Modeling Outcome of Implantable Defibrillator Patients

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Modeling Outcome of Implantable Defibrillator Patients

Onderzoeken naar de uitkomst na implantatie van een defibrillator

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Erasmus Universiteit Rotterdam

op gezag van de

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en volgens besluit van het College voor Promoties.

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CHAPTER 1

INTRODUCTION

INTRODUCTION

Sudden cardiac arrest (SCA) is the sudden cessation of cardiac activity so that the victim becomes unresponsive, with no normal breathing and no signs of circulation. If corrective measures are not taken rapidly, this condition progresses to sudden cardiac death (SCD).[1] Sudden cardiac death is caused by ventricular arrhythmias in the majority of cases. Implantable cardioverter-defibrillator (ICD) therapy has shown to be highly effective in terminating these life-threatening arrhythmias, but is associated with potentially severe complications and high costs. In this chapter, we review the current knowledge on the epidemiology, the etiology, and the preventive therapy of SCD. Also, the topic of cost-effectiveness of ICD therapy is introduced.

EPIDEMIOLOGY OF SUDDEN CARDIAC DEATH

The incidence rate of SCD is estimated at 1 case per 1000 person-years in the general population.[2-6] Sudden cardiac death is estimated to occur 300000 to 350000 times per year in the United States of America, and comparable event rates are observed in Europe.[7] The incidence of SCD increases as a function of advancing age (Figure 1), and parallels the increasing incidence of atherosclerotic coronary heart disease with age.[8] From the eighth decade of life onwards, the slope of this increase seems to decline; this is probably attributable to the competing risk of other causes of death.[9] Men are two to three times more likely to experience SCD than women (Figure 1). Up to 80% of all SCD victims suffer from ischemic heart disease. Therefore, the epidemiology of SCD parallels that of atherosclerotic coronary heart disease to a large extent. Population-based studies demonstrated that advanced age, hypertension, left ventricular hypertrophy, intra-ventricular conduction disturbances, elevated serum cholesterol level, glucose intolerance, decreased vital lung capacity, tobacco smoking, obesity, and increased heart rate at rest are all meaningfully correlated with the incidence of SCD.[10] Long-term follow-up data showed that the incidence of SCD is also related to the clinical manifestation of coronary heart disease (Figure 2). The risk of SCD is highest in patients with myocardial infarction, intermediate in patients with angina pectoris, and lowest in patients with coronary heart disease without symptoms.[8]

Left ventricular dysfunction is an important determinant of the risk of SCD, both in patients with ischemic heart disease and in patients with non-ischemic heart disease. Left ventricular ejection fraction is currently the most important parameter influencing the clinical decision whether a primary prophylactic ICD is indicated or not. Also, the degree of functional impairment as indicated by the New York Heart Association (NYHA) classification, is an important predictor of the risk of SCD. It has to be noted that the relationship between left ventricular function and the risk of SCD is not linear; as functional impairment increases,

the total mortality and absolute number of SCD's also increases but the proportion of deaths due to cardiac arrhythmias decreases.[11,12] Further, electrocardiographic patterns as the presence of atrioventricular conduction block, intra-ventricular conduction delay, QT interval prolongation, increased resting heart rate, increased QT dispersion, and decreased heart rate variability are all associated with an increased risk of SCD.

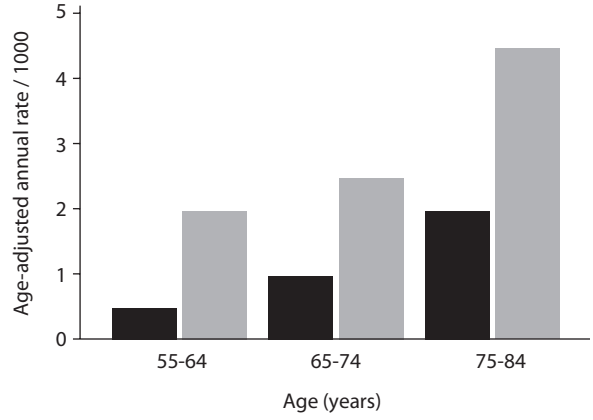

Figure 1. Sudden cardiac death incidence by age and gender: Framingham study 38-year follow-up.[8]
Black bars represent females, grey bars represent males.

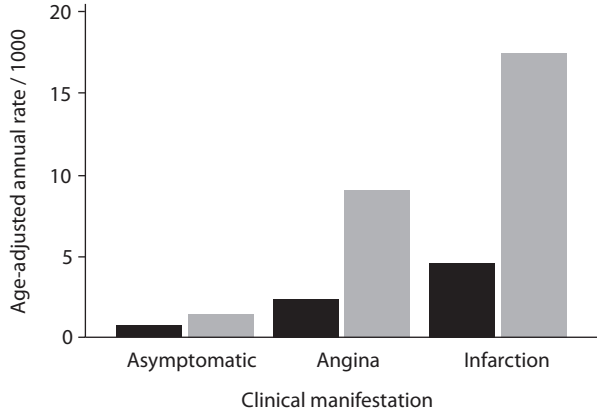

Figure 2. Sudden cardiac death incidence by clinical manifestation and gender: Framingham study 38-year follow-up data.[8]

Black bars represent females, grey bars represent males.

Unfortunately, all known risk factors and risk indicators lack sufficient predictive value to discriminate accurately between patients at high risk and patients at low risk of SCD.[13] The absolute number of SCD's occurring in the group of patients at highest relative risk of SCD is still small (Figure 3). As a result, the majority of patients treated with an ICD never experience appropriate ICD interventions (i.e. antitachycardia pacing or shock for ventricular tachyarrhythmias), and a large number of individuals currently not qualifying for ICD therapy die suddenly from cardiac arrest without being protected by an ICD. Both from the point-of-view of the patient, the physician, as from a public health perspective, the importance of better risk stratification for (recurrent) ventricular arrhythmias is paramount.

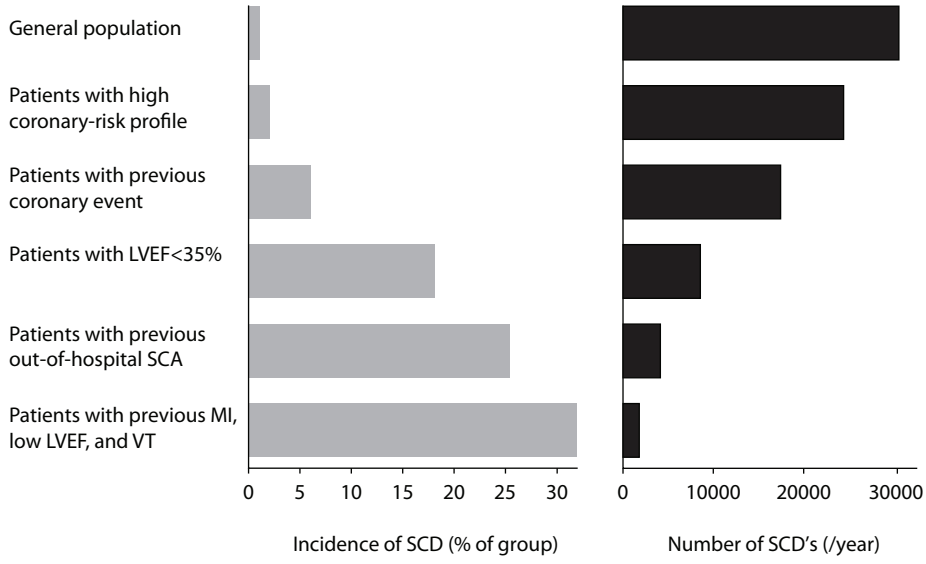

Figure 3. Incidence of SCD in the general population and in specific high-risk subpopulations, compared with the absolute annual numbers of SCD in these groups.[13]

Abbreviations: LVEF = left ventricular ejection fraction; SCA = sudden cardiac arrest; SCD = sudden cardiac death; MI = myocardial infarction; VT = ventricular tachycardia.

MECHANISMS OF SUDDEN CARDIAC DEATH

The fundamental mechanisms of SCD consist of electromechanical dissociation, complete atrioventricular conduction block, asystole, and ventricular fibrillation or ventricular tachycardia.[13] Evidence from observational studies suggests that 75% to 80% of all SCD's occur because of ventricular tachyarrhythmias (i.e. ventricular tachycardia or ventricular

fibrillation). The rhythm most often recorded during SCD is ventricular fibrillation (VF). The typical sequence of electrical events in SCD is the initiation of ventricular tachycardia (VT), degenerating into VF. If VF perpetuates, asystole will follow within minutes. Therefore, the first recorded rhythm is closely correlated with the interval between initiation of the arrhythmia causing hemodynamic compromise, and the arrival of professional medical help. Analysis of electrocardiogram (ECG) data in ambulatory patients who experienced SCD while undergoing Holter recording revealed VT degenerating into VF in 62% of cases, primary VF in 8% of cases, and Torsades des Pointes in 13% of cases. Bradyarrhythmias (including advanced atrioventricular conduction block and asystole) were responsible for 17% of cases.[14] It has to be noted that ventricular tachyarrhythmias also can be triggered by bradyarrhythmias.

SUBSTRATES FOR SUDDEN CARDIAC DEATH

Sudden cardiac death can occur in patients with structural heart disease as well as in patients without any apparent structural cardiac abnormalities. Figure 4 summarizes the underlying mechanisms of SCD. In this paragraph, we give an overview of the most important substrates for SCD.

Ischemic cardiomyopathy

Left ventricular dysfunction due to atherosclerotic coronary artery disease is responsible for 80% of all SCD's, and it is estimated that SCD accounts for 30% to 50% of all coronary deaths. However, less than 50% of successfully resuscitated patients from VF develop enzymatic evidence of myocardial infarction, and less than 25% electrocardiographic evidence of myocardial infarction. Acute myocardial ischemia seems to be a trigger for ventricular arrhythmias leading to SCD; autopsy studies in SCD victims showed a recent coronary artery occlusion in 15% to 64% of patients.[15,16] The risk of SCD is highest during and immediate after acute myocardial infarction, and declines in phases over the following days to months. Approximately 25% of all infarction-related SCD's occur in the first 3 months after infarction, and approximately half in the first year.[17,18] The incidence of SCD eventually stabilizes after this period, but remains elevated compared with individuals without prior myocardial infarction.[19] This is probably attributable to fibrosis and electrical remodeling occurring after myocardial infarction.[20] Non-atherosclerotic coronary artery abnormalities as coronary dissection, congenital malformations, coronary arteritis, coronary embolism, and anomalous anatomy of the coronary arteries account for only a very small number of SCD's. Patients with ischemic cardiomyopathy qualifying for ICD therapy were included in the studies presented in this thesis.

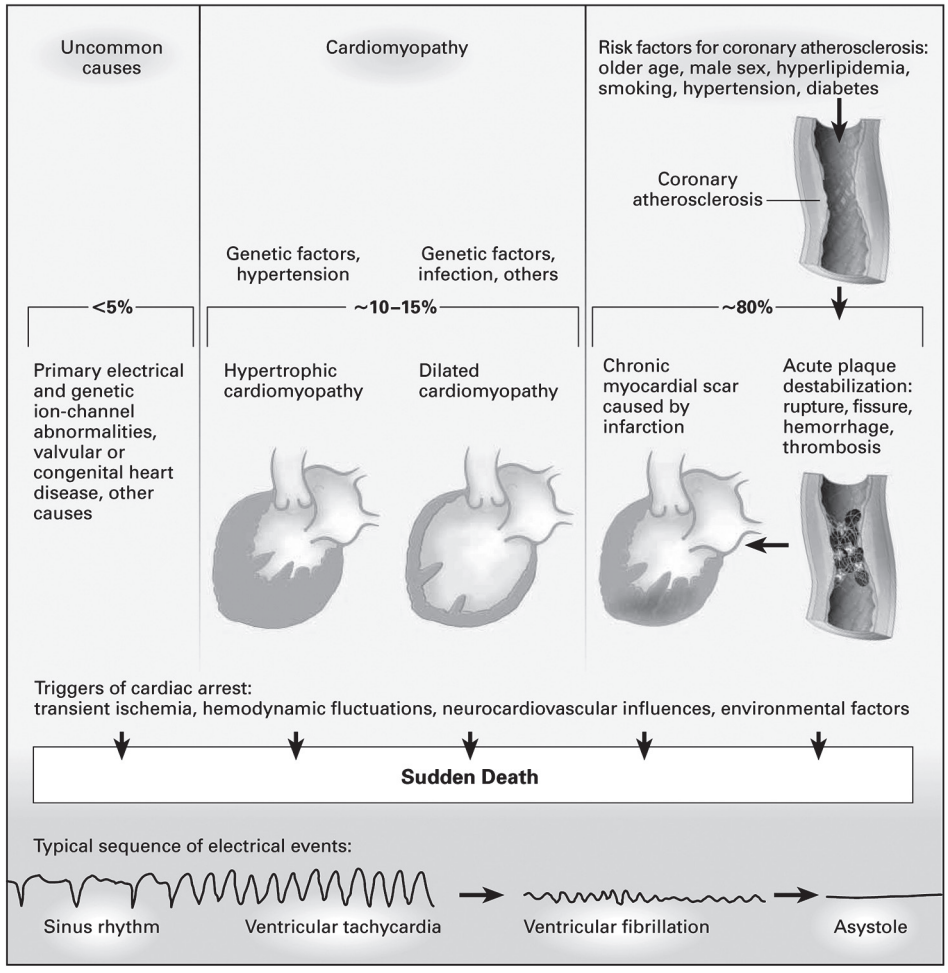

Figure 4. Schematic overview of the pathophysiology of sudden cardiac death.[13]

Non-ischemic dilated cardiomyopathy

Non-ischemic dilated cardiomyopathy (NIDCM, or DCM) accounts for the second largest group of patients qualifying for primary prevention ICD therapy. Dilated cardiomyopathy is characterized by dilatation and contractile impairment of one or both ventricles.[22] The majority of DCM patients present between the age of 20 years and 60 years, but DCM can occur at any age. Affected individuals can present with signs and symptoms of heart failure, with symptoms of coexisting arrhythmias, conduction disturbances, thromboembolisms,

or with SCD.[23] Dilated cardiomyopathy can be caused by different underlying disorders, and is considered idiopathic if coronary artery disease, active myocarditis, or a primary or secondary form of heart muscle disease has been excluded. This is the case in approximately 50% of patients. Patients with non-ischemic DCM qualifying for ICD therapy were also included in the studies presented in this thesis.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is a disease of the genes encoding for the myocardial contractile apparatus. In its typical form, hypertrophic cardiomyopathy (HCM) is characterized by hypertrophy of the left ventricle, most notably of the interventricular septum. However, the morphologic and hemodynamic abnormalities vary widely, as do the clinical symptoms. The estimated prevalence in the general population is 0.16 to 0.29 percent.[24-26] Patients with HCM are prone to both supraventricular and ventricular arrhythmias. Sudden cardiac death can be the presenting symptom of HCM. Implantable defibrillator therapy is a treatment option in these patients. Implantable defibrillator therapy in HCM was not the subject of the research presented in this thesis.

Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC), also called arrhythmogenic right ventricular dysplasia (ARVD), is characterized by fibrofatty replacement of cardiomyocytes of the right ventricular myocardium, leading to increased ventricular arrhythmogenesis, wall motion abnormalities, eventually leading to right ventricular dilatation and failure. [22] The prevalence of ARVC in the general adult population is estimated at 1 case per 1000 individuals.[27] Patients with ARVC typically present with symptomatic ventricular arrhythmias, ranging from premature ventricular complexes to sustained VT.[28] Sudden cardiac death occurs in ARVC, and can be the first presentation of the disease. Implantable defibrillator therapy in ARVC patients was not the subject of the research presented in this thesis.

The Brugada syndrome

The Brugada syndrome is characterized by ST-segment elevation with coved morphology in the right precordial leads and complete or incomplete right bundle branch block. Three different electrocardiographic patterns have been described. This arrhythmia syndrome is also associated with an increased risk of SCD. Sudden cardiac arrest may be the first and only clinical event in Brugada syndrome patients.[29] A variety of factors may contribute to the clinical manifestation of the syndrome, including right ventricular abnormalities, mutations in genes encoding the cardiac sodium channel, autonomic tone, and the use of psychotropic drugs. The Brugada syndrome is more prevalent in men than in women. In Brugada syndrome patients, arrhythmias are more commonly observed during sleep than while awake, and are usually not correlated with exercise. Studies suggest that fever is an

important trigger of arrhythmias. Currently, the only proven therapy for the prevention of SCD in selected Brugada syndrome patients is ICD therapy. Brugada syndrome patients were not included in the studies presented in this thesis.

Channelopathies

In the last fifteen years, several genetic ion channel abnormalities (i.e. channelopathies) causing ventricular arrhythmias have been identified. The long QT syndrome (LQTS) is the most well-known disease entity within this group of channelopathies. Long QT syndrome is defined as an arrhythmogenic disorder in the structurally normal heart presenting with QT interval prolongation often associated with peculiar ST-T segment morphology, syncope, and SCD.[30] Over the last years, the number of known genes causing LQTS increased to at least thirteen. In summary, LQTS is caused by either a loss-of-function mutation in a channel that conducts a repolarizing current, or by a gain-of-function mutation in a channel carrying a depolarizing current. When opposite effects occur, mutations cause completely different disease entities such as short QT syndrome (SQTS) and the Brugada syndrome. The short QT syndrome is a very rare genetic channelopathy, with less than 70 described cases worldwide. Catecholaminergic polymorphic ventricular tachycardia (CPVT) leads to a specific pattern of ventricular arrhythmias triggered by catecholamines, for example during exercise or acute emotion. Genetic research identified genetic mutations leading to abnormal calcium handling. Patients at increased risk of SCD due to channelopathies were not included in the studies presented in this thesis.

PREVENTION OF SUDDEN CARDIAC DEATH

Preventive therapy in general may be divided into two general categories – primary prevention and secondary prevention. Primary prevention refers to the prevention of a primary (i.e. first) event; secondary prevention refers to the prevention of recurrence of an event. The prevention of SCD involves both pharmacological and invasive interventions. Also, lifestyle habits play an important role in the prevention of SCD.

Risk factor reduction

Atherosclerotic coronary artery disease plays a pivoting role in the occurrence of SCD. Therefore, management of coronary risk factors may decrease the risk of SCD. Further, many of the traditional atherosclerotic coronary risk factors are also independently associated with the risk of SCD. Interventions aiming at risk factor reduction include effective treatment of dyslipidemia, treatment of hypertension, treatment of diabetes, cessation of tobacco smoking, moderation of alcohol consumption, regular physical exercise, and adoption of a balanced diet. Although convincing evidence of the effectiveness of risk factor reduction

on the occurrence of SCD in the general population is unavailable, there are several reports suggesting that this approach is important. A Belgian multifactorial, randomized controlled trial evaluated the effect of efforts aimed at reducing serum cholesterol (via dietary habits), increased physical activity, cessation of smoking, and treatment of hypertension and obesity on mortality. Individuals in the intervention group had a significant lower incidence of coronary artery disease and coronary death, compared with the control group.[31]

Pharmacological therapy

Randomized clinical trials demonstrated that anti-arrhythmic drugs were ineffective in reducing the incidence of SCD. Their role in prevention of SCD remains therefore limited. Pharmacological therapy is however of great importance in the management of post-myocardial infarction patients and heart failure patients; beta-blockers, statins, and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB's) reduce mortality in these patients.

Implantable Cardioverter-Defibrillators

As mentioned above, ventricular tachyarrhythmias are the most common mechanism of SCD. Although cardiopulmonary resuscitation including chest-compressions and assisted ventilation can provide transient circulatory support, the only effective approach to terminate VT or VF is electrical defibrillation and subsequently starting the 'chain of survival'. The first ICD's were implanted in humans who survived episodes of ventricular tachyarrhythmias in 1980.[32] Implantable defibrillator systems consist of pacing/sensing electrodes, defibrillation electrodes, and a pulse generator. Current ICD's are usually implanted in the pectoral region in a similar fashion to a pacemaker system. The system utilizes one, two, or three intracardial leads. Recently, totally subcutaneous ICD systems were introduced.[33]

Implantable Cardioverter-Defibrillators for secondary prevention

The effectiveness of ICD therapy in reducing the risk of recurrent SCA in survivors of a prior SCA was strongly suggested by observational studies.[34-36] Three large randomized controlled trials (the Cardiac Arrest Study Hamburg (CASH), the Canadian Implantable Defibrillator Study (CIDS), and the Antiarrhythmics versus Implantable Defibrillator study (AVID)) evaluated the effectiveness of ICD therapy after SCA, compared with pharmacological therapy with amiodarone, beta-blockers, sotalol, and propafenone.[37-39] A meta-analysis of these trials demonstrated a 25% relative risk reduction of all-cause mortality in patients treated with an ICD, compared with pharmacological therapy.[40] This reduction was entirely due to a 50% risk reduction of SCD. The number-needed-to-treat (NNT) was estimated at 15 in order to prevent one SCD.

Implantable Cardioverter-Defibrillators for primary prevention

The role of ICD therapy for primary prevention of SCD is limited to specific high-risk groups. Multiple large randomized controlled trials (RCT's) have been performed both in patients with ischemic heart disease, and in patients with non-ischemic heart disease. The Multicenter Automatic Defibrillator Implantation Trial (MADIT, now also referred to as MADIT-I) was the first large RCT evaluating the effectiveness of ICD therapy in patients at high risk of SCD. One hundred ninety-six post-myocardial infarction patients with a left ventricular ejection fraction (LVEF) ≤35%, non-sustained VT on monitoring, and inducible VT that was also inducible after intravenous administration of procainamide were enrolled.[41] The study population was randomly assigned to ICD therapy or optimal medical therapy only (which could include an anti-arrhythmic drug at the discretion of the physician). The major finding was a significant reduction of the overall mortality, arrhythmic mortality, and cardiac mortality in patients treated with an ICD. The MADIT-I trial had major limitations; the reproducibility of non-sustained VT on monitoring showed to be low, the enrolled patient group seemed to have selection bias in favor of non-responders to anti-arrhythmic drugs (caused by the criterion that inducible VT also had to be inducible after procainamide infusion), there was a disproportionately high use of beta-blockers in the ICD group, and a potential over-mortality in the control group because of pro-arrhythmic effects of anti-arrhythmic drugs.[42]

In an attempt to overcome the problems of MADIT-I trial, the MADIT-II trial was initiated. This RCT enrolled 1232 patients with a myocardial infarction more than 30 days prior to enrollment, more than 3 months from coronary bypass surgery (if this was performed), and LVEF ≤30%.[43] Holter monitoring or invasive electrophysiological studies were no longer needed. Included patients were randomly assigned to ICD therapy or conventional medical therapy. The study was terminated prematurely because of a significant mortality reduction in the ICD group (relative risk 0.65, 95% confidence interval 0.51 – 0.93). The observed survival benefit was entirely due to reduction of arrhythmic death.

After the MADIT-II trial, the Coronary Artery Bypass Graft Patch (CABG-Patch) trial evaluated the effectiveness of concomitant epicardial ICD implantation at time of elective coronary bypass surgery.[44] This trial showed no benefit of ICD implantation. Also, the Multicenter Unsustained Tachycardia Trial – in fact a study that was not designed to investigate the effectiveness of ICD therapy – was performed and showed no effect of ICD therapy.[45]

In 2004, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) was published. This was the first RCT examining the role of ICD therapy both in patients with ischemic cardiomyopathy, and in patients with non-ischemic DCM. This trial enrolled 2521 patients with LVEF ≤35% because of ischemic or non-ischemic dilated heart disease, who were in NYHA class II – III. These patients were randomly assigned to ICD therapy, amiodarone, or placebo. At five years of follow-up, ICD therapy showed to reduce all-cause mortality by 33% compared with both amiodarone and placebo therapy.[46]

The SCD-HeFT trial was the first to demonstrate the effectiveness of primary preventive ICD therapy in non-ischemic DCM patients. The Cardiomyopathy Trial (CAT) randomly assigned 104 patients with recent onset DCM and LVEF ≤30% to ICD therapy or regular medical therapy. Mortality showed to be similar after two and four years of follow-up. Also, the Amiodarone Versus Implantable Cardioverter-Defibrillator Trial (AMIOVIRT) showed no benefit of ICD therapy in 103 DCM patients in NYHA class I – III, LVEF ≤35%, and non-sustained VT.[47] These negative findings are probably due to lack of statistical power and unexpected low incidence of mortality.

In contrast to the previous trials, the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial did find a trend towards mortality reduction in 458 DCM patients with LVEF ≤35% and non-sustained VT or ventricular premature beats.[48] The results of these negative and positive trials are hard to interpret for the clinician. As a result, the debate about primary preventive ICD therapy in DCM persists; patients with non-ischemic DCM are often not considered to have an indication as strong as ischemic cardiomyopathy patients, although this is not advised in the international guidelines. Therefore, one of the aims of this thesis is to investigate and quantify the effectiveness of primary preventive ICD therapy in patients with non-ischemic DCM, compared with patients with ischemic heart disease.

COST-EFFECTIVENESS OF ICD THERAPY

Healthcare interventions must be effective and safe to be approved for clinical use. However, because new preventive, therapeutic, and diagnostic interventions become available in a rapid pace, and because healthcare resources are limited, the cost-effectiveness of an intervention has become an extremely important topic. Cost-effectiveness analysis assesses the value (i.e. efficiency) of a certain intervention. In this paragraph, we summarize the basics of cost-effectiveness analysis.

When assessing the value of a new healthcare intervention, there are usually >1 health outcome measures of interest. Therefore, aggregated outcome measures are usually used in these studies. The typical outcome measure of cost-effectiveness studies is quality-adjusted life expectancy, expressed in quality-adjusted life-years (QALY's). The advantage of this approach is that it allows direct comparison of the cost-effectiveness of different interventions.

A healthcare intervention is considered cost-effective when its additional benefit is deemed worth its additional costs. The cost-effectiveness is expressed as costs per QALY. If the costs per QALY are below the applicable threshold, the intervention is considered cost-effective. A universally accepted threshold does not exist; the Dutch council for healthcare resource studies advises a willingness-to-pay threshold of € 80000 per QALY for

therapeutic interventions. The World Health Organization provides a simple rule-of-thumb: all interventions with incremental cost-effectiveness ratio's (ICER's) below three times the Gross Domestic Product (GDP) per capita can be considered cost-effective.

Cost-effectiveness analyses are sometimes performed alongside a clinical trial. This design has the advantage that data on the effectiveness of the intervention and data on used resources are readily available and have high internal validity. Disadvantages consist mainly of a low generalizability to the 'real world' population (i.e. low external validity), a lack of long-term follow-up data, and unreliable estimates of rare events. An alternative design for cost-effectiveness analyses is the use of a decision model combining the best-available evidence from various sources. For example, a decision model can combine effectiveness data derived from a meta-analysis, data on costs from separate cost-analyses, data on the frequency of rare adverse events from observational studies, and data on long-term follow-up from registries.

Implantable defibrillator therapy is costly, with high upfront costs. The cost-effectiveness of both primary and secondary preventive ICD therapy has been subject of many studies in the United States. The cost-effectiveness of primary preventive ICD therapy in Europe remains unclear; previous studies have focused on the cost-effectiveness of ICD's in the North American setting, or – if focusing on Europe – have significant methodological flaws. Therefore, one of the aims of the present thesis was to analyze the cost-effectiveness of primary preventive ICD therapy in European patients with ischemic or non-ischemic dilated cardiomyopathy. Furthermore, recent lead-related problems made insight in this more important.

AIMS AND OUTLINE OF THIS THESIS

In this thesis, studies modeling outcome after defibrillator implantation are being presented. The primary aim was to study the effectiveness, the cost, and the cost-effectiveness of primary prevention implantable defibrillator-only therapy in patients with ischemic or non-ischemic heart disease in Europe. Secondly, we aimed to study the utility of new risk indicators and multivariable risk prediction models in ICD patients.

Chapter 2 describes a meta-analysis on the effectiveness of primary prevention ICD therapy in reducing all-cause mortality in patients with ischemic or non-ischemic heart disease, the largest two subgroups of patients qualifying for this therapy.

Chapter 3 describes the incidence of mortality and ICD interventions in a Dutch cohort of patients with ischemic or non-ischemic heart disease, who received an ICD (without cardiac resynchronization therapy) for the primary prevention of sudden cardiac death. In

this study, we explored the differences in long-term follow-up between the ischemic and non-ischemic heart disease patients.

We performed a study on the incidence of healthcare utilization after ICD implantation, described in **Chapter 4**.

Chapter 5 describes a model-based cost-effectiveness analysis of primary prevention ICD therapy in patients with ischemic heart disease in the European healthcare setting. Using the data of the meta-analysis described in Chapter 2, the data of the cohort study described in Chapter 3, the data of the cost study described in Chapter 4, and literature data, we combined the best-available evidence for primary prevention ICD-patients in a European healthcare setting.

In **Chapter 6**, it was demonstrated that the Seattle Heart Failure Model, a well-validated prediction model in heart failure patients and in ICD patients, provides well-calibrated risk estimates for mortality of heart failure patients treated with a defibrillator combined with cardiac resynchronization therapy (CRT-D). Further, we demonstrated that this prediction model is capable of discriminating between patients with high and low mortality risk.

In **Chapter 7**, we used competing risk methodology to analyze the relationship between the competing risks of mortality and ICD interventions prior to death in CRT-D patients.

Chapter 8 describes a study showing the potential use of C-reactive protein as risk-indicator for appropriate ICD interventions in ICD patients in general.

Chapter 9 describes a cohort of survivors of sudden cardiac arrest due to documented ventricular fibrillation, and the non-invasive therapy that they receive at long-term follow-up. This study was performed to investigate the adherence of physicians and ICD patients to the advised treatment regime.

Finally, in **Chapter 10** the main findings of the work described in this thesis and their relation to prior literature and current clinical practice are discussed.

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CHAPTER 2

EFFECTIVENESS OF PROPHYLACTIC IMPLANTATION OF CARDIOVERTER-DEFIBRILLATORS WITHOUT CARDIAC RESYNCHRONIZATION THERAPY IN PATIENTS WITH ISCHEMIC OR NON-ISCHEMIC HEART DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: Much controversy exists concerning the efficacy of primary prophylactic implantable defibrillators (ICD's) in patients with low ejection fraction due to coronary artery disease (CAD) or dilated cardiomyopathy (DCM). This is also related to the bias created by function improving interventions added to ICD therapy, e.g. resynchronization therapy.

Objective: The aim was to investigate the efficacy of ICD-only therapy in primary prevention in patients with CAD or DCM.

