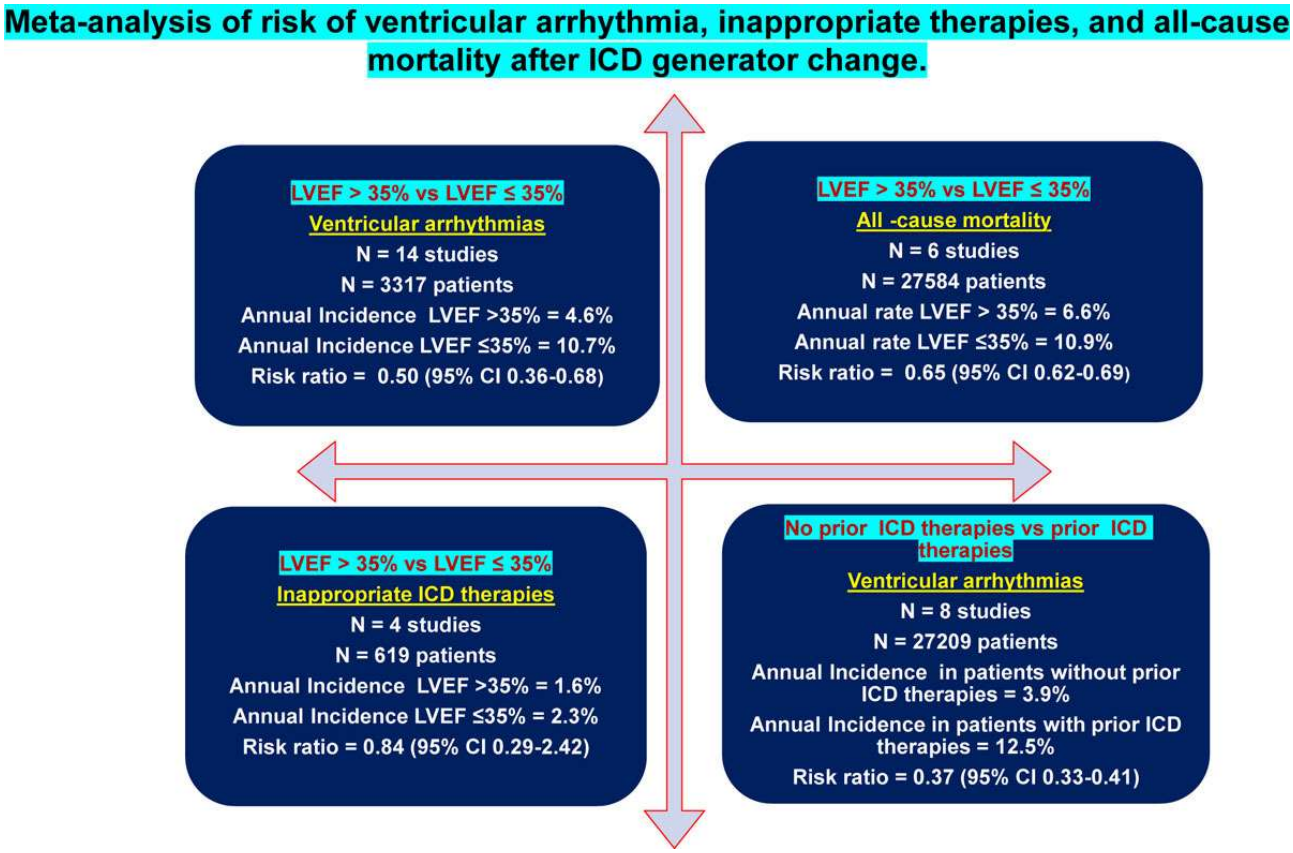


Figure 11. Reproduced with permission from (Yuyun MF et al. Ongoing Risk of Ventricular Arrhythmias and All-Cause Mortality at Implantable Cardioverter Defibrillator Generator Change: A Systematic Review and Meta-Analysis. Circ Arrhythm Electrophysiol. 2021), Copyright Lippinkott, Williams & Wilkins

The importance of LVEF recovery in primary prevention ICD and CRT-D patients on reducing VTAs has been shown in multiple studies (LVEF data acquired not at generator replacement, but at time

of repeated echocardiogram)[4,234,235], but there seem to sustain a residual risk of VTA among patients with LVEF recovery to more than 35%. As shown in Paper IV a complete recovery of LVEF >50% was associated with a very low risk of VTAs or appropriate shock among CRT-D patients[4]. The most important factor for appropriate ICD therapy in the second generator period has consistently shown to be an episode of prior appropriate ICD therapy. In the Latitude Register 24,203 ICD patients had generator replacement performed. Cumulative incidence of appropriate ICD shocks was 24.3% in the second generator period, compared to 9.2% among patients with no prior appropriate ICD therapy[236]. Comparable, it was found in two smaller studies that 13-14% of the patients had appropriate therapy without any events in the first generator period [229,237]. With improved medical therapy and management of HF the rate of SCD has declined significantly[238-240] for that population as highlighted by Shen et al. They found a 44% decline in rates of SCD among 40,195 patients enrolled in major HF trials in the period from 1995 to 2014[241]. They speculate that an improvement in LVEF still occur between six and 12 months after the initiation of HF medication[242] and therefore the three month of pharmacological uptitration and re-evaluation of LVEF may be too short a period before choosing the need for an ICD. These finding collectively calls for more research on preventative ICDs prior to both first implantation and at generator replacements and maybe a need to re-do the initial trials in a modern setting with six or more months of uptitration including all new HF medication. The on-going RESET-CRT will provide some answers and aims to demonstrate non-inferiority comparing CRT-P versus CRT-D for patients, who have an indication for CRT (www.clinicaltrials.gov, NCT03494933), see Chapter 4.3. Conclusively, we estimated that there was a significant residual risk of appropriate ICD therapy in the second generator period even in patients with advanced age and for those with no prior therapies. On the other hand, many patients died without having ever used the device, which was highly influenced by non-cardiac comorbidity burden and competing risk of non-cardiac death. At this point in time, there is insufficient data available to guide clinicians, when considering whether or not to replace an ICD, but advanced age, comorbidity burden, and no prior ICD therapies may be considered for the shared decision-making with the patient.