Methods: Public domain databases, MEDLINE, EMBASE, and Cochrane Register of Controlled Trials were searched from 1980 to 2009 for randomized clinical trials of ICD vs. conventional therapy. Two investigators independently abstracted data. Pooled estimates were calculated using both fixed-effects and random-effects models.

Results: Eight trials were included in the final analysis (5343 patients). Implantable cardioverter-defibrillators significantly reduced arrhythmic mortality (relative risk (RR), 0.40; 95% CI, 0.27 – 0.67) and all-cause mortality (RR 0.73; 95% CI, 0.64 – 0.82). Regardless of etiology of heart disease, ICD benefit was similar for CAD (RR 0.67; 95% CI, 0.51 – 0.88) vs. DCM (RR 0.74; 95% CI, 0.59 – 0.93).

Conclusions: The results of this meta-analysis provide strong evidence for the beneficial effect of ICD-only therapy on the survival of patients with ischemic or non-ischemic heart disease, with a left ventricular ejection fraction ≤35%, if they are 40 days from myocardial infarction and ≥3 months from a coronary revascularization procedure.

INTRODUCTION

Sudden cardiac and arrhythmic death (SCD) account for approximately 50% of the mortality in patients with left ventricular dysfunction.[1] Life-threatening ventricular arrhythmias are involved in the majority of SCD occurrences.[2] Randomized clinical trials have shown that the implantable cardioverter-defibrillator (ICD) is the most effective therapy currently available to prevent SCD by terminating ventricular arrhythmias.[3-6] Therefore, the ICD has become the standard therapy for primary and secondary prevention of SCD in patients with left ventricular dysfunction.[7,8] The addition of cardiac resynchronization therapy (CRT) to device therapy created not only possibilities to improve cardiac function in subgroups, but also influenced the outcome with respect to morbidity and mortality.[9,10] In contrast, concerns were raised on the magnitude of the effectiveness of ICD therapy certainly in this era when the majority of infarction patients receive primary coronary intervention in a reasonable time frame.[11] Some complications became more evident in the last few years, and co-morbidity became considered as limitation as it is associated with a less favorable outcome.[12,13] Given these recent concerns about ICD therapy, we performed a systematic review and meta-analysis of randomized trials of primary prevention of SCD in patients with heart failure due to coronary artery disease (CAD) or dilated cardiomyopathy (DCM), which constitute the largest two subgroups of potential ICD recipients. We examined the efficacy of ICD-only therapy without CRT on rates of all-cause mortality and arrhythmic mortality. In addition, we assessed the rates of delivered ICD therapies.

METHODS

Search strategy

A comprehensive search of public domain databases was performed to identify randomized clinical trials comparing ICD therapy with conventional medical therapy in patients with left ventricular dysfunction. The public domain databases MEDLINE (January 1980 to January 2009), EMBASE (1991 to the last quarter of 2008), and the Cochrane Central Register of Controlled Trials (last quarter of 2008) were searched using the terms *implantable cardioverter-defibrillator, implantable defibrillator, randomized controlled trials, clinical trials, mortality, sudden death,* and *prevention*. The search was restricted to humans and English language literature. In addition, we performed a manual search of secondary sources including references of initially identified articles and a search of reviews, editorials, commentaries, and proceedings from international cardiology meetings.

Eligibility and data abstraction

Studies considered for inclusion met the following criteria: the design was a randomized controlled clinical trial; patients were randomly assigned to ICD-only therapy excluding CRT versus conventional medical therapy; the study population consisted of patients with left ventricular dysfunction deemed to be at high risk for sudden cardiac death or developing ventricular arrhythmias; and the main endpoints included all-cause mortality, cardiac mortality, or arrhythmic mortality. Trials in patients who survived sudden cardiac death or unstable ventricular arrhythmias (secondary prevention) were excluded. We also excluded trials in patients with inherited arrhythmic disorders, trials that did not report any of the main endpoints of interest, or trials with crossover rates greater than 50% between study groups.

The selection of studies, quality assessment, and data abstraction were performed independently by 2 investigators (DAMJT and LJ). The criteria for quality assessment included study design aspects as randomized clinical trial, description of crossover, withdrawals, and dropouts, completeness of follow-up, and objectivity of the outcome assessment.[14] Data regarding detailed inclusion criteria as patient characteristics (number, mean age, gender, left ventricular ejection fraction (LVEF)), ICD device type, duration of follow-up, rates of crossover, all-cause mortality, cardiac mortality, and arrhythmic mortality (as available) were abstracted from each study. Studies were grouped according to the etiology of cardiomyopathy.

Data analysis

A meta-analysis of summary statistics from the individual trials was performed. For each study, data regarding all-cause mortality were used to calculate risk ratios (RR's) and 95% confidence intervals (CI's). The RR's from each included trial were pooled using both fixed- and random-effects models that used weighting based on the inverse of the variance calculated according to DerSimonian and Laird.[15] Evidence of statistical heterogeneity among the trial-specific RR's was checked and quantified by the I^2 statistic and a *P*-value ≤ 0.05 was considered statistically significant. When no significant statistical heterogeneity was identified, the fixed effect was preferentially used as the summary measure. In case of statistical heterogeneity, sensitivity analysis was performed to assess the contribution of each study to the pooled estimate by excluding individual studies one at a time and the pooled estimate was recalculated for the remaining studies. When pooled analysis still resulted in a significant heterogeneity, the random effects model was used. Data analysis was performed with Cochrane Review Manager for Windows (release 5.0.24, the Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Search results

The selection of the included randomized clinical trials is shown in Figure 1. The search retrieved 435 potential relevant manuscripts. A total of 372 were excluded after examination of the title and abstract. Of the 63 articles retrieved for further examination, 8 randomized clinical trials of ICD therapy for primary prevention were included for analysis. No evidence of publication bias was found by funnel-plot analysis.

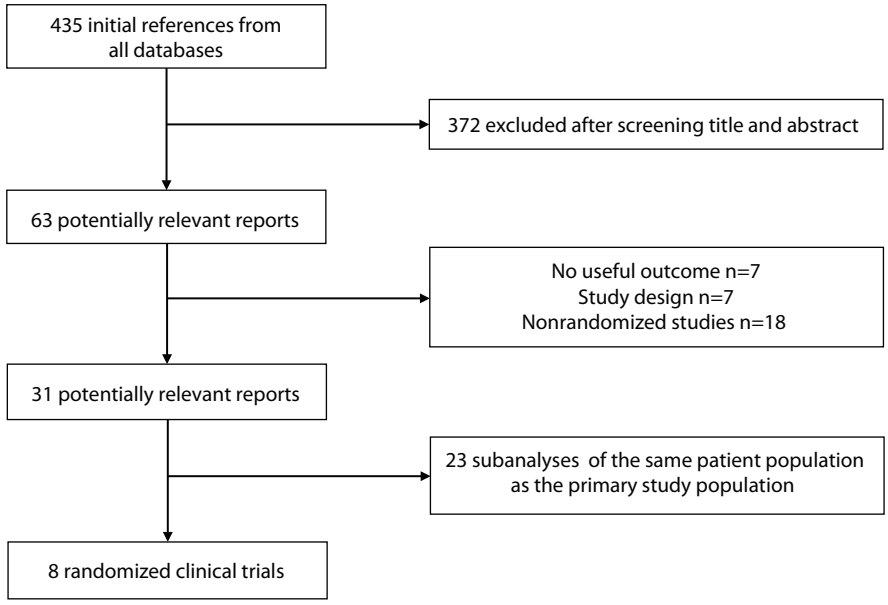

Figure 1. Selection of trials included in the meta-analysis.

Qualitative findings

The included trials were randomized and controlled. The analyzed primary prevention trials were the Multicenter Automatic Defibrillator Implantation Trial (MADIT),[3] the Coronary Artery Bypass Graft Patch trial (CABG Patch),[16] the Cardiomyopathy Trial (CAT),[17] the second Multicenter Automatic Defibrillator Implantation Trial (MADIT II),[5] the Amiodarone vs. Implantable Cardioverter-Defibrillator Randomized Trial (AMIOVIRT),[18] the Defibrillator in Non-ischaemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial,[19] the Defibrillators

in Acute Myocardial Infarction Trial (DINAMIT),[20] and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT).[6] The Multicenter Unsustained Tachycardia Trial (MUSTT) and the Comparison of Medical Therapy, Pacing and Defibrillators in Chronic Heart Failure (COMPANION) trial were excluded from analysis.[21, 22] The MUSTT trial was not a randomized controlled trial of ICD therapy, but compared electrophysiologic study guided antiarrhythmic therapy, including Class Ic drugs, in this way selecting patients for ICD therapy with empirical therapy. It is well known that Class Ic drugs can be proarrhythmic.[23,24] The COMPANION trial was not a comparison between ICD and conventional therapy, but studied the effects of CRT in a subgroup with pacing and a subgroup with ICD's, and therefore is not reporting on the effect of ICD-only therapy.

The characteristics of the included trials are presented in Table 1. In the eight trials, 5343 patients were randomly assigned to ICD therapy or conventional therapy. Of these trials, four trials evaluated patients with ischemic heart disease (MADIT, CABG Patch, MADIT II, and DINAMIT), three trials examined patients with non-ischemic heart disease (CAT, AMIOVIRT, and DEFINITE), and one trial (SCD-HeFT) enrolled patients with CAD or DCM.

The baseline clinical characteristics of patients are presented in Table 2. The mean age of the trial participants was 60 years, 79% were male, and CAD was present in 73%. The mean LVEF was 25% (range 21% – 28%), 59% of patients had New York Heart Association (NYHA) Class II heart failure symptoms, and 26% NYHA Class III.

Quantitative findings

All-cause mortality: Coronary artery disease

The MADIT, MADIT II, and SCD-HeFT trials showed significant reductions in all-cause mortality with relative risk reductions ranging from 22% to 59%. In CABG Patch and DINAMIT, no reductions in all-cause mortality were found (RR 1.07; 95% CI, 0.81 – 1.42, and RR 1.08; 95% CI, 0.76 – 1.55, respectively). All these trials, except DINAMIT, mandated that patients should be enrolled if they were at least 3 weeks after myocardial infarction. The DINAMIT was the only study designed to test ICD therapy as primary prevention in patients recovering from an acute myocardial infarction. The MADIT, MADIT II, and SCD-HeFT trials excluded patients who underwent coronary revascularization within 1 month before enrollment, whereas in CABG Patch, patients were enrolled at the time of coronary artery bypass surgery.

When the results of the 5 randomized trials were pooled, we found statistical evidence of heterogeneity ($I^2 = 74.9\%$; $P = 0.003$). To assess the impact of heterogeneity on the pooled effect estimate, we performed sensitivity analysis (Table 3). After exclusion of CABG Patch and DINAMIT, no statistical evidence of heterogeneity was present ($I^2 = 61.5\%$; $P = 0.07$). Pooled analysis using a fixed-effects model of the remaining studies showed a 29% relative risk reduction in all-cause mortality with ICD therapy (95% CI, 17% – 39%; $P < 0.0001$). Analysis with a random-effects model yielded a 33% relative risk reduction in all-cause mortality (95% CI, 12% – 49%; $P = 0.004$).

Table 1. Characteristics of included studies.

Study	Inclusion criteria	Patients (n)	ICD (n)	Follow-up (months)	Main result
MADIT, 1996	EF ≤0.35; MI ≥3 weeks before entry; NSVT; NYHA I – III	196	95	27	ICD therapy resulted in 54% RR reduction, $P = 0.009$
CABG Patch, 1997	EF ≤0.35; abnormal SAECG, scheduled for CABG; NYHA I – III	900	446	32	ICD therapy did not reduce mortality, $P = 0.64$
CAT, 2002	EF ≤0.30; new onset DCM; NYHA II – III	104	50	66	ICD therapy did not reduce mortality, $P = 0.55$
MADIT II, 2002	EF ≤0.30; MI ≥1 month before entry; NYHA I – III	1232	742	20	ICD therapy resulted in 31% RR reduction, $P = 0.016$
AMIOVIRT, 2003	EF ≤0.35; DCM; asymptomatic NSVT; NYHA I – III	103	51	36	ICD therapy did not reduce mortality, $P = 0.80$
DEFINITE, 2004	EF ≤0.35; DCM; NSVT, NYHA I – III	458	229	29	ICD therapy resulted in 35% RR reduction, $P = 0.08$
DINAMIT, 2004	EF ≤0.35; within 6 – 40 days of MI; NYHA I – III; abnormal HRV	674	332	33	ICD therapy did not reduce mortality, $P = 0.66$
SCD-HeFT, 2005	EF ≤0.35; 3 months optimal medical therapy; NYHA II - III	2521	829	45.5*	ICD therapy resulted in 23% RR reduction, $P = 0.007$

* median

Abbreviations: AMIOVIRT = Amiodarone vs. Implantable Defibrillator Randomized Trial; CABG Patch = Coronary Artery Bypass Graft Patch Trial; CAT = Cardiomyopathy Trial; DCM = dilated cardiomyopathy; DEFINITE = Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT = Defibrillator in Acute Myocardial Infarction Trial; EF = left ventricular ejection fraction; HRV = heart rate variability; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MI = myocardial infarction; NYHA = New York Heart Association; NSVT = non-sustained ventricular tachycardia; RR = relative risk; SAECG = signal-averaged ECG; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial.

Table 2. Baseline clinical characteristics of patients assigned to ICD therapy.

	Age (y)	Men (%)	EF (%)	NYHA (%)		CAD (%)	Pharmacologic therapy (%)			
Study				**II**	**III**		**Amiodarone**	**β-blocker**	**Digoxin**	**ACE/ARB**
MADIT	62 ± 9	92	27 ± 7	II or III, 63		100	2	26	58	60
CABG Patch	64 ± 9	87	27 ± 6	II or III, 71		100	4	18	69	55
CAT	52 ± 12	86	24 ± 6	67	33	0	NA	4	86	94
MADIT II	64 ± 10	84	23 ± 5	35	25	100	13	70	72	68
AMIOVIRT	58 ± 11	67	22 ± 10	64	16	0	NA	52	71	85
DEFINITE	58	73	21	54	21	0	4	86	42	97
DINAMIT	62 ± 11	76	28 ± 5	NA	NA	100	8	87	NA	95
SCD-HeFT	60*	76	25*	71	29	52	NA	69	67	94

* Median

Abbreviations: ACE/ARB = angiotensin-converting enzyme/angiotensin receptor blocker; AMIOVIRT = Amiodarone vs. Implantable Defibrillator Randomized Trial; CABG Patch = Coronary Artery Bypass Graft Patch Trial; CAD = coronary artery disease; CAT = Cardiomyopathy Trial; DEFINITE = Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT = Defibrillator in Acute Myocardial Infarction Trial; EF = left ventricular ejection fraction; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MI = myocardial infarction; NA = not available; NYHA = New York Heart Association; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial.

Table 3. Sensitivity analysis of randomized primary prevention trials in patients with ischemic heart disease.

Study removed	RR	95% CI	Heterogeneity (*P*-value)	ICD benefit (*P*-value)
MADIT	0.87	0.77 – 0.99	0.04	0.03
CABG Patch	0.77	0.68 – 0.88	0.01	0.0002
MADIT II	0.88	0.77 – 1.00	0.003	0.05
DINAMIT	0.80	0.70 – 0.91	0.005	0.0005
SCD-HeFT	0.86	0.74 – 1.00	0.002	0.05

Removal of each trial (shown in column 1) followed by re-analysis of the pooled relative risk (RR) (column 2) and 95% confidence intervals (95% CI) (column 3) for the remaining trials. *P*-values for heterogeneity and ICD benefit are shown in column 4 and 5.