Chapter 4.9

Temporal reduction in incidence of appropriate and inappropriate ICD therapy

As described above, the general and specialized management of HF has improved significantly over time in the last two decades leading to decline in all-cause mortality and SCD. The previous papers in this thesis have evaluated multiple outcomes among ICD and CRT-D patients and subgroups and underscoring the effect of novel ICD programming. Because the field of HF and secondary preventive ICD patients is continuously evolving with changes of paradigm it becomes difficult to compare trial outcomes and standard-of-care. To explore temporal rates and changes in appropriate and inappropriate ICD therapy over time we aimed to specifically do this in a group of ICD patients, where the improvements in medical therapy have not been so overwhelming as in the primary prevention ICD HF patients. The secondary prevention ICD patients are a very heterogenous group of patients with different etiological arrhythmogenic substrates and risks. We therefore aimed to explore the temporal risk of ICD therapies and outcomes based on (presumed) underlying etiology at time of ICD implantation. Secondary prevention ICD trials[15-17] were conducted at times prior to the ICD programming trials and most of ICD programming trials, mainly MADIT-RIT and ADVANCE III primarily enrolled primary prevention ICD patients[67,176]. Contemporary data on ICD therapies in secondary prevention patients by the underlying cardiac diagnose is particularly limited. We therefore conducted an observational study, exploring real-life data from the DPIR on this issue. In Paper X, the cohort of secondary prevention ICDs consisted of 4,587 patients. The cohort was dominated by IHD accounting for 71% of the patients. DCM (12%), HCM (3%), other cardiomyopathies (4%), idiopathic VF (5%), ARVC (5%), and channelopathies (2%) were the other entities explored. We found that during a mean follow-up of 3.6 ±2.4 years a total of 30% of the patients experienced at least one episode of appropriate ICD therapy (16.8% shock) and 7.6% experienced inappropriate ICD therapy (4.6% shock). From 2007 to 2016 we observed a decrease in rate of all ICD therapies. Appropriate ICD therapy decreased from 28.2 to 7.9 per 100 person-years and inappropriate ICD therapy decreased from 10.0 to 1.0 per 100 person-years. The rate of ICD therapies differed markedly between assumed cardiac diagnoses at time of implantation. The patients with ARVC had the highest incidence of appropriate ICD therapies with a 5-year cumulative incidence of 57.5% compared to 20.4% for patients with HCM. The relative risk of appropriate ICD therapy, when compared to patients with IHD was HR 2.45, CI 1.77-3.39,

p<0.0001 for ARVC and HR 0.62, CI 0.42-0.93, p=0.02 for HCM. The risk of inappropriate ICD therapy was rather uniform with DCM patients having a little higher risk HR 1.52, CI 1.14-2.02, p=0.0045 compared to IHD. Overall mortality rates in the cohort were around 5% per year. The rates of appropriate ICD therapy were in contrast to previously published data from the AVID trial (1997), where 51% of the patients had appropriate ICD therapy within the first year and 63% had experienced an appropriate ICD shock at two years[17,243,244]. In MIRACLE-ICD (2004) secondary prevention subgroup[245] 31% had an appropriate ICD therapy, while more recent observational data suggested cumulative incidences of 47% to 58% (follow-up for 4.5 to 6.8 years)[246-248]. Over the years a reduction in appropriate ICD therapies has been observed in primary prevention patients, where an annual rate of appropriate shock was observed in MADIT-II of 17% (2002)[22] to 5% in SCD-HeFT (2005)[23] and PREPARE (2008)[174], 3% in MADIT-RIT[67] and 1% to 4% from observational data from 2013 and 2015[249,250]. Inappropriate ICD therapies and shocks were reduced over time and in accordance with low event rates of 2-3% per year from the primary prevention ICD programming studies[67,176,223], contemporary DCM patients from the DANISH study[140] and incidence from Danish primary prevention ICDs[249], Table 2. Proposed factors that were responsible for this reduction in both appropriate and inappropriate ICD therapy was improved medical management, in particular those with HF, improvements and more conservative ICD programming, less severe cardiac disease at time of implantation, more durable hardware with less lead fractures, remote monitoring, and more. Thus, the temporal reduction and declining rates of ICD therapy was likely multifactorial and cannot be tributed to specifically one factor responsible for the improvements in the last decade[251]. The paper adds important register data of real-life ICD patients complementing the data from ICD trial patients presented in earlier papers.

Chapter 5

Future perspectives

CRT has been established as a very effective therapy for HF with low LVEF and LBBB QRS morphology with significant improvements in mortality, functional capacity, symptoms, and reduction in costly HF hospitalizations. Despite of this, optimization for pre-and post-procedural HF care is still needed. Strategies to improve outcomes now involve focus on world-wide under-utilization of CRTs and improvements of referrals, refining pre-implant characteristics and

improving procedure/technical issues, and optimizing a post-implant care pathway. Many efforts to optimize the post-care pathway have already been made[105,252,253]. Through numerous trials better implant characteristics have now been defined, but many unsolved issues still remain. The ongoing RAFT-PermAF (www.clinicaltrials.gov, NCT01994252) will hopefully help to resolve whether or not there is a benefit of CRT among patients with permanent AF, while the role of AV node ablation with CRT is also better defined and explored[137]. Another major issue in CRT is to determine clinical benefit and cost-benefit among patients upgraded from ICD to CRT-D due to high percentage of right ventricular pacing, which the ongoing BUDAPEST-CRT[254] (www.clinicaltrials.gov, NCT02270840) will help establish. Improved placement of left ventricle lead based on knowledge of the latest electrically active segments in the left ventricle is currently under investigation in the DANISH-CRT trial (www.clinicaltrials.gov, NCT03280862) that plans to enrol 1000 patients and compare to standard CRT left ventricle lead placement. Expansion of an indication of CRT to higher levels of LVEF i.e., 36-50% is of considerable interest, but a large-scale industry sponsored trial targeting this population was terminated early due to low enrolment (www.clinicaltrials.gov, NCT01735916). Conduction system pacing and wireless CRT as alternatives for CRT[255-259], has not yet been established, but is promising for the future and awaits further research, beyond the scope of this thesis. For ICDs, the Danish DanICD (www.clinicaltrials.gov, NCT04576130) aim to better establish the indication for secondary prophylactic ICD among patients with aborted SCD due to VTA or VF, who undergo complete revascularization, and where LVEF is above 35%. The RESET-CRT (www.clinicaltrials.gov, NCT03494933), as noted previously, aims to prove non-inferiority of CRT-P compared to CRT-D in patients elective for CRT on all-cause death. The PROFID-reduced trial (www.clinicaltrials.gov, NCT04540354) aims to re-evaluate the SCD-HeFT and MADIT II primary prophylactic ICD criteria by showing non-inferiority of ICD compared to modern medical treatment in post-MI patients with LVEF ≤35%, who are optimally medically treated (by 2016 guidelines) and have a low risk of SCD (<2.5%) according to a clinical risk calculator (to be published). Following the contents of the present thesis, it would be of further interest to investigate implantable loop recorders in post-MI patients with LVEF 35-50% - prior to or after medication uptitration with interventions on recorded symptomatic VTAs, by implanting ICD, by ablations strategies or by medications. The Pause-SCD recently presented at HRS-2021 further suggested benefit of early (first-line) VT ablation ahead of ICD implantation in

patients with a secondary prevention ICD indication (www.clinicaltrials.gov, NCT02848781). Other more specific patient-tailored approaches relate to the use and clinical evidence of wearable cardioverter-defibrillators as bridge to device decision[260,261] and subcutaneous ICD as alternatives for transvenous ICDs[262,263]. Implantable loop recorders and other wearable technologies are also beyond the scope of this thesis. Improvement of the well-established remote monitoring[264-267] and the continuous evaluation and intervention of monitored episodes of arrhythmias i.e., atrial high-rate episodes in device patients are also of considerable interest in future perspectives of CRT and ICD patients. Worth to mention here is the ARTESiA trial (www.clinicaltrials.gov, NCT01938248) randomizing patients to non-vitamin K oral anticoagulation versus aspirin in patients with atrial high-rate episodes on risk of stroke and systemic embolism. With expanding therapies in cardiology, a continuous expansion and refinement of indications and re-evaluation of current otherwise well-accepted practice is paramount. Treatment re-affirmation of ICD indications and patient selection, subgroup benefits, and personalization in the modern era of invasive revascularization, improved HF medications, cardiac magnetic resonance imaging, and other tools of risk prediction as well as post-procedure optimizations of care pathways are necessary to further develop the field of cardiology. This thesis aimed to touch upon some of these aspects and evaluated important outcomes and patient optimizations for both trial patients and real-life ICD and CRT-D patients over the past decade.

Chapter 6

Summary and conclusions

The studies and ten papers included in this doctoral thesis were conducted and written over a period of eight years. They are based on data from the multicenter, randomized controlled trials, the MADIT-CRT consisting of 1,820 patients with ICD or CRT-Ds, the MADIT-RIT ICD programming trial consisting of 1,500 patients and two large cohorts of ICD patients from the nationwide Danish Pacemaker and ICD register. The overall aim of this thesis was to evaluate the prognosis of HF patients with CRT-D or ICD devices and the effect of various modifiable (risk) factors for optimal patient selection, device programming, device utilization and outcomes both for patients enrolled in clinical controlled trials and for real-life patients. The thesis focuses on evaluation of the outcomes of patient subgroups and the influence of several factors such as medication, left

ventricular ejection fraction normalization, the influence of ectopic beats, and the clinical effect of ICD programming on outcomes. Important measured outcomes in the papers were mortality, HF hospitalizations, ventricular tachyarrhythmias, syncope, and inappropriate ICD activation. To appreciate the evolvement over years of device implantation, the thesis further evaluated the outcomes in real-life patients after ICD generator replacement and the temporal development in appropriate and inappropriate device activation over a decade of implantations. Overall, the thesis reports that carvedilol was associated with better outcomes as compared to metoprolol, that low burden of ectopic beats was associated with highest BIV pacing percentage and improved outcomes. Normalization of left ventricular ejection fraction after CRT implantation led to very low risk of ventricular arrhythmias and a good prognosis and ventricular arrhythmias follow circadian patterns, where some were related to increased mortality. Less aggressive ICD programming with high-rate cut-off led to better outcomes and reduced inappropriate device activation without an increase in syncope. Syncope is an ominous sign in HF ICD patients and was tied to increased mortality no matter the underlying cause. The effect of ICD programming was equally pronounced in both ischemic and nonischemic cardiomyopathy subtypes as well as diabetic patients and non-diabetic patients, while patients with DM had lower risk of inappropriate ICD therapy but higher risk of appropriate ICD therapy and mortality. Finally, among real-life patients, there was a significant residual risk of appropriate ICD therapy for patients receiving an ICD generator replacement due to battery depletion even among patients with advanced age and without ICD therapy in the first generator period. Over the decade, there was a significant multifactorial decline in incidence of both inappropriate and appropriate ICD therapies that differed by the underlying cardiac diagnosis. In conclusion, the thesis reports the outcomes of patients with ICD and CRT-Ds by patient selection, modifiable factors, treatment and ICD programming and evaluated and put it into perspective in over a decade of device and patient management improvements.