All-cause mortality: Dilated Cardiomyopathy

A tendency towards a reduction in all-cause mortality by ICD therapy was found in two trials (DEFINITE and SCD-HeFT). The DEFINITE trial showed a relative risk of 0.65 for all-cause mortality with ICD therapy (95% CI, 0.40 – 1.06; $P = 0.08$). The relative risk for all-cause mortality was 0.74 in the SCD-HeFT (95% CI, 0.55 – 1.00). The CAT and AMIOVIRT trials found no reduction in all-cause mortality with ICD therapy compared with conventional

therapy. When we pooled the data, the relative risk for all-cause mortality was 0.74 (95% CI, 0.59 – 0.93; $P = 0.009$) both in a random- and fixed-effects model. No statistical evidence for heterogeneity was present among the trials enrolling patients with DCM ($I^2 = 0\%$; $P = 0.98$).

All-cause mortality: combined analysis

When we pooled the data of CAD and DCM, the summary relative risk for all-cause mortality was 0.72 (95% CI, 0.64 – 0.82; $P < 0.0001$) with ICD therapy (Figure 2). No statistical evidence of heterogeneity was found ($I^2 = 0\%$; $P = 0.49$). The pooled analysis using a fixed-effects model demonstrates that ICD therapy significantly reduces all-cause mortality, both in patients with CAD (RR 0.71; 95% CI, 0.61 – 0.83) and DCM (RR 0.74; 95% CI, 0.59 – 0.93). No significant differences in ICD benefit were found between ischemic and non-ischemic heart disease ($I^2 = 0\%$; $P = 0.82$).

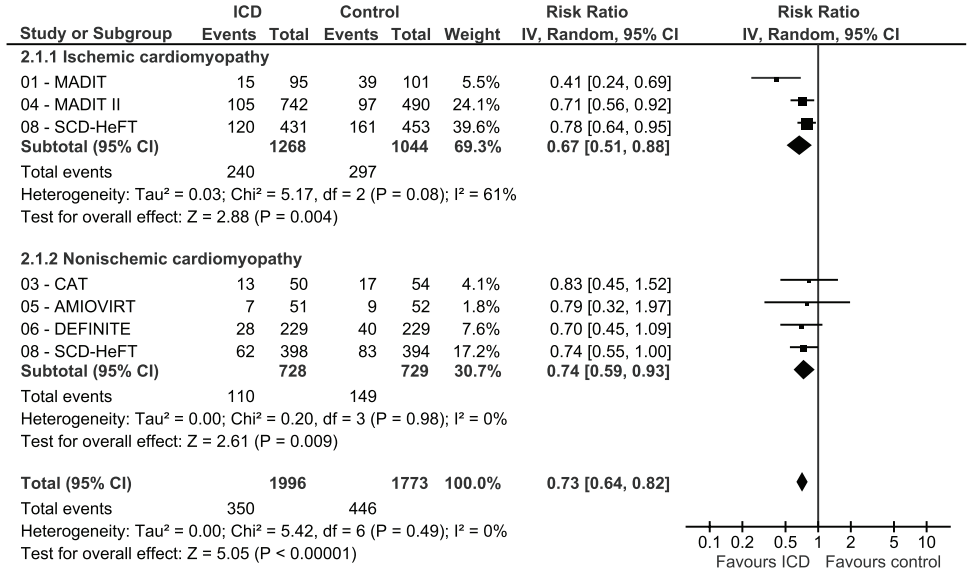

Figure 2. All-cause mortality among patients with ischemic or non-ischemic heart disease randomized to ICD vs. conventional therapy in primary prevention.

For each randomized trial, the number of deaths (events) and the number assigned (total) are shown. The point estimates of the relative risk (RR) for individual studies are represented by squares with 95% confidence intervals (CI) shown as bars. The midpoint of the diamond represents the overall pooled estimate of the RR, and the 95% CI is represented by the horizontal tips of the diamond.

Abbreviations: AMIOVIRT = Amiodarone vs. Implantable Defibrillator Randomized Trial; CAT = Cardiomyopathy Trial; DEFINITE = Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; MADIT = Multicenter Automatic Defibrillator Implantation Trial; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial.

Arrhythmic mortality; combined analysis

Among the 2774 patients randomized to ICD therapy, there were 98 sudden cardiac deaths, compared with 227 sudden cardiac deaths among the 2569 patients randomized to conventional therapy. Pooled analysis using a fixed-effects model demonstrated a 60% relative risk reduction in arrhythmic mortality (RR 0.40; 95% CI, 0.31 – 0.50; $P < 0.0001$) with ICD therapy (Figure 3). No statistical heterogeneity was found among the trials ($I^2 = 0\%$; $P = 0.84$). Subanalysis of SCD-HeFT demonstrated a significant reduction of arrhythmic mortality in CAD (RR 0.43; 95% CI, 0.27 – 0.67) and DCM (RR 0.34; 95% CI, 0.17 – 0.70).

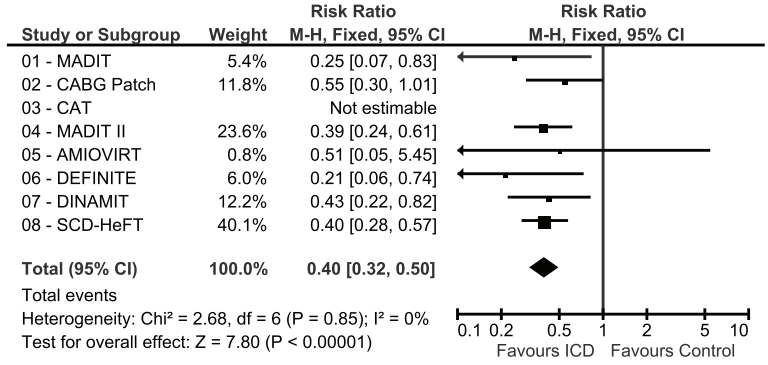

Figure 3. Arrhythmic mortality among primary prevention trials.

For each randomized trial, the number of deaths (n) and the number assigned (N) are shown. The point estimates of the relative risk (RR) for individual studies are represented by squares with 95% confidence intervals (CI) shown as bars. The midpoint of the diamond represents the overall pooled estimate of the RR, and the 95% CI is represented by the horizontal tips of the diamond.

Abbreviations: AMIOVIRT = Amiodarone vs. Implantable Defibrillator Randomized Trial; CAT = Cardiomyopathy Trial; CABG Patch = Coronary Artery Bypass Graft Patch Trial; DEFINITE = Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT = Defibrillator In Acute Myocardial Infarction Trial; MADIT = Multicenter Automatic Defibrillator Implantation Trial; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial; CABG Patch = Coronary Artery Bypass Graft Patch Trial.

ICD therapy during follow-up

The appropriateness of ICD therapy could not be assessed reliably in the MADIT and the CABG Patch trial, since only a small number of devices had the capacity of electrogram storage. The remaining six trials presented data on the number of patients who experienced appropriate ICD therapy delivered for ventricular tachyarrhythmias (Figure 4). The mean proportion of patients with appropriate ICD therapy was 22.9% (range 17.8% – 31.4%). The delivery of inappropriate ICD therapy was observed in 16.5% of patients.

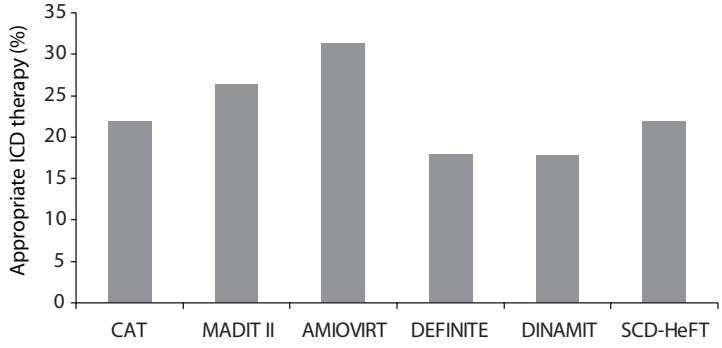

Figure 4. Rates of appropriate ICD therapy.

Abbreviations: AMIOVIRT = Amiodarone vs. Implantable Defibrillator Randomized Trial; CAT = Cardiomyopathy Trial; DEFINITE = Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT = Defibrillator In Acute Myocardial Infarction Trial; MADIT = Multicenter Automatic Defibrillator Implantation Trial; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial.

DISCUSSION

Arrhythmic death and ICD interventions

Previous meta-analyses demonstrated that ICD therapy is associated with a 50% relative risk reduction for arrhythmic death in secondary prevention patients.[25,26] In primary prevention, the risk reduction for arrhythmic death is similar. In SCD-HeFT, as was confirmed in this analysis, the benefit of ICD therapy in reducing arrhythmic death is similar, regardless of whether a patient had left ventricular dysfunction caused by CAD or DCM.[27] The proportion of ICD interventions in the follow-up can not be used as a surrogate for its efficacy in preventing mortality, but shows that ICD's are effective in terminating ventricular arrhythmias.

All-cause mortality

In contrast to arrhythmic mortality, the results on all-cause mortality are heterogeneous. We confirmed with this meta-analysis that there is a substantial benefit (a risk reduction of 27%), which is comparable with former analysis.[28] Former meta-analysis did not exclude DINAMIT and CABG Patch, which both contributed significantly in the heterogeneity of the pooled analysis in CAD. This resulted in a homogeneous CAD population in our observation. The observed benefit for the entire group and for DCM remains present in spite of the inclusion of small negative trials studying DCM, and additional exclusion of trials as MUSTT, comparing ICD therapy with potentially pro-arrhythmic drug therapy as control.[23, 24] Further, in contrast to previous meta-analysis[26,28-30] we excluded trials with a potential benefit

of CRT (as COMPANION), as CRT alone has already a benefit on survival.[9,10] This is part of the explanation that ICD therapy in non-ischemic cardiomyopathy only received a recommended class I-B indication in the 2006 and 2008 international guidelines.[7,8] The benefit of CRT is most evident in patients with DCM and left bundle branch block,[31] but its impact on mortality in comparison to ICD was not evident in a recent study in patients with mild heart failure,[32] confirming our position that the benefit of both intervention modalities (ICD and CRT) should be further clarified.

Implantable cardioverter-defibrillator-only benefit

A huge variation exists in the utilization of ICD's with or without CRT in different social and medical environments.[33] Uncertainty of the effect of the ICD alone in the present era of infarction therapy, and doubts on the value of ICD's for DCM, e.g. in the Dutch guidelines,[34] prompted us to perform this meta-analysis, which was performed for the first time with unpublished data on SCD-HeFT (separate mortality data for ischemic and non-ischemic cardiomyopathy).

The timing of device implantation after myocardial infarction remains debated. The role of ICD therapy in the early post myocardial infarction period was examined by the DINAMIT study.[20] No benefit of ICD therapy in reducing all-cause mortality was observed when device implantation occurred within 40 days after acute myocardial infarction. The recent Immediate Risk Stratification Improves Survival (IRIS) study, which included patients very early after infarction with additional risk factors, confirmed this finding.[35] Time-dependent benefit of ICD therapy was observed in the MADIT II study.[36] Benefit was present for remote events more than 18 months after myocardial infarction, as could be expected from other observations.[2]

Thus, this analysis confirms that ICD-only therapy reduces the relative risk for all-cause mortality by 27% for patients with a LVEF ≤35%, if they are 40 days from myocardial infarction and ≥3 months from a coronary revascularization procedure, without a previous cardiac arrest or symptomatic ventricular arrhythmias. This beneficial effect of ICD-only therapy on survival exists regardless of whether a patient has left ventricular dysfunction due to CAD or DCM.

Study limitations

Our analysis has several limitations. First, we could not obtain individual patient data, which offers the possibility to explore subgroups that may benefit more or less from ICD therapy. The conclusions of this analysis are limited by the available data. Another possible limitation of our analysis is the influence of publication bias. This type of bias was minimized by an extensive search and through the inclusion of unpublished data in our analysis. We performed funnel plot analysis, which did not indicate publication bias, although the power is limited due to the small number of included studies.

Conclusion

The results of our meta-analysis provide strong evidence, supporting the beneficial effect of ICD-only therapy on survival of patients with LVEF ≤35% due to ischemic or non-ischemic heart disease, if they are at least 40 days from myocardial infarction and at least 3 months from a coronary revascularization procedure.

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CHAPTER 3

LONG-TERM FOLLOW-UP OF PROPHYLACTIC IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR-ONLY THERAPY: COMPARISON OF ISCHEMIC AND NON-ISCHEMIC HEART DISEASE

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ABSTRACT

Background: The benefits of primary prophylactic implantable cardioverter-defibrillators (ICD's) are actually debated, as some drawbacks become more apparent and as the natural history of cardiac disease seems to improve. Therefore, contemporary follow-up data of non-trial populations treated according to current guidelines remain necessary. The aim of this study was to evaluate the mortality and the occurrence of ICD interventions in patients with coronary artery disease (CAD) or dilated cardiomyopathy (DCM) who received a primary prophylactic ICD without resynchronization therapy in the recent era.

Hypothesis: Survival and event-free rates from appropriate ICD therapy are different between ischemic and non-ischemic ICD patients.

Methods: Prospective cohort study of 427 consecutive primary prevention ICD patients with ischemic or non-ischemic heart disease, excluding patients with resynchronization.

Results: Ischemic heart disease was present in 290 patients (68%), non-ischemic heart disease in 137 patients (32%). During a median follow-up of 31 months (interquartile range [IQR] 15 – 45 months), 30 patients (7%) died. Mortality was not different in both disease categories. The incidence of appropriate ICD interventions was similar in CAD and DCM (23% vs. 21%). Appropriate ICD intervention occurred more frequently in patients with atrial fibrillation (29% vs. 19%). Inappropriate ICD intervention occurred in 11% of patients.

Conclusions: The clinical course of ischemic and non-ischemic heart disease patients treated with a primary prophylactic ICD is similar with respect to mortality and to appropriate and inappropriate ICD interventions, in spite of a younger age at baseline of the DCM patients.

INTRODUCTION

Real-world follow-up data of ICD patients who receive an ICD according to the international guidelines are useful in the translation of clinical trial data to clinical practice.[1,2] The landmark trials on primary prevention[3-5] were indeed interpreted in a variable way by different national cardiac societies and reimbursement authorities[6] resulting in different practices often not consistent with the available evidence[7] and the international guidelines.[8,9]

The indication for primary prophylactic ICD's in patients with dilated cardiomyopathy (DCM) is especially not fully appreciated by all, and the use of resynchronization therapy (CRT) only confounds the interpretation of the outcome of device therapy.[10-13] Therefore, the aim of the present study was to evaluate the mortality and occurrence of ICD interventions in patients with left ventricular dysfunction due to coronary artery disease (CAD) or DCM, who received primary prophylactic ICD-only therapy (i.e. without CRT) according to the international guidelines in the recent era.

METHODS

Study population

The basis for this study was the prospective ICD registry of the Erasmus MC, including all consecutive patients who received an ICD since 1998 in our institution. All consecutive patients with CAD or DCM who received a first ICD-only implantation for primary prevention between January 2004 and June 2009 were selected. Patients who received a CRT-defibrillator (CRT-D) (all according to the guidelines) were excluded. In addition, patients with hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, congenital structural heart disease, the Brugada syndrome, or inherited arrhythmia disorders were excluded.

Coronary artery disease had to be documented clinically by a history of a myocardial infarction according to the definitions by the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC), if coronary artery bypass grafting (CABG) or a percutaneous coronary intervention (PCI) had been performed, or if significant coronary artery stenosis was documented with coronary angiography.

The majority of patients (82%) had the device programmed in a 2-zone configuration, with the rate cut-off for detection of ventricular tachycardia (VT) at 170 to 180 beats per minute (bpm), and for detection of ventricular fibrillation (VF) at 200 to 220 bpm. Antitachycardia pacing (ATP) in combination with cardioversion/defibrillation therapy features was activated in those with 2 zones. ICD programming was tailored to avoid inappropriate therapy as published.[14] In brief, the stability criterion was programmed at 30

to 40 ms, the onset criterion at 15% to 20%, and morphology was activated when available. In all dual-chamber devices, the respective dual-chamber discrimination algorithm was activated.

Data collection

Follow-up started at the time of ICD implantation. All patients were regularly followed at 3-month intervals for the first 12 months, and thereafter every 6 months. The patients were advised to contact the outpatient clinic after a symptomatic event as soon as possible. All spontaneous episodes with stored electrograms that resulted in ventricular therapies were reviewed and classified by 2 of the authors (D.T., L.J.). In case of disagreement between the 2 reviewers about the stored electrograms, a third electrophysiologist was consulted and made the decision. For each episode, the date, type, morphology, and mean cycle length of the tachyarrhythmia, and the type and outcome of delivered ICD intervention were recorded. The arrhythmias were classified as 1) ventricular tachyarrhythmia, or 2) atrial tachyarrhythmia without a coexistent ventricular arrhythmia. When an atrial electrogram was available, the presence of atrioventricular dissociation was used to classify a ventricular tachyarrhythmia. Otherwise, a ventricular tachyarrhythmia was defined as an event with a sudden increase in rate combined with a change in electrogram morphology from the baseline rhythm. Intervention triggered by a ventricular tachyarrhythmia was considered appropriate, while intervention delivered for atrial tachyarrhythmia (including atrial fibrillation, atrial flutter, atrial tachycardia, and sinus tachycardia) and interference by other cardiac or extra-cardiac signals was defined as inappropriate. Atrial fibrillation was diagnosed with all available means. For all patients, the renal function was assessed by estimating the baseline glomerular filtration rate (eGFR) using the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation: eGFR (mL / min / 1.73m^2 of body surface area) = 186 × (serum creatinine in mg/dL) − 1.154 × (age) − 0.203 (× 0.742, in female subjects). Impaired renal function was defined as an eGFR <60 mL / min / 1.73 m^2.

Statistical analysis

Continuous variables were expressed as the mean ± standard deviation (SD) if normally distributed, or otherwise as the median and interquartile range (IQR). Continuous variables were compared with the Student T-test or one-way analysis of variance (ANOVA). Categorical data were summarized as frequency. The chi-square test was used to compare categorical variables. Survival and event-free rates from ICD intervention were calculated according to the Kaplan-Meier method. Survival time was defined as the date from ICD implantation to the date of death as verified in the civil registry. Patients who underwent heart transplantation were censored from the moment of transplantation. Differences between pairs of survival curves were tested by the log-rank test. A Cox proportional hazards model was used to identify predictors of mortality. The proportional hazards

assumption was checked graphically by assessing log-log survival curves. In addition, the proportional hazards assumption was tested for all covariates using Schoenfeld residuals. Hazard ratios (HR's) were reported with corresponding 95% confidence intervals (CI's). A two-tailed *P*-value <0.05 was considered statistically significant. Statistical analyses were performed with SPSS for Windows (release 16.0; SPSS, Inc., Chicago, IL) and with STATA for Windows (release 11; StataCorp, TX).

RESULTS

Study population

The study population consisted of 427 patients who received an ICD for primary prevention of sudden cardiac death. Coronary artery disease was present in 290 patients (68%) and DCM in 137 patients (32%). The mean age of the study population was 58 ± 14 years; the mean left ventricular ejection fraction (LVEF) was 27% ± 9%. Baseline characteristics and differences in characteristics between CAD and DCM patients are presented in Table 1. Dilated cardiomyopathy patients were younger than CAD patients and were more often of the female gender. Coronary artery disease patients were more often in New York Heart Association (NYHA) class I-II compared with DCM patients (69% vs. 52%, $P < 0.001$). The use of digoxin was not significantly different between CAD patients and DCM patients (18% vs. 25%), whereas use of beta-blockers (82% vs. 69%, $P = 0.004$) and statins (82% vs. 19%, $P < 0.001$) was more frequent in CAD patients compared with DCM patients. The implanted devices were 317 single-chamber ICD's (74%), and 110 dual-chamber ICD's (26%). Patients with DCM more often received a dual-chamber device compared with CAD patients (32% vs. 23%, $P = 0.044$).

Mortality

During a median follow-up of 31 months (IQR 15 – 45 months), 30 (7%) patients died and 14 (3.3%) patients underwent heart transplantation. The total follow-up consisted of 1070 person-years; the crude death rate was 2.8 deaths per 100 person-years. For the total cohort, the cumulative incidence of all-cause mortality was 2.4%, 4.3%, and 14.7% at 1, 2, and 5 years of follow-up, respectively. The cumulative incidence of all-cause mortality was 2.4%, 9.2%, and 15.7% for CAD patients and 2.2%, 7.7%, and 12.5% for DCM patients at 1, 2, and 5 years of follow-up, respectively. No significant difference in mortality was observed between CAD patients and DCM patients (Figure 1A). Univariate analyses for mortality are shown in Table 2. Patients older than 65 years of age at time of ICD implantation had a higher mortality compared with patients younger than 65 years of age (Figure 1B). Also, mortality was higher in males, and in patients in NYHA class III-IV.

Table 1. Baseline characteristics.

Characteristic	All (n = 427)	CAD (n = 290)	DCM (n = 137)	*P*-value
Age, years	58 ± 14	62 ± 10	49 ± 15	<0.001
Male gender, n(%)	336 (79%)	248 (86%)	88 (64%)	<0.001
Left ventricular ejection fraction, %	27 ± 9	27 ± 7	28 ± 12	NS
History of myocardial infarction, n(%)	261 (61%)	261 (61%)	N/a	N/a
NYHA class at time of ICD implantation, n(%)				
NYHA I-II	347 (82%)	255 (88%)	95 (70%)	<0.001
NYHA III-IV	77 (18%)	37 (12%)	40 (30%)	
Previous revascularization, n(%)				
CABG	90 (21%)	90 (31%)	N/a	N/a
PCI	141 (33%)	141 (49%)	N/a	N/a
History of atrial fibrillation, n(%)	112 (26%)	80 (28%)	32 (24%)	NS
QRS duration, ms	116 ± 26	117 ± 26	112 ± 27	NS
QRS >0.12 s, n(%)	133 (31%)	100 (35%)	33 (24%)	0.034
Serum creatinin (µmol/L)	97 ± 41	99 ± 37	94 ± 46	NS
eGFR (mL/min/1.73 m^2)	78 ± 26	76 ± 25	80 ± 26	0.07
Diabetes, n(%)	88 (21%)	70 (24%)	18 (13%)	0.01
Renal failure, n(%)	106 (25%)	79 (27%)	27 (20%)	0.1
Implanted devices, n(%)				
Single-chamber ICD	317 (74%)	224 (77%)	93 (68%)	0.044
Dual-chamber ICD	110 (26%)	66 (28%)	44 (32%)	
Cardiovascular medication, n(%)				
Amiodarone	46 (11%)	29 (10%)	17 (13%)	NS
Beta-blocker	332 (78%)	238 (82%)	94 (69%)	0.004
Digoxin	87 (20%)	53 (18%)	34 (25%)	0.1
ACE inhibitor	330 (78%)	228 (79%)	102 (75%)	NS
Diuretic	252 (59%)	170 (59%)	82 (60%)	NS
Statin	265 (62%)	238 (82%)	27 (20%)	<0.001

Abbreviations: ACE = angiotensin-converting enzyme; CABG = coronary artery bypass grafting; CAD = coronary artery disease; DCM = dilated cardiomyopathy; eGFR = estimated glomerular filtration rate, PCI = percutaneous coronary intervention, N/a = not applicable, NS = not significant, NYHA = New York Heart Association.

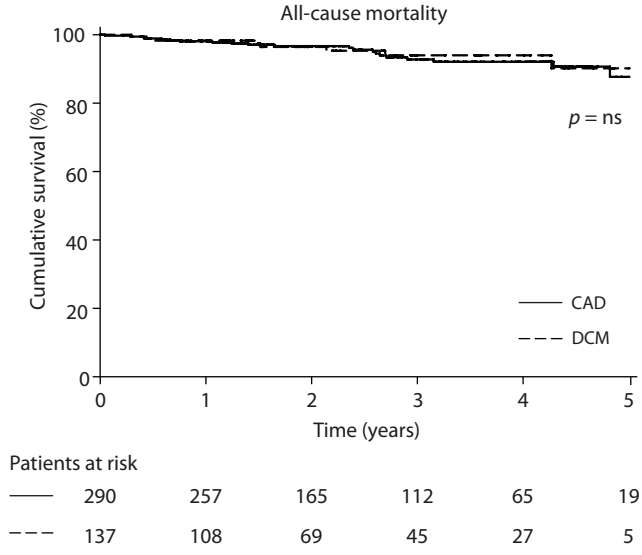

Figure 1A. All-cause mortality: coronary artery disease vs. dilated cardiomyopathy.
Chi-square 0.14, *P* = 0.71

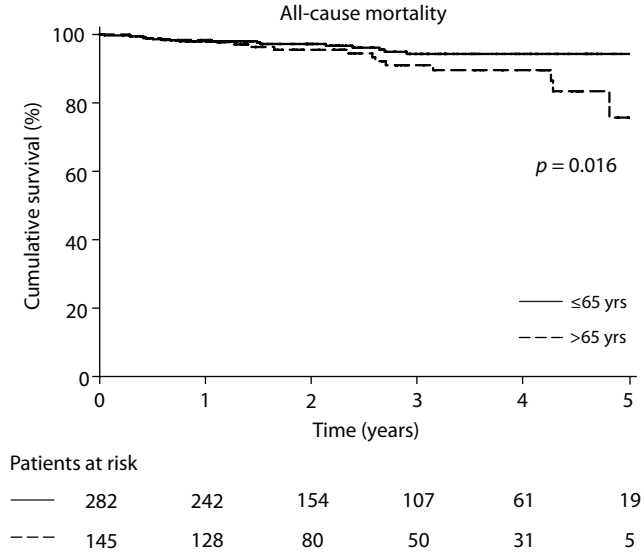

Figure 1B. All-cause mortality: ≤65 years vs. >65 years.
Chi-square 5.84, *P* = 0.0157
Abbreviations: CAD = coronary artery disease; DCM = dilated cardiomyopathy; NS = not significant.

Table 2. Univariate analysis for all-cause mortality.

Characteristic	All (n = 427)	Survived (n = 397)	Deceased (n = 30)	*P*-value
Age <65 years	282 (66%)	268 (68%)	14 (47%)	0.03
Male gender, n(%)	336 (79%)	307 (77%)	29 (97%)	0.01
Left ventricular ejection fraction, %	27 ± 9	27 ± 9	25 ± 9	NS
Coronary artery disease, n(%)	290 (68%)	268 (68%)	22 (73%)	NS
History of myocardial infarction, n(%)	261 (61%)	241 (61%)	20 (67%)	NS
NYHA class at time of ICD implantation, n(%)				
NYHA I-II	347 (82%)	328 (83%)	19 (63%)	<0.001
NYHA III-IV	77 (18%)	66 (17%)	11 (37%)	
History of atrial fibrillation, n(%)	112 (26%)	102 (26%)	10 (33%)	NS
QRS >0.12 s, n(%)	133 (31%)	122 (31%)	11 (37%)	NS
Serum creatinin (µmol/L)	97 ± 41	96 ± 89	110 ± 98	NS
eGFR (mL/min/1.73 m^2)	78 ± 25	78 ± 25	74 ± 34	NS
Diabetes, n(%)	88 (21%)	80 (20%)	8 (27%)	NS
Renal failure, n(%)	106 (25%)	95 (24%)	11 (37%)	NS
Cardiovascular medication, n(%)				
Amiodarone	46 (11%)	43 (11%)	3 (10%)	NS
Beta-blocker	332 (78%)	311 (79%)	21 (70%)	NS
Digoxin	87 (21%)	81 (21%)	6 (20%)	NS
ACE inhibitor	330 (78%)	303 (77%)	27 (90%)	0.1
Diuretic	252 (59%)	230 (59%)	22 (73%)	0.1
Statin	265 (62%)	249 (63%)	16 (53%)	NS

Abbreviations: ACE = angiotensin-converting enzyme; CABG = coronary artery bypass grafting; CAD = coronary artery disease; DCM = dilated cardiomyopathy; eGFR = estimated glomerular filtration rate, PCI = percutaneous coronary intervention, NS = not significant, NYHA = New York Heart Association.

Multivariate prediction of mortality

A Cox proportional hazards model was fitted with age, male gender, NYHA class III-IV, diuretic drug use, angiotensin-converting enzyme (ACE) inhibitor use, and renal failure as independent variables, and mortality as dependent variable. This model showed that age <65 years (HR 0.43; 95% CI, 0.20 – 0.90), and NYHA class III-IV (HR 1.77; 95% CI, 1.20 – 2.63) were independent predictors of mortality (Table 3).

Table 3. Cox proportional hazards analysis for all-cause mortality.

Covariate	β	SE(β)	HR	95% CI	*P*-value
Age<65 years	-0.85	0.38	0.43	0.20 – 0.90	0.026
Male gender	1.96	1.02	7.13	0.96 – 52.92	0.055
NYHA III-IV	0.57	0.20	1.77	1.20 – 2.63	0.005
Diuretic use	0.48	0.43	1.62	0.70 – 3.79	NS
ACE inhibitor use	0.82	0.62	2.26	0.68 – 7.52	NS
Renal failure	0.51	0.42	1.66	0.73 – 3.77	NS

Abbreviations: ACE = angiotensin-converting enzyme; β = beta coefficient; CI = confidence interval; SE = standard error; HR = hazard ratio; NYHA = New York Heart Association; NS = not significant.

Appropriate ICD interventions

During follow-up, 92 patients (22%) experienced at least 1 episode of a ventricular tachyarrhythmia triggering ICD intervention. ATP was observed in 68 patients (16%) and ICD shock in 55 patients (13%). The first appropriate device intervention occurred at a median interval of 6.8 months (IQR 1.7 – 15.1 months) after ICD implantation. The mean cycle length of ventricular arrhythmias triggering appropriate ICD intervention was 290 ± 55 ms. The proportion of patients free from ICD interventions was 85.4%, 78.8%, and 71.7%, at 1, 2, and 5 years of follow-up, respectively. No significant difference was observed in the occurrence of appropriate ICD interventions between CAD patients and DCM patients (23% vs. 21%, $P = 0.71$) (Figure 2A). Death or heart transplantation without prior appropriate ICD intervention was observed in 28 (64%) of the deceased/transplanted patients, whereas 36% of patients received appropriate device intervention prior to death or heart transplantation. Univariate analysis showed that appropriate ICD interventions occurred significantly more frequent in patients with AF compared with patients without AF (29% vs. 19%, $P = 0.023$) (Figure 2B).