Chapter 7

Dansk resume og konklusion

Studierne og de ti artikler i nærværende doktor disputats blev udført over en periode på otte år og er baseret på data fra to randomiserede, kontrollerede forsøg samt de danske registre. De første

fem artikler evaluerer data fra device-studiet MADIT-CRT, der inkluderede 1,820 patienter til behandling med implanterbar cardioverter-defibrillator (ICD) eller kardiel resynkroniserings terapi med ICD (CRT-D) . De næste tre artikler undersøger data fra device-studiet MADIT-RIT, som var et ICD programmings forsøg med 1,500 patienter, mens de sidste to artikler benytter data fra to kohorter af ICD patienter fra Det Danske Pacemaker og ICD register. Afhandlingen fokuserer på en grundig evaluering af vigtige endepunkter fra disse studier, herunder vurderinger af subgrupper af patienter og behandlingseffekt, og sætter dette i perspektiv til tidligere udførte studier, baggrundslitteraturen og fremtidig forskning. Der rapporteres, hvordan faktorer såsom specifik type af beta-blokker medicin, normalisering af hjertets pumpefunktion og præmature ekstra hjerteslag påvirker patienternes risiko for død, hjertesvigtshospitalisering, alvorlige hjerterytmeforstyrrelser og uhensigtsmæssig aktivering af ICD'en. Herudover demonsterer afhandlingen, hvordan der har været et fald i utilsigtede og tilsigtede stød fra ICD'en over en periode fra 2007 til 2016, samt en vurdering af mængden af tilsigtede stød efter elektivt generatorskifte af ICD'en afhængigt af komorbiditetsbyrden og tilstedeværelsen af tilsigtet stød i første periode af ICD generatoren. Samlet set viser afhandlingen, at carvedilol som valg af beta-blokker er associeret med mindre hjertesvigtshospitalisering og færre livstruende arrytmier og utilsigtet ICD aktivering sammenlignet med metoprolol. Den viser, at en lav byrde af præmature ekstraslag er associeret med højere andel af vigtig biventrikulær pacing, bedre hæmodynamisk respons og reduceret morbiditet for patienterne. Den viser, at en normalisering af hjertets pumpefunktion efter CRT implantation fører til en efterfølgende meget lav risiko for livstruende hjertearytmier og en bedre overlevelse. Livstruende arytmier følger et circadiansk mønster med lavest incidens om natten, og arytmi om morgenen ser ud til at være associeret med højere risiko for død. En mindre aggresiv ICD programmering (med high-rate cut-off) førte til reduktion i utilsigtede stød og dødelighed uden en større risiko for besvimelse. Denne reduktion var lige god for patienter med iskæmisk hjertesvigt som for hjertesvigt uden iskæmisk årsag. Samme fund blev rapporteret for patienter med og uden diabetes, hvor diabetes herudover var associeret med lavere risiko for utilsigtede stød men samtidig en generelt højere risiko for tilsigtede stød og død. I Danmark blev risikoen for tilsigtet ICD terapi og stød, efter patienter elektivt havde fået skiftet ICD generatoren på grund af udløb af batteri, undersøgt. Resultatet var, at patienter, på trods af høj alder og en hel periode uden ICD terapi i første generatorperiode fortsat havde en vis og ikke-

negligeabel risiko for livstruende hjertearytmi. Komorbiditetsbyrde og alder er betydelige faktorer og øgede sandsynligheden for død af ikke-kardiel årsag og ikke-brug af ICD generatoren betydeligt. I løbet af et årti var der en betydelig og formentlig multifaktoriel reduktion i incidensen af både tilsigtet og utilsigtet ICD terapi og stød. Risikoen for ICD terapi afhang i betydelig grad af, hvilken tilgrundliggende hjertesygdom, der var årsag til ICD implantationen. Sammenfattende viser afhandlingen nye fund fra store randomiserede devicestudier med øget overlevelse og reduceret morbiditet hos ICD og CRT-D patienter, der afhænger af faktorer såsom hjertesvigtsmedicinering, patient selection og komorbiditet, ICD programmerings og CRT effekt. Alt sat i en kontekst med forbedringer og perspektivering over en dekades opfølgning på danske ICD patienter.

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Effect of Metoprolol Versus Carvedilol on Outcomes in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy)

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Objectives This study sought to compare the effects of metoprolol and carvedilol in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) study.

Background The impact of beta-blockers in heart failure (HF) patients with devices is uninvestigated.

Methods All patients receiving either metoprolol or carvedilol in the MADIT-CRT study were identified and compared. Time-dependent Cox proportional hazard regression analyses were performed to assess differences in hospitalization for HF or death and ventricular arrhythmias.

Results Hospitalization for HF or death occurred in 30% of the patients on metoprolol and in 23% on carvedilol. Treatment with carvedilol was associated with a significantly decreased risk of hospitalization for HF or death when compared with metoprolol (hazard ratio [HR]: 0.70, [95% confidence interval (CI): 0.57 to 0.87], $p = 0.001$). This reduction in risk was further attenuated in the subgroup of cardiac resynchronization therapy with implantable cardioverter-defibrillator (CRT-D) patients (HR: 0.61 [95% CI: 0.46 to 0.82], $p = 0.001$) and CRT-D patients with left bundle branch block (LBBB) (HR: 0.51 [95% CI: 0.35 to 0.76], $p < 0.001$). Ventricular arrhythmias occurred in 26% and in 22%, respectively, of the patients receiving metoprolol or carvedilol (HR: 0.80 [95% CI: 0.63 to 1.00], $p = 0.050$). General use of beta-blockers and adherence in this study was high, and a clear dose-dependent relationship was found in carvedilol, but not in metoprolol.

Conclusions In HF patients in New York Heart Association functional class I and II and with wide QRS complexes, carvedilol was associated with a 30% reduction in hospitalizations for HF or death when compared with metoprolol. A novel beneficial and synergistic effect of carvedilol was seen in patients with CRT-D and LBBB. Furthermore, we found a pronounced dose-dependent relationship in carvedilol, but not in metoprolol. (MADIT-CRT: Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy; NCT00180271) (J Am Coll Cardiol 2013;61:1518–26) © 2013 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) has emerged as an important device-based therapy for selected patients with systolic heart failure (HF). Landmark clinical trials have demonstrated the efficacy of CRT in patients with mild or advanced HF symptoms despite optimal pharmacological therapy (1–5). Optimal pharmacological therapy is considered a prerequisite to consideration for CRT (6), and beta-blockers (BBs) in particular have been proven to improve quality of life and reduce mortality in large populations of patients with systolic HF (7–9).

Presently, metoprolol and carvedilol are the BBs most often used in the management of patients with HF, and the choice

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Impact of Carvedilol and Metoprolol on Inappropriate Implantable Cardioverter-Defibrillator Therapy

The MADIT-CRT Trial (Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy)

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Objectives The goal of this study was to evaluate the effects of carvedilol and metoprolol on the endpoint of inappropriate implantable cardioverter-defibrillator therapy in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy) study.

Background The impact of carvedilol and metoprolol on inappropriate therapy in heart failure patients with devices has not yet been investigated.

Methods All patients in the MADIT-CRT study who received a device (N = 1,790) were identified. Using time-dependent Cox regression analysis, we compared patients treated with different types of beta-blockers or no beta-blockers on the primary endpoint of inappropriate therapy, delivered as antitachycardia pacing (ATP) or shock therapy. Secondary endpoints were inappropriate therapy due to atrial fibrillation and atrial tachyarrhythmias, also evaluated as ATP or shock therapy.

Results Inappropriate therapy occurred in 253 (14%) of 1,790 patients during a follow-up period of 3.4 ± 1.1 years. Treatment with carvedilol was associated with a significantly decreased risk of inappropriate therapy compared with metoprolol (hazard ratio [HR]: 0.64 [95% confidence interval (CI): 0.48 to 0.85]; p = 0.002). The reduction in risk was consistent for inappropriate ATP (HR: 0.66 [95% CI: 0.48 to 0.90]; p = 0.009) and inappropriate shock therapy (HR: 0.54 [95% CI: 0.36 to 0.80]; p = 0.002). The risk of inappropriate therapy caused by atrial fibrillation was also reduced in patients receiving carvedilol compared with metoprolol (HR: 0.50 [95% CI: 0.32 to 0.81]; p = 0.004). General use of beta-blockers (93%) and adherence in this study was high.

Conclusions In heart failure patients undergoing either cardiac resynchronization therapy with a defibrillator or with an implantable cardioverter-defibrillator device, carvedilol was associated with a 36% lower rate of inappropriate ATP and shock therapy compared with metoprolol. Inappropriate therapy due to atrial fibrillation was associated with a 50% lower rate in patients receiving carvedilol compared with those receiving metoprolol. (MADIT-CRT: Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy; NCT00180271) (J Am Coll Cardiol 2013;62:1343–50) © 2013 by the American College of Cardiology Foundation

Inappropriate implantable cardio-verter-defibrillator (ICD) therapy remains a devastating problem for patients treated with ICDs and cardiac resynchronization therapy with defibrillators (CRT-Ds), leading to pain and impaired quality of life (1–5). Multiple inappropriate shocks may lead to progression of heart failure (HF) (3,6). Strategies to

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Association Between Frequency of Atrial and Ventricular Ectopic Beats and Biventricular Pacing Percentage and Outcomes in Patients With Cardiac Resynchronization Therapy

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ABSTRACT

BACKGROUND A high percentage of biventricular pacing is required for optimal outcome in patients treated with cardiac resynchronization therapy (CRT), but the influence of ectopic beats on the success of biventricular pacing has not been well established.

OBJECTIVES This study sought to determine if increased ectopic beats reduce the chance of high biventricular pacing percentage and are associated with subsequent adverse outcomes.

METHODS From the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy), 801 patients with an implanted CRT-defibrillator device with data available on biventricular pacing percentage and pre-implantation 24-h Holter recordings were included. Using logistic regression, we estimated the influence of ectopic beats on the percentage of biventricular pacing. Reverse remodeling was measured as reductions in atrial and left ventricular end-systolic volumes (LVESV) at 1 year. Cox models were used to assess the influence of ectopic beats on the outcomes of heart failure (HF) or death, ventricular tachyarrhythmias (VTAs), and death.

RESULTS In the pre-implantation Holter recording, ectopic beats accounted for a mean 3.2 ± 5.5% of all beats. The probability of subsequent low biventricular pacing percentage (<97%) was increased 3-fold (odds ratio: 3.37; 95% confidence interval: 1.74 to 6.50; $p < 0.001$) in patients with 0.1% to 1.5% ectopic beats and 13-fold (odds ratio: 13.42; 95% confidence interval: 7.02 to 25.66; $p < 0.001$) in patients with >1.5% ectopic beats compared with those with <0.1% ectopic beats. Patients with ≥0.1% ectopic beats had significantly less reverse remodeling (percent reduction in LVESV 31 ± 15%) than patients with <0.1% ectopic beats (percent reduction in LVESV 39 ± 14%; $p < 0.001$). The risk of HF/death and VTA was increased significantly in those with 0.1% to 1.5% ectopic beats (hazard ratio: 3.13 and 1.84, respectively) and for >1.5% ectopic beats (hazard ratio: 2.38 and 2.74, respectively).

CONCLUSIONS Relatively low frequencies of ectopic beats (≥0.1%) dramatically increase the probability of low biventricular pacing (<97%), with reduced CRT efficacy by less reverse remodeling and higher risk of HF/death and VTA. This supports pre-implantation Holter monitoring of patients selected for CRT for optimal outcome. (MADIT-CRT: Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy; NCT00180271)
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Left Ventricular Ejection Fraction Normalization in Cardiac Resynchronization Therapy and Risk of Ventricular Arrhythmias and Clinical Outcomes

Results From the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT–CRT) Trial

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Background—Appropriate guideline criteria for use of implantable cardioverter-defibrillators (ICDs) do not take into account potential recovery of left ventricular ejection fraction (LVEF) in patients treated with CRT-defibrillator.