Inappropriate ICD interventions

Forty-six patients (10.8%) experienced at least 1 inappropriately delivered ICD intervention, which occurred at a median interval of 7.3 months (IQR 1.3 – 14.6 months). The proportion of patients free from inappropriate ICD interventions was 92.0%, 88.9%, and 85.7%, at 1, 2, and 5 years of follow-up, respectively. A total of 23 patients (5.4%) received an inappropriate ICD shock. The proportion of patients free from inappropriate ICD shocks was 96.2%, 95.2%, and 92.2%, at 1, 2, and 5 years of follow-up, respectively. There was no significant difference in the occurrence of any inappropriate ICD intervention (ATP or shock) during follow-up between patients with CAD and DCM. No significant difference in any inappropriate ICD therapy was observed between patients with AF and those without AF. Univariate analysis identified no factors associated with the occurrence of inappropriate ICD interventions.

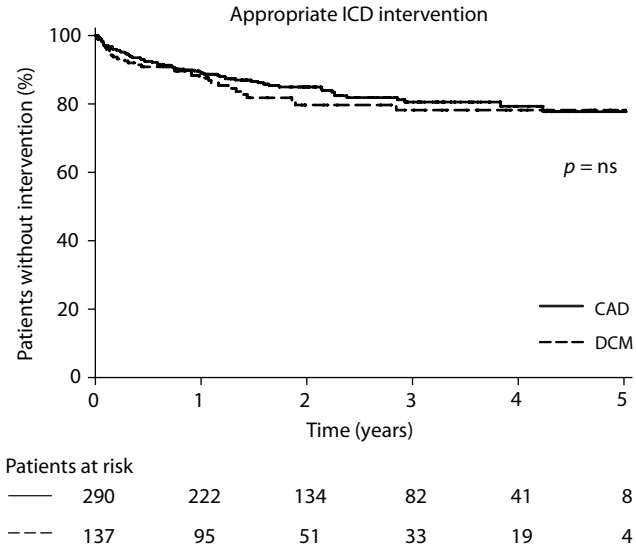

Figure 2A. Appropriate ICD interventions: coronary artery disease vs. dilated cardiomyopathy.
Chi-square 0.43, *P* = 0.5103

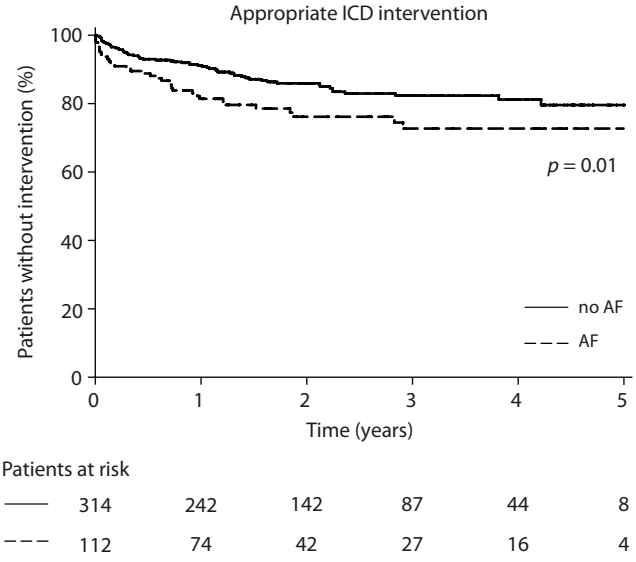

Figure 2B. Appropriate ICD interventions: atrial fibrillation vs. no atrial fibrillation.

Chi-square 6.30, *P* = 0.0121
Abbreviations: AF = atrial fibrillation; CAD = coronary artery disease; DCM = dilated cardiomyopathy; ICD = implantable cardioverter-defibrillator; NS = not significant.

DISCUSSION

The present study evaluated the mortality and occurrence of ICD interventions in two major disease categories for which primary prophylactic ICD's are used: left ventricular dysfunction due to CAD or DCM. All received the device according to the international guidelines in the recent era (2004 – 2009). The major findings of this study are as follows: 1) after primary prophylactic ICD implantation, mortality is the same in CAD and DCM patients despite the younger age of the latter; 2) the incidence of appropriate ICD intervention was similar in CAD and DCM patients; 3) higher age at time of ICD implantation and appropriate ICD interventions during follow-up are independent predictors of mortality; 4) AF is a predictor of appropriate ICD interventions; 5) inappropriate ICD interventions occur equally frequently in CAD patients and DCM patients.

Mortality

The observed all-cause mortality in this cohort study is low; the cumulative incidence of all-cause mortality at 5-years of follow-up was 15%, with a median follow-up of 31 months, whereas Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) reported a mortality of 16% at 2 years.[4] Mortality was also lower compared with the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), which also included CAD and DCM patients.[5] In SCD-HeFT, the cumulative 5-year mortality was 29% with a median follow-up of 46 months. The crude death rate in SCD-HeFT was 5.7 deaths per 100 person-years, compared with 2.8 deaths per 100 person-years in our study cohort. Long-term data of MADIT-II show a 52% cumulative mortality at 8 years of follow-up in patients with CAD.[15] Recent European registries had a comparable low mortality.[1,2] The observed low mortality in our study group can possibly be explained by the age of the patients, which was certainly lower than that of MADIT-II patients (mean 64 years) and the patients in the two cited registries (mean 63 and 66 years, respectively).[1,2,4] The low observed mortality cannot be explained by differences in pharmacological therapy, as these are small; beta-blockers were used by 82% of CAD patients (vs. 70% in MADIT-II), ACE inhibitors were used by 79% of CAD patients (vs. 68% in MADIT-II), and statins by 82% (vs. 67% in MADIT-II). This low mortality might indeed be a reason to reanalyze the value of ICD's for this indication, if it is assumed that disadvantages of ICD therapy became more important in recent times.

Appropriate ICD interventions

In the present study, appropriate ICD interventions were delivered in 22% of patients. This is comparable with the reported proportions of patients with appropriate ICD interventions in the primary prevention trials (range 7.8% - 31.4%).[3-5,16-19] No differences in the incidence of appropriate interventions between CAD and DCM patients were observed. These data show that in a "real-world" population of patients with prophylactic ICD implantation,

appropriate ICD intervention is delivered in the same proportion of patients as in the landmark randomized clinical trials. The occurrence of appropriate ICD interventions is predicted by high age and by AF, as was previously shown by our group, and several others in ICD patients in general.[20-22] This is not surprising, as AF can be a consequence of advancing heart failure, and as this can initiate ventricular arrhythmias in those who are prone for such events. The excess mortality in those receiving appropriate ICD interventions during follow-up was also observed in recent studies.[23] Whether this is due to progression of the disease remains unclear. Our data were not influenced by the addition of CRT, which has a moderate effect on mortality, but a substantial effect on morbidity, if given to the right patients.[10,24,25] The observed rate of appropriate ICD interventions in both disease categories can be regarded as an indication that the actual guidelines remain valid.

Inappropriate ICD interventions

Delivery of inappropriate interventions due to misclassification of atrial tachyarrhythmias as ventricular tachyarrhythmias is the most reported adverse event in ICD recipients.[2,14,26] Frequencies of inappropriate device interventions up to 21% were reported in the primary prevention trials.[18,27] The proportion of patients with any inappropriate ICD intervention (ATP or shock) is only 11% in our study, with a cumulative incidence of 14% at 5 years of follow-up. This probably is due to consequent programming.[14] Strategic programming can further reduce inappropriate device interventions.[28] The frequency of inappropriate delivered shocks can probably be further lowered, both by adaptations from software and hardware.[29,30]

Limitations

Because this is an observational study without control group, no statements about the benefit of ICD therapy can be made. We did include a significant number of DCM patients. This can be due to the fact that we serve as a tertiary referral center for heart transplantation, which would imply that several of these patients have a rather unfavorable prognosis. This can be the explanation that they have the same mortality, in spite of their younger age.

Conclusion

In conclusion, the present study shows that the mortality and the occurrence of appropriate and inappropriate ICD interventions in a "real-world" population are similar after primary prophylactic ICD-only implantation for both disease categories. Mortality is predicted by high age at time of ICD implantation and by symptoms in NYHA class III-IV. ICD interventions are predicted by the presence of AF. This suggests that DCM, even at a younger age, is a strong indication for prophylactic ICD therapy, as described in the current guidelines, but which is unfortunately not always appreciated in current practice. It has to be pointed out that these data excluded patients with a CRT-D indication.

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CHAPTER 4

HEALTHCARE UTILIZATION AFTER DEFIBRILLATOR IMPLANTATION FOR PRIMARY PREVENTION ACCORDING TO THE GUIDELINES IN TWO DUTCH ACADEMIC MEDICAL CENTRES

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ABSTRACT

Background: The benefit of implantable defibrillators (ICD's) for primary prevention remains debated. We analyzed the implications of prophylactic ICD implantation according to the guidelines in two tertiary hospitals, and made a healthcare utilization inventory.

Methods: The cohort consisted of all consecutive patients with coronary artery disease (CAD) or dilated cardiomyopathy (DCM) receiving a primary prophylactic ICD in a contemporary setting (2004 – 2008). Follow-up was obtained from hospital databases, and mortality checked at the civil registry. Additional data came from questionnaires sent to general practitioners.

Results: There were no demographic differences between the two centres; one had proportionally more CAD patients and more resynchronization therapy (CRT-D). The 587 patients were followed over a median of 28 months, and 50 (8.5%) patients died. Appropriate ICD intervention occurred in 123 patients (21%). There was a small difference in intervention-free survival between the two centres. The questionnaires revealed 338 hospital admissions in 52% of the responders. Device-related admissions happened on 68 occasions, in 49/276 responders. The most frequently reported ICD-related admission was due to shocks (20/49 patients); for other cardiac problems it was mainly heart failure (52/99). Additional outpatient visits occurred in 19%.

Conclusions: Over a median follow-up of two years, one fifth of prophylactic ICD patients receive appropriate interventions. A substantial group undergoes readmission and additional visits. The high number of admissions points to a very ill population. Overall mortality was 8.5%. The two centres employed a similar procedure with respect to patient selection. One centre used more CRT-D, and observed more appropriate ICD interventions.

INTRODUCTION

Implantable defibrillator (ICD) therapy is without doubt the most effective therapy available to prevent sudden cardiac death (SCD) in selected patient groups.[1-5] Convincing evidence of the effectiveness of primary prophylactic ICD therapy exists for coronary artery disease (CAD) and dilated cardiomyopathy (DCM).[6-10] Like most state-of-the-art therapeutic modalities, ICD therapy is costly.[11-17] With the current improvement in heart failure therapy, the recent increased number of device recalls, and the trend towards more lead failure, the debate about prophylactic ICD therapy has shifted from 'effectiveness' toward 'cost-effectiveness'.[18-22] Nevertheless, some authors remain convinced that a serious underutilization continues to exist in Europe.[23,24]

The costs of a therapy cannot be assessed without assessing its clinical benefit. In fact, only few modern therapies – mostly those that prevent costly events – are cost-effective. In contrary, ICD therapy prevents SCD, an event that costs little to nothing to treat, when an ICD is in place.[25] Cost-effectiveness analyses showed that a large part of the lifetime costs of a primary prophylactic ICD patient occur at the time of ICD implantation. However, it takes years to accrue the benefit of a primary prophylactic ICD since this effect is time-dependent. In this perspective, the healthcare costs that accumulate during these years (i.e. hospitalization costs, costs for unscheduled outpatient consultations) should also be taken into account when analyzing the cost-effectiveness, especially when considering that primary prevention ICD candidates are heart failure patients with a potential high need for specialized care. Unfortunately, no data on the burden of medical care are available in a real world setting for this kind of patients in the Netherlands.

The aim of this study was to analyze the frequency of hospitalization and unscheduled outpatient consultations in primary prophylactic ICD patients, as documented in the hospital records of two major university hospitals, supplemented with data obtained with a survey among general practitioners, who could provide data on otherwise unknown admissions in other institutions.

METHODS

Study population

The study population consisted of all consecutive patients with CAD or DCM, who received an ICD according to the European Society of Cardiology (ESC) / American Heart Association (AHA) / American College of Cardiology (ACC) 2006 guidelines for primary prophylaxis of sudden cardiac death in the Erasmus MC between January 2004 and July 2008, and of all similar consecutive patients in the Amsterdam University Medical Centre (AMC) in the year 2006. The presence of CAD had to be documented clinically by a history of a myocardial

infarction according to the definitions by ESC / AHA / ACC, if coronary artery bypass grafting (CABG) or a percutaneous coronary intervention (PCI) had been performed, or if significant coronary artery stenosis was documented with coronary angiography. Dilated cardiomyopathy was defined as a primary myocardial disease with dilatation without valvular or congenital etiology. Patients with channelopathies and specific diseases as arrythmogenic right ventricular cardiomyopathy or the Brugada syndrome were excluded. All ICD's were implanted by a transvenous technique in the cardiac catheterization laboratory, or if necessary by a cardiac surgeon (e.g. for placement of epicardial leads).

Data collection

Baseline characteristics included age, gender, underlying disease, presence of prior myocardial infarction, and left ventricular function at the time of ICD implantation. Follow-up started at the time of ICD implantation, with conventional ICD follow-up. All patients were followed at 3-month intervals and were advised to contact the outpatient clinic after a symptomatic event. At each follow-up visit, arrhythmic events with stored electrograms (EGM's) were retrieved from the device's memory. Two independent reviewers analyzed the stored electrograms to classify the arrhythmia and assess the appropriateness of device classification and therapy. In case of disagreement, a third reviewer was consulted to provide the final diagnosis.

The electronic hospital files and the electronic ICD database were reviewed to record and understand the impact of complications. Procedure-related complications were defined as occurring within 30 days after implantation.

In order to make a better healthcare utilization inventory, we sent questionnaires to the general practitioners of 464 of the included patients (all AMC and the first 355 Erasmus MC patients). This questionnaire examined the frequency and duration of hospital admissions for ICD-related problems, hospital admissions for non-ICD related cardiac problems, and hospital admissions for other conditions. We also asked for the number of additional outpatient visits. Regular outpatient control visits and admissions for elective ICD generator replacements because of battery depletion were not taken into account. Follow-up for vital status was obtained by consulting the civil registry. The duration of the hospitalization was only obtained from the AMC sample. Follow-up was completed until 31 December 2008.

Statistical analysis

Continuous variables are expressed as the mean ± SD, or as the median with the interquartile range (IQR) when not normally distributed. Categorical variables are expressed as frequency (percentage). Group differences were analyzed with Chi-square tests and independent sample T-tests where appropriate. The assumption of normality was checked for all variables tested. If not normally distributed, we used non-parametric tests. Alpha was set at 0.05 for all statistical tests. Cumulative survival and event-free rates of appropriate ICD therapy were

calculated according to the Kaplan-Meier method and were compared with the log-rank test. Patients who underwent heart transplantation were censored alive from the moment of transplantation.