Methods and Results—Patients randomized to CRT-defibrillator from the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) trial who survived and had paired echocardiograms at enrollment and at 12 months (n=752) were included. Patients were evaluated by LVEF recovery in 3 groups (LVEF ≤35% [reference], 36%–50%, and >50%) on outcomes of ventricular tachyarrhythmias (VTAs), VTA ≥200 bpm, ICD shock, heart failure or death, and inappropriate ICD therapy by multivariable Cox models. A total of 7.3% achieved LVEF normalization (>50%). The average follow-up was 2.2±0.8 years. The risk of VTA was reduced in patients with LVEF >50% (hazard ratio [HR], 0.24; 95% confidence interval [CI], 0.07–0.82; P=0.023) and LVEF of 36% to 50% (HR, 0.44; 95% CI, 0.28–0.68; P<0.001). Among patients with LVEF >50%, only 1 patient had VTA ≥200 bpm (HR, 0.16; 95% CI, 0.02–1.51), none were shocked by the ICD, and 2 died of nonarrhythmic causes. The risk of HF or death was reduced with improvements in LVEF (LVEF >50%: HR, 0.29; 95% CI, 0.09–0.97; P=0.045; and LVEF of 36%–50%: HR, 0.44; 95% CI, 0.28–0.69; P<0.001). For inappropriate ICD therapy, no additional risk reduction for LVEF>50% was seen compared with an LVEF of 36% to 50%. A total of 6 factors were associated with LVEF normalization, and patients with all factors present (n=42) did not experience VTAs (positive predictive value, 100%).

Conclusions—Patients who achieve LVEF normalization (>50%) have very low absolute and relative risk of VTAs and a favorable clinical course within 2.2 years of follow-up. Risk of inappropriate ICD therapy is still present, and these patients could be considered for downgrade from CRT-defibrillator to CRT-pacemaker at the time of battery depletion if no VTAs have occurred.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00180271.

(*Circulation*. 2014;130:2278-2286.)

Key Words: arrhythmias, cardiac ■ cardiac resynchronization therapy ■ defibrillators, implantable ■ prognosis ■ ventricular dysfunction, left

Considerable clinical decision making revolves around the use of left ventricular ejection fraction (LVEF) for prognosis and for indications for use of both implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT). Guidelines support implantation for CRT for heart failure (HF) patients with LVEF ≤30% with left bundle-branch block (LBBB), sinus rhythm, and New York Heart Association (NYHA) class II, class III, and ambulatory class IV HF symptoms (*Class IA* recommendation). Similarly, guidelines support implantation of an ICD in post–myocardial infarction patients with LVEF ≤35% (*Class IA* recommendation) and in nonischemic cardiomyopathy HF

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Circadian Distribution of Ventricular Tachyarrhythmias and Association with Mortality in the MADIT-CRT Trial

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Ventricular Tachyarrhythmias and Death. ***Background:*** **It is unknown whether circadian variation of ventricular tachyarrhythmias (VTA) affects clinical outcome in heart failure patients.**

Methods: **A total of 1,790 patients (males 75%) with heart failure, NYHA class I and II and implantable cardioverter defibrillators (ICD) or cardiac resynchronization (CRT-D) enrolled in the MADIT-CRT study were included. Time of first and all VTAs as detected and treated by the device with appropriate ICD therapy (antitachycardia pacing or shock) was evaluated by hours of the day and weekdays and related to all-cause mortality using Cox regression analyses.**

Results: **During a mean follow-up period of 40 months, a total of 3,300 VTA episodes were registered. Of all VTAs recorded, most of them (n = 2977, 90%) occurred in males. Recurrent as well as first VTA episodes were more common in the morning and evening with bimodal peaks from 7:00 to 10:59 (21%) and 18:00–21:59 (23%). VTAs that occurred during morning hours were associated with higher mortality when compared to VTA episodes occurring at other hours (hazard ratios [HR] = 2.07; confidence interval [CI]: 1.135–3.77; P = 0.018) with a significant gender interaction placing females at significantly higher risk of death (HR 6.78; CI 1.55–29.860; P = 0.011) than males (HR 1.79; CI 0.92–3.46; P = 0.086) (interaction P = 0.041) despite an overall lower probability for morning VTA among females (HR 0.32; CI 0.16–0.68; P = 0.003).**

Conclusions: **The occurrence of VTAs in heart failure patients shows a circadian variation with highest incidence during morning hours that translates into a significant higher risk of all-cause mortality, with significantly higher risk among females than males.** *(J Cardiovasc Electrophysiol, Vol. pp. 1-9)*

circadian rhythms, biventricular pacing, death, gender, implantable cardioverter defibrillator, MADIT-CRT, ventricular arrhythmias

Introduction

Implantable cardioverter defibrillators (ICD) terminate ventricular tachyarrhythmias (VTA) and reduce the occurrence of sudden death.[1,2] However, patients with implanted ICDs frequently receive treatment for VTAs associated with adverse clinical outcome.[3,4]

It has previously been shown that there is circadian and seasonal variation in distribution of VTAs[5-7] as well as sudden death[8,9] with peaks during morning hours and wintertime. Furthermore, there is also evidence that acute myocardial infarction,[10-12] cardiac mortality,[13] and coronary death[14] also present with some variations through day, week, season, and weather.[15-18] This circadian distribution of VTA was recently disputed and could not be reproduced in a substudy of 811 ICD heart failure patients from the SCD-HeFT,[19] indicating a possible change in neurohormonal blockade with modern heart failure therapy. Further, no difference has been shown in occurrence of VTAs for gender or etiology of cardiomyopathy. It has been speculated that increased occurrence of VTA would follow the circadian pattern of myocardial ischemia and thrombosis, mainly occurring with increased frequency during morning hours.

Whether first VTAs occurring in the high-incidence periods, i.e., morning periods, where levels of stress, physical activity, and catecholamines are thought to be highest, also translate into a higher risk of subsequent recurrent VTA

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Syncope in High-Risk Cardiomyopathy Patients With Implantable Defibrillators: Frequency, Risk Factors, Mechanisms, and Association With Mortality

Results From the Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate Therapy (MADIT-RIT) Study

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Background—There is a relative paucity of studies investigating the mechanisms of syncope among heart failure patients with implantable cardioverter-defibrillators, and it is controversial whether nonarrhythmogenic syncope is associated with increased mortality.

Methods and Results—The Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate Therapy (MADIT-RIT) randomized 1500 patients to 3 different implantable cardioverter-defibrillator programming arms: (1) Conventional programming with therapy for ventricular tachycardia ≥170 bpm; (2) high-rate cutoff with therapy for ventricular tachycardia ≥200 bpm and a monitoring zone at 170 to 199 bpm, and (3) prolonged 60-second delay with a monitoring zone before therapy. Syncope was a prespecified safety end point that was adjudicated independently. Multivariable Cox models were used to identify risk factors associated with syncope and to analyze subsequent risk of mortality. During follow-up, 64 of 1500 patients (4.3%) had syncope. The incidence of syncope was similar across the 3 treatment arms. Prognostic factors for all-cause syncope included the presence of ischemic cardiomyopathy (hazard ratio [HR], 2.48; 95% confidence interval [CI], 1.42–4.34; *P*=0.002), previous ventricular arrhythmias (HR, 2.99; 95% CI, 1.18–7.59; *P*=0.021), left ventricular ejection fraction ≤25% (HR, 1.65; 95% CI, 0.98–2.77; *P*=0.059), and younger age (by 10 years; HR, 1.25; 95% CI, 1.00–1.52; *P*=0.046). Syncope was associated with increased risk of death regardless of its cause (arrhythmogenic syncope: HR, 4.51; 95% CI, 1.39–14.64, *P*=0.012; nonarrhythmogenic syncope: HR, 2.97; 95% CI, 1.07–8.28, *P*=0.038).

Conclusions—Innovative programming of implantable cardioverter-defibrillators with therapy for ventricular tachycardia ≥200 bpm or a long delay is not associated with increased risk of arrhythmogenic or all-cause syncope, and syncope caused by slow ventricular tachycardias (<200 bpm) is a rare event. The clinical risk factors associated with syncope are related to increased cardiovascular risk profile, and syncope is associated with increased mortality irrespective of the cause.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00947310.

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Key Words: heart failure ■ implantable cardioverter-defibrillators ■ prognosis ■ syncope ■ ventricular tachycardia

Syncope in heart failure patients with or without an implantable cardioverter-defibrillator (ICD) may be associated with a poor prognosis regardless of the cause of the syncope, but syncope caused by life-threatening ventricular arrhythmias is associated with an increased risk of death.[1–4] Because no large study in high-risk patients with heart failure has specifically addressed syncope as a safety end point, there is a lack of evidence on which factors are associated with all-cause syncope, arrhythmogenic syncope, and nonarrhythmogenic syncope.

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Furthermore, it is not known whether slow ventricular tachycardia (VT) (170–199 bpm) may induce hemodynamic instability and syncope in high-risk heart failure patients or whether the duration of ventricular arrhythmias until ICD

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The Effect of ICD Programming on Inappropriate and Appropriate ICD Therapies in Ischemic and Nonischemic Cardiomyopathy: The MADIT-RIT Trial

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ICD Programming in Ischemic and Nonischemic Cardiomyopathy. ***Introduction:*** **The MADIT-RIT trial demonstrated reduction of inappropriate and appropriate ICD therapies and mortality by high-rate cut-off and 60-second-delayed VT therapy ICD programming in patients with a primary prophylactic ICD indication. The aim of this analysis was to study effects of MADIT-RIT ICD programming in patients with ischemic and nonischemic cardiomyopathy.**

Methods and Results: **First and total occurrences of both inappropriate and appropriate ICD therapies were analyzed by multivariate Cox models in 791 (53%) patients with ischemic and 707 (47%) patients with nonischemic cardiomyopathy.**

Patients with ischemic and nonischemic cardiomyopathy had similar incidence of first inappropriate (9% and 11%, P = 0.21) and first appropriate ICD therapy (11.6% and 14.1%, P = 0.15). Patients with ischemic cardiomyopathy had higher mortality rate (6.1% vs. 3.3%, P = 0.01).

MADIT-RIT high-rate cut-off (arm B) and delayed VT therapy ICD programming (arm C) compared with conventional (arm A) ICD programming were associated with a significant risk reduction of first inappropriate and appropriate ICD therapy in patients with ischemic and nonischemic cardiomyopathy (HR range 0.11–0.34, P < 0.001 for all comparisons).

Occurrence of total inappropriate and appropriate ICD therapies was significantly reduced by high-rate cut-off ICD programming and delayed VT therapy ICD programming in both ischemic and nonischemic cardiomyopathy patients.

Conclusion: **High-rate cut-off and delayed VT therapy ICD programming are associated with significant reduction in first and total inappropriate and appropriate ICD therapy in patients with ischemic and nonischemic cardiomyopathy.** *(J Cardiovasc Electrophysiol, Vol. 26, pp. 424-433, April 2015)*

appropriate ICD therapy, implantable cardioverter defibrillators, inappropriate ICD therapy, ischemic cardiomyopathy, MADIT-RIT trial, nonischemic cardiomyopathy

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Influence of Diabetes Mellitus on Inappropriate and Appropriate Implantable Cardioverter-Defibrillator Therapy and Mortality in the Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate Therapy (MADIT-RIT) Trial

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Background—The relationship between diabetes mellitus and risk of inappropriate or appropriate therapy in patients receiving an implantable cardioverter-defibrillator (ICD) and resynchronization therapy has not been investigated thoroughly. The effect of innovative ICD programming on therapy delivery in these patients is unknown.