RESULTS

Study population

The study population consisted of a total group of 587 patients: 478 patients originated from the Erasmus MC Rotterdam, 109 patients from the AMC Amsterdam. The baseline characteristics of the study population are presented in Table 1. The median follow-up till death or the closure date was 28 months (IQR 14 – 37 months). The follow-up of the Erasmus MC patients was shorter (Table 2). There were slightly more patients with CAD in the group from the Erasmus MC. The mean ejection fraction was the same. Five percent of patients were in New York Heart Association (NYHA) class I, 51% in NYHA class II, 44% in class III, and only 1% in class IV. Heart transplantation was performed in 17 patients of a total of 41 patients who were on the transplantation list of the Erasmus MC. There were significant differences in the device type used in the two centres, with the Erasmus MC using more cardiac resynchronization therapy systems with defibrillation (CRT-D).

Table 1. Baseline characteristics.

Characteristic	Erasmus MC (n = 478)	AMC (n = 109)	*P*-value
Follow-up (days)	762 ± 446	969 ± 185	<0.0001
Age (years)	59 ± 12	61 ± 12	NS
Male gender (n, %)	374 (78%)	84 (77%)	NS
Etiology of LV dysfunction			
CAD (n, %)	319 (67%)	61 (54%)	0.023
DCM (n, %)	159 (33%)	45 (41%)	
LVEF (%)	25 ± 8	22 ± 6	NS
ICD type			
Single chamber	200 (42%)	65 (61%)	<0.001
Dual chamber	74 (15%)	38 (35%)	
CRT-D	204 (43%)	4 (4%)	

Abbreviations: CAD = coronary artery disease; CRT-D = cardiac resynchronization therapy with defibrillation; DCM = dilated cardiomyopathy; LVEF = left ventricular ejection fraction; NS = not significant.

Mortality

During the reported follow-up, 50 patients (8.5%) died (Table 2), at a median time since implantation of 359 days (IQR 159 – 759 days). The survival curves for Erasmus MC patients and AMC patients are depicted in Figure 1. No significant difference in mortality was observed between Erasmus MC patients and AMC patients (log rank = 0.573; *P*-value = NS).

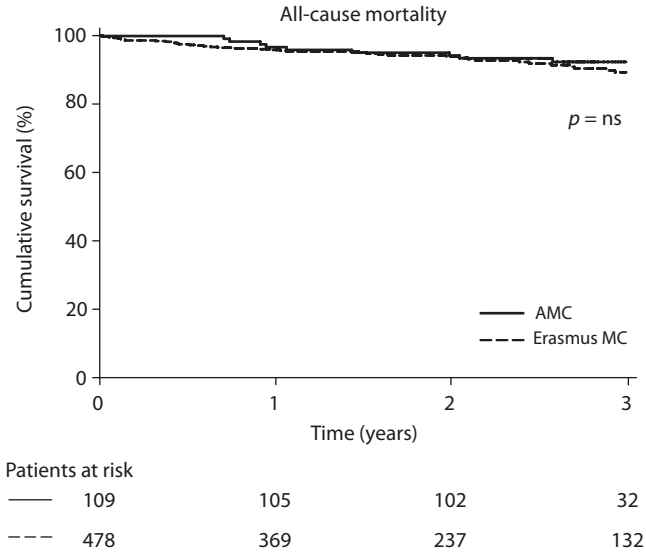

Figure 1. All-cause mortality, Erasmus MC vs. AMC.
Abbreviations: NS = not significant.

Table 2. Follow-up data from hospital records.

Characteristic	Erasmus MC (n=478)	AMC (n=109)	*P*-value
Follow-up (days)	762 ± 446	969 ± 185	<0.0001
Appropriate ICD intervention (n, %)	105 (22%)	18 (17%)	NS
Interval to first appropriate event (days)	313 ± 315	414 ± 271	NS
Late complications (n, %)*	38 (8%)	9 (8%)	NS
Mortality (n, %)	41 (9%)	9 (8%)	NS

* number of patients experiencing ≥1 late complication(s).
Abbreviations: ICD = implantable cardioverter-defibrillator; NS = not significant.

ICD interventions

During follow-up, 123 patients (21%) experienced at least one episode of ventricular tachyarrhythmia triggering appropriate ICD intervention, including 16/50 of the deceased patients (32%), and 9/41 patients (22%) who were on the heart transplantation list. The median interval to the first appropriate ICD intervention was 251 days (IQR 65 – 507 days). Differences in this parameter between the 2 institutions were not significant. Figure 2 shows the Kaplan-Meier curves for appropriate ICD interventions for patients originating from both centres. Nevertheless, the cumulative incidence of appropriate ICD interventions was significantly higher in Erasmus MC patients compared with AMC patients (log rank = 4.340; *P*-value = 0.037).

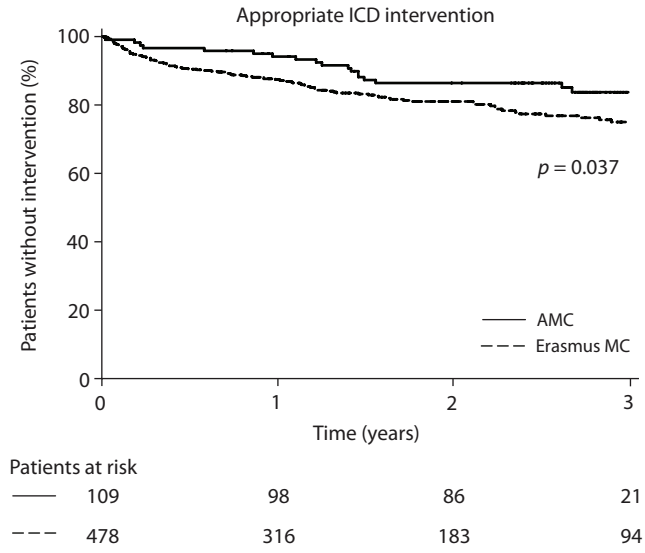

Figure 2. Appropriate ICD interventions, Erasmus MC vs. AMC.

Re-admissions for lead and ICD problems

As obtained from the patient records, there were 54 late complications in 47 patients (8%), similar for both hospitals. This included 8 lead repositions, 12 lead replacements of which 3 were because of a recall (Sprint Fidelis). A total number of 27 ICD replacements occurred, including 15 replacements within 36 months and 3 pocket infections. There were no recalls for pulse generators in this time frame in both institutions.

Hospitalization and unscheduled outpatient consultations

A questionnaire was sent to 464 patients. A completed questionnaire was received from 276 patients, making the response rate 59%. A total number of 338 hospital admissions were reported, occurring in 144 patients (52% of the responders, and 31% of the group to whom a questionnaire was sent). In total, 79/144 patients were admitted twice; of these, 44 a third time, and 27 at least four times. The median interval between ICD implantation and first hospitalization was 407 days (IQR 132 – 800 days). The cumulative incidence of first hospitalization after ICD implantation is depicted in Figure 3. No significant difference is observed between the centres.

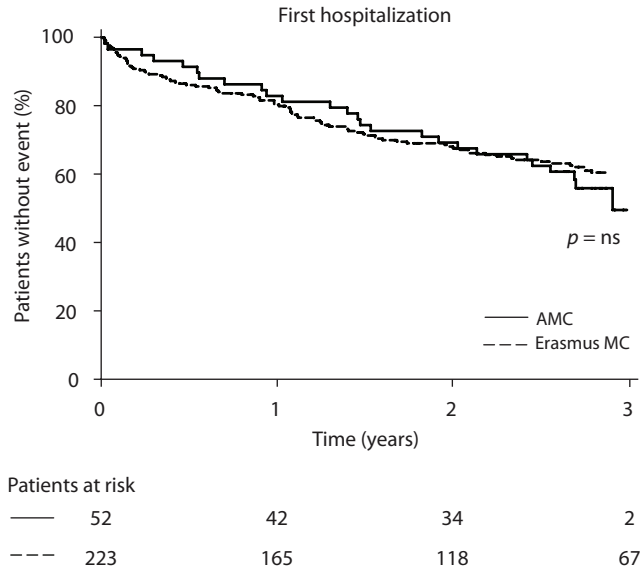

Figure 3. Interval to first hospital readmission, Erasmus MC vs. AMC.
Abbreviations: NS = not significant.

Analysis of the questionnaires is presented in Table 3. The median duration of hospitalization was 2.5 days (IQR 1 – 12 days). From the 338 reported hospital admissions, 68 (20%) were ICD related; 180 (53%) were for other cardiac reasons, and 90 (27%) were for non-cardiac pathology. Figure 4 shows the distribution of the reasons per admission category. Of 49 patients with an ICD-related admission, 20 were admitted because of a shock (41%); of 99 patients with other cardiac admissions, heart failure or associated conditions were the reason in 52 occasions (53%). The largest non-cardiac cause for hospital admission was related to internal medicine (25/58 patients). Additional unscheduled cardiac outpatient consultations were observed in 51 (19%) of patients (Table 3).

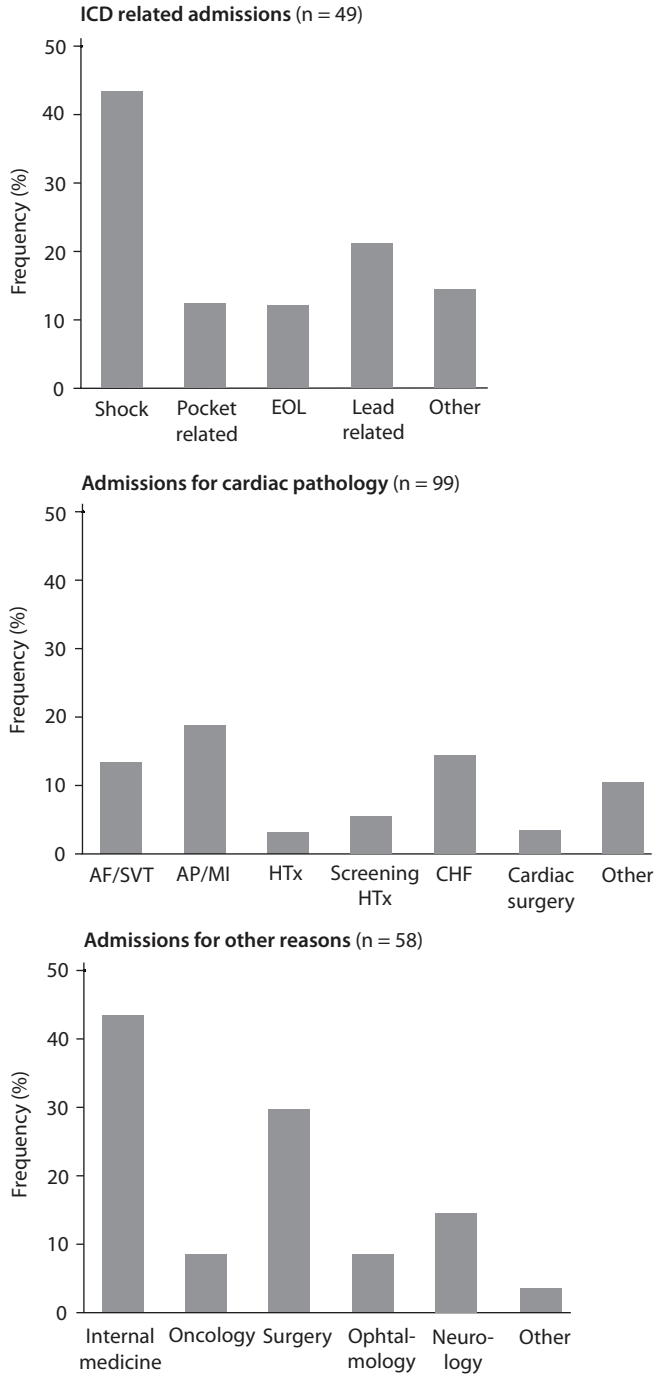

Figure 4. Reason for readmissions and unscheduled outpatient visits.

Abbreviations: AF = atrial fibrillation; AP = angina pectoris; CHF = congestive heart failure; EOL: end-of-life, HTx = heart transplantation; MI = myocardial infarction; SVT = supraventricular tachycardia.

Table 3. Hospitalization (≥1) and unscheduled outpatient consultations per patient as obtained from the questionnaires.

Characteristic	All (n = 276)	Erasmus MC (n = 224/355)	AMC (n = 52/109)	*P*-value
ICD-related admission	49 (18%)	40 (18%)	9 (17%)	NS
Cardiac admission	99 (36%)	78 (35%)	21 (40%)	NS
Other admission	58 (21%)	48 (21%)	10 (19%)	NS
Additional outpatient cardiac visit	51 (19%)	38 (17%)	13 (25%)	NS

Abbreviations: ICD = implantable cardioverter-defibrillator, NS = not significant.

DISCUSSION

This study of patients in two different Dutch university hospitals shows that in spite of an apparent different attitude, but with formal adherence to the actual guidelines, the outcome of the patients was completely comparable with respect to a hard endpoint as mortality, and to a softer endpoint as hospitalization.[26] Nevertheless, we have seen differences in the underlying cardiac disease of the patients (the prevalence of coronary artery disease was higher in Rotterdam), and in the type of implanted defibrillation systems (higher number of CRT-D; also in Rotterdam). The only different outcome between the two centers was the occurrence of appropriate ICD therapy, which cannot be explained at first glance.

Mortality

The mortality is less than 10% in both centres, even with a median follow-up of more than 2 years. These data correspond with recent real world data.[27,28] The landmark trials (the Multicenter Automatic Defibrillator Implantation Trial (MADIT), MADIT II, and the Sudden Cardiac Death in Heart Failure Trial) all had a mortality rate in the active arm of 14%, 22%, and 18%, respectively, at 3 years.[1-3] This implicates that today, the practice in the Netherlands can still be compared with the trials as they were published. The outcome of the heart transplantation patients, a typically censored group, was not different in this respect from the others.

Appropriate ICD interventions (shocks / anti-tachycardia pacing)

In both centres, approximately one fifth of the patients received appropriate ICD interventions, over a median follow-up of more than two years. This intervention rate is high, and supports the idea that the right patients were selected. This patient selection was in line with the actual guidelines and was more or less conservative, meaning that early post infarct patients were avoided, in line with recent studies.[29,30] It is striking that one centre had

a higher rate of device therapy than the other, which might be attributed to the presence of patients with advanced heart failure (as might be suggested by the higher proportion of CRT-D) or simply to different programming strategies. The latter is a very likely explanation. Although, there was no obvious difference in the standard programming of rate cut-offs for arrhythmia detection. On the other hand, differences in time to intervention, and the use of ATP may certainly influence the rate of interventions.[31] It is reassuring to observe that this higher intervention rate is not associated with a different mortality or real morbidity. Further, in both centres, the rate of inappropriate interventions was low as is reported elsewhere.[32]

Morbidity

The readmission rate was very high, and the questionnaire did not really yield a different outcome in respect to what was known from the hospital files e.g. for lead reintervention. This supports the idea that the questionnaire was reliable as well as the observation that these patients were very ill, with a high readmission rate, also for non-cardiac causes. This might be an indication that more attention should be given to comorbidity in general, before implantation.[33-35] It is known that diabetes, renal failure and high age contribute to the morbidity after implantation. Further, not all cardiac admissions occurred because of device therapy. Only a minority of admissions was reported to occur because of shock therapy. The most important reason for admission remains heart failure, which confirms previous findings.[38,39]

Limitations

It might be that our method (i.e. the survey) resulted in over-reporting, as general practitioners might have responded more frequently if they had encountered problematic patients. However, it was the only way to understand what was happening with the patients at home and in the referral centre. Further, the rate of specific complications as reported coincided with the rate as known from the hospital records.