Methods and Results—The Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate Therapy (MADIT-RIT) randomized patients with a primary prophylactic ICD indication to 3 different types of ICD programming: conventional programming with a ventricular tachycardia zone of 170 to 199 bpm (arm A), high-rate cutoff with a ventricular tachycardia zone ≥200 bpm (arm B), or 60-second-delayed therapy (arm C). The end points of inappropriate therapy, appropriate therapy, and death were assessed among 485 patients with and 998 without diabetes mellitus. Innovative ICD programming reduced the risk of inappropriate therapy regardless of diabetes mellitus, although a trend toward a more pronounced effect of high-rate cutoff programming was seen in patients without diabetes mellitus (*P* for interaction=0.06). Diabetes mellitus was associated with a decreased risk of inappropriate therapy (hazard ratio, 0.54; 95% confidence interval, 0.36–0.80; *P*=0.002) and increased risk of appropriate therapy (hazard ratio,1.58; 95% confidence interval, 1.17–2.14; *P*=0.003). In diabetic patients, there was significantly increased risk of death in those who had inappropriate therapy (hazard ratio, 4.17; 95% confidence interval, 1.52–11.40; *P*=0.005) and appropriate therapy (hazard ratio, 2.49; 95% confidence interval, 1.06–5.87; *P*=0.037) compared with those who did not.

Conclusions—Innovative high-rate cutoff or delayed ICD programming was associated with a reduction in inappropriate therapy in patients with and without diabetes mellitus. Diabetes mellitus was associated with lower risk of inappropriate therapy but higher risk of appropriate therapy. Appropriate and inappropriate ICD therapy was associated with increased mortality in diabetic patients.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00947310.

(*Circulation*. 2013;128:694-701.)

Key Words: defibrillators, implantable ■ diabetes mellitus ■ heart failure ■ mortality

The Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate Therapy (MADIT-RIT) showed that innovative implantable cardioverter-defibrillator (ICD) programming was associated with a reduction in inappropriate therapy and mortality.[1] The MADIT-RIT trial randomized patients with a primary prophylactic ICD indication to 3 different types of ICD programming: conventional programming with a ventricular tachycardia (VT) zone of 170 to 199 bpm, high-rate cutoff with a VT zone ≥200 bpm, or 60-second-delayed therapy during a VT zone of 170 to 199 bpm.

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CLINICAL RESEARCH

Incidence of appropriate implantable cardioverter-defibrillator therapy and mortality after implantable cardioverter-defibrillator generator replacement: results from a real-world nationwide cohort

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Aims The safety of omitting implantable cardioverter-defibrillator (ICD) generator replacement in patients with no prior appropriate therapy, comorbid conditions, and advanced age is unclear. The aim was to investigate incidence of appropriate ICD therapy after generator replacement.

Methods and results We identified patients implanted with a primary prevention ICD ($n = 4630$) from 2007 to 2016, who subsequently underwent an elective ICD generator replacement ($n = 670$) from the Danish Pacemaker and ICD Register. The data were linked to other databases and evaluated the outcomes of appropriate therapy and death. Predictors of ICD therapy were identified using multivariate Cox regression analyses. A total of 670 patients underwent elective ICD generator replacement. Of these, 197 (29.4%) patients had experienced appropriate therapy in their 1st generator period. During follow-up of 2.0 ± 1.6 years, 95 (14.2%) patients experienced appropriate therapy. Predictors of appropriate therapy in 2nd generator period was low initial left ventricular ejection fraction (≤25%) [hazard ratio (HR) 1.87, confidence interval (CI) 1.13–1.95] and appropriate therapy in 1st generator period (HR 3.95, CI 2.57–6.06). For patients with appropriate therapy in 1st generator period, 4-year incidence of appropriate therapy was 50.6% vs. 16.4% in those without ($P < 0.001$). Among patients >80 years with no prior appropriate therapy 8.8% of patients experienced appropriate therapy after replacement. Comorbidity burden and advanced age were associated with reduced device utilization after replacement and a high competing risk of death without preceding appropriate therapy.

Conclusion A significant residual risk of appropriate therapy in the 2nd generator was present even among patients with advanced age and with a full prior generator period without any appropriate ICD events.

Keywords Implantable cardioverter-defibrillator • Appropriate therapy • Ventricular arrhythmias • Mortality • Comorbidity • Generator

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Temporal Incidence of Appropriate and Inappropriate Therapy and Mortality in Secondary Prevention ICD Patients by Cardiac Diagnosis

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ABSTRACT

OBJECTIVES This study sought to estimate the temporal development in rates and incidences of appropriate and inappropriate implantable cardioverter-defibrillator (ICD) therapy and shocks by cardiac diagnosis in a real-world population of patients with secondary prevention ICDs.

BACKGROUND Data on cardiac diagnoses and temporal development of ICD therapies in patients with secondary prevention ICDs are limited.

METHODS Patients (N = 4,587) with a secondary prevention ICD were identified from the Danish Pacemaker and ICD Register (January 1, 2007, to December 31, 2016) and linked to nationwide administrative registers. The outcome of appropriate and inappropriate ICD therapy and all-cause mortality were analyzed by annual event rates, cumulative incidence plots, and Cox regression models.

RESULTS During a mean follow-up of 3.6 ± 2.4 years, 1,362 patients (30%) experienced appropriate ICD therapy (16.8% shocks), and 350 patients (7.6%) experienced inappropriate ICD therapy (4.6% shocks). From 2007 to 2016, there was a significant temporal reduction in both appropriate and inappropriate ICD therapy from 28.2 (95% confidence interval [CI]: 21.6 to 37.0) to 7.9 (95% CI: 6.8 to 9.1) and 10.0 (95% CI: 6.4 to 15.5) to 1.0 (95% CI: 0.7 to 1.5) per 100 person-years (p for trends <0.001). Multivariate Cox regression analyses showed that arrhythmogenic right ventricular cardiomyopathy was associated with the highest probability of appropriate ICD therapy (hazard ratio: 2.45; 95% CI: 1.77 to 3.39; p < 0.0001), whereas patients with hypertrophic cardiomyopathy had the lowest probability (hazard ratio: 0.62; 95% CI: 0.42 to 0.93; p = 0.0196) when compared to patients with ischemic heart disease.

CONCLUSIONS In this nationwide real-life cohort of patients with secondary prevention ICDs, we observed a significant temporal decline in delivered appropriate and inappropriate shocks and ICD therapies in the last decade. A large proportion of patients still experienced ICD therapy but with significant differences by cardiac diagnosis.
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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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