Conclusions

The two centres behaved in a similar way with respect to patient selection. Mortality and readmission were the same during follow-up. However, one centre more often used CRT, and observed a higher ICD therapy rate for ventricular arrhythmias.

Further, the high readmission rate, mainly for heart failure, is a reason to organize a good follow-up for these patients. It is clear that the referring cardiologist still has a role after implantation. This role could even increase when it is accepted that ICD control is performed in those centres. On the other hand, the high early complication rate demands a tight control to improve the quality at the time of implantation. One important measure could be to maintain a limited number of experienced implanting centres.[36,37] It is clear that patient selection, according to the actual guidelines, results in a reproducible outcome, even in different centres.

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CHAPTER 5

THE COST-EFFECTIVENESS OF PRIMARY PROPHYLACTIC IMPLANTABLE DEFIBRILLATOR THERAPY IN PATIENTS WITH ISCHEMIC OR NON-ISCHEMIC HEART DISEASE: A EUROPEAN ANALYSIS

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ABSTRACT

Aims: It remains unclear whether primary prophylactic ICD therapy is cost-effective compared with a 'no ICD strategy' in the European healthcare setting. We performed a cost-effectiveness analysis for a cohort of patients with a left ventricular ejection fraction <40% and ischemic or non-ischemic heart disease.

Methods and Results: A Markov decision analytic model was used to evaluate long-term survival, quality-adjusted life years (QALY's), and lifetime costs for a cohort of patients with a reduced left ventricular function without previous arrhythmias, managed with a prophylactic ICD. Input data on effectiveness was derived from a meta-analysis of primary prophylactic ICD-only therapy randomized trials, from a prospective cohort study of ICD patients, from a healthcare utilization survey, and from the literature. Input data on costs was derived from a micro-cost analysis. Data on quality-of-life was derived from the literature. Deterministic and probabilistic sensitivity analysis was performed to assess the uncertainty. Probabilistic sensitivity analysis demonstrated a mean lifetime cost of €50685 ± €4604 and 6.26 ± 0.64 QALY's for patients in the 'no ICD strategy'. Patients in the 'ICD strategy' accumulated €86759 ± €3343 and an effectiveness of 7.08 ± 0.71 QALY's yielding an incremental cost-effectiveness ratio (ICER) of €43993/QALY gained compared with the 'no ICD strategy'. The probability that ICD therapy is cost-effective was 65% at a willingness-to-pay threshold of €80000/QALY.

Conclusion: Our results suggest that primary prophylactic ICD therapy in patients with a left ventricular ejection fraction <40% and ischemic or non-ischemic heart disease is cost-effective in the European setting.

INTRODUCTION

The implantable cardioverter-defibrillator (ICD) has become a proven and well-accepted therapy for both the primary and the secondary prevention of sudden cardiac death (SCD) in patients with ischemic or non-ischemic heart disease.[1-5] The European guidelines state that primary prophylactic ICD's are indicated in patients with severe left ventricular dysfunction with a reasonable life expectancy, who have symptoms in New York Heart Association (NYHA) class I, II, or III.[6] This was confirmed by the European Task Force on Heart Failure.[7]

Implantable defibrillator therapy is expensive, with high upfront costs.[1] Complications of ICD therapy are not to be neglected, and frequent.[8] The cost-effectiveness of primary prophylactic ICD therapy was thoroughly evaluated in the American population, both in within-trial evaluations and in lifetime extrapolations.[9-11] The costs and benefits of this therapy in the European healthcare system however, remain less clear. A recent industry-driven analysis using Belgian input data showed an economically attractive result.[12] Remarkably, a similar analysis using contemporary source data from the same country resulted in a different conclusion.[13]

From a healthcare point of view, an intervention is considered cost-effective when its additional benefit is deemed worth its additional costs; cost-effectiveness analysis assesses the 'value-for-money' of an intervention. Cost-effectiveness analyses are sometimes performed alongside a clinical trial. This design has the advantage that data on the effectiveness of the intervention and data on used resources are readily available and have high internal validity. Disadvantages consist mainly of a low generalizability to the 'real world' population (i.e. low external validity), a lack of long-term follow-up data, and unreliable estimates of rare events. An alternative design for cost-effectiveness analyses is the use of a decision model combining the best-available evidence from various sources. For example, a decision model can combine effectiveness data derived from a meta-analysis, data on costs from separate cost-analyses, data on the frequency of rare adverse events from observational studies, and data on long-term follow-up from registries.

The purpose of this study was to determine the cost-effectiveness of primary prophylactic ICD therapy in patients with ischemic or non-ischemic heart disease with a left ventricular ejection fraction (LVEF) ≤40% without previous arrhythmias, as it is currently being performed according to the European guidelines, using a decision modeling approach combining the best-available evidence from various sources.

METHODS

Decision model

We developed a Markov decision analytic model to evaluate the cost-effectiveness of primary prophylactic ICD therapy compared with a 'no ICD strategy' in The Netherlands (implying that patients only received an ICD as secondary preventive therapy). The structure of the model is presented in Figure 1.

A decision model is a mathematical method to weigh risks, benefits, patient preferences and costs of clinical strategies. A decision tree models the immediate consequences of clinical strategies, and a Markov model represents the subsequent follow-up. In a Markov model patients are simulated as they transition between various health states over the course of their remaining lifetime. The analysis of a Markov model provides estimates of the cumulative duration spent in each health state, which is adjusted for the quality-of-life (QOL) in that state, and which is used to estimate the cumulative follow-up costs.

Model structure

In the 'ICD strategy' of the model, all patients received an ICD (Figure 1, 'ICD implantation'). Patients could die perioperatively within the first 30 days. If patients survived, they were at risk of dying, or of developing non-fatal events. Non-fatal events included hospital admissions, ventricular arrhythmias, and adverse events such as inappropriate ICD shocks. Patients could experience a complication, defined as an adverse event requiring an intervention leading to de-implantation of the device and re-implantation of a new ICD (Figure 1, 'De-implantation'), or leading to 'Revision'. Patients subsequently moved to the 'Post-implantation' state. During follow-up in the 'Post-implantation' state, patients are at risk of dying, developing non-fatal events, and experiencing complications. We used tunnel states to model elective generator replacements. Device longevity was calculated according to the mean survival of devices used in the time frame under observation, derived from literature and from a cohort of ICD patients from the Erasmus MC.[14] After the projected lifetime of the initial ICD, patients went to the 'ICD replacement' state of the model and received a new generator. The 'ICD replacement' state is identical in structure to the 'ICD implantation' state, but was modeled with different probabilities, costs, and (dis)utilities.

In the 'No ICD strategy' of the model, all patients were at risk of dying, could experience successfully resuscitated cardiac arrest leading to ICD implantation in a fraction of these patients, and could encounter non-fatal adverse events. All-cause mortality was modeled by multiplying the inverse of the hazard rate ratio (HRR) for all-cause mortality, derived from a meta-analysis of randomized clinical trials comparing primary preventive ICD-only therapy with conservative therapy, by the all-cause mortality rate of ICD patients.[5]

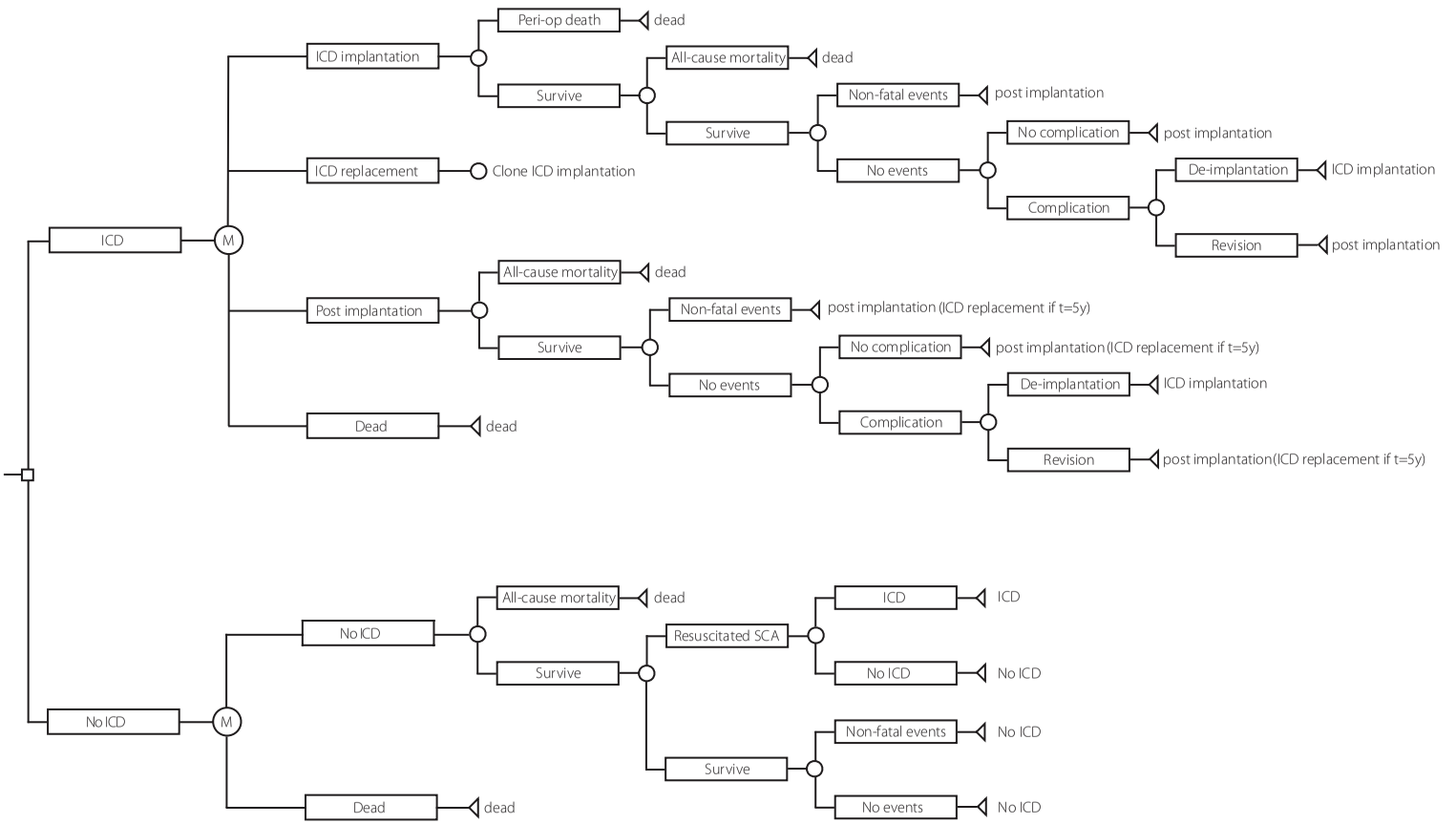

Figure 1. Model structure.

The decision tree shows decision nodes as squares (□), chance nodes as circles (O) and Markov nodes (M).

Patients included in the decision analysis

According to the current guidelines of the Dutch Cardiac Society, which are based on the 2006 international guidelines, patients with left ventricular dysfunction due to coronary artery disease (CAD) or non-ischemic dilated cardiomyopathy (DCM) were considered eligible for ICD implantation.[6] Patients qualified if they had a left ventricular ejection fraction <40%. Patients were considered to suffer from CAD if a myocardial infarction occurred, if coronary-artery bypass surgery or a percutaneous coronary intervention was performed, or if significant coronary artery stenosis was documented with conventional coronary angiography.

Data sources and assumptions

We used both data from the Erasmus MC ICD registry and data from the literature to estimate the variable values (Table 1). All variables were estimated with corresponding distributions. A meta-analysis of randomized controlled trials (RCT's) performed in Europe and the USA on the effectiveness of primary prophylactic ICD-only therapy in reducing all-cause mortality was used to derive estimates on effectiveness.[5] This meta-analysis included the first and second 'Multicenter Automatic Defibrillator Implantation Trial' (MADIT-I and MADIT-II), the 'Sudden Cardiac Death in Heart Failure Trial' (SCD-HeFT), the Cardiomyopathy Trial (CAT), the Amiodarone versus Implantable Cardioverter-Defibrillator Randomized Trial (AMIOVIRT), and the Defibrillator in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE). We assumed that the effectiveness of ICD therapy in reducing all-cause mortality in the RCT's was representative of the Western European setting. Mortality rates for ICD patients were based on the follow-up data of the Erasmus MC ICD registry and on recent literature.[15-17] The Erasmus MC ICD registry comprises a prospectively collected cohort of ICD patients who received an ICD according to the international guidelines, and are also treated pharmacologically according to the guidelines. Based on these data, a survival function was constructed using regression techniques, which was in line with available recent literature on survival of heart failure patients and post-myocardial infarction survival (Figure 2).[18,19]

The meta-analysis of RCT's was used to derive estimates on the incidence of mortality of patients in the 'No ICD strategy'. All-cause mortality of patients in the 'No ICD strategy' was calculated by multiplying the inverse of the hazard rate ratio (HRR) for all-cause mortality with an ICD vs. no ICD (derived from the meta-analysis) by the absolute all-cause mortality rate among patients with an ICD (derived from the Erasmus MC ICD registry). Costs were estimated for ICD implantation, routine follow-up, and for events occurring during follow-up by a micro-costing analysis according to the bottom-up approach.[20] Estimates on the frequency of events during follow-up were derived from the current literature. Additional information on frequency of events was derived from a survey among general practitioners.[21,22] These data were translated into a cost estimate, reported in Euro's for the year 2010. The price of the ICD was estimated by using the weighted average (for the

proportion of used device types) of ICD retail prices of three academic medical centers in The Netherlands for the year 2010. All costs calculated before 2010 were adjusted for inflation by using the standard consumer price index.[23] Quality-of-life estimates were derived from the literature.[9]

Table 1. Model parameters.

Model input	ICD strategy	No ICD strategy	Reference
All-cause mortality	Figure 2	Figure 2	15
HRR all cause mortality	0.72	1 / 0.72	5
Operative mortality	0.006	N/a	15,40
Operative mortality replacement	0	N/a	15,40
Non fatal events	0.60 / 5 year	0.53 / year	15,21
Complication related to implantation	0.047	N/a	15,40
Complication related to replacement	0.032	N/a	15,40
Fraction of complications leading to de-implant/ re-implant in implantation cycle	0.06	N/a	15,40
Fraction of complications leading to ICD revision in implantation cycle	0.94	N/a	14,15,40
Complication in the post-implantation cycle	0.125 / 5 years	N/a	15
Fraction of complications leading to de-implant/ re-implant post implantation	0.21	N/a	14,15,40
Fraction of complications leading to ICD revision post implantation	0.79	N/a	14,15,40
Frequency of generator replacement	Every 60 months	N/a	14,15
Resuscitated cardiac arrest	N/a	0.011 / 2.08 year	18
Fraction of resuscitated cardiac arrest patients receiving ICD	N/a	0.55	Assumption
Costs of ICD implantation (€)	30623	N/a	14, microcost analysis
Costs of patient follow-up (€/yr)	1224	720	14, microcost analysis
Costs of non-fatal event (€)	1532	9708	14, 15, microcost analysis
Costs of complication leading to de-implant/ re-implant	27308	N/a	14, microcost analysis
Costs of complication leading to ICD revision	1747	N/a	14, microcost analysis
Costs of generator replacement	25776	N/a	14, microcost analysis
Costs of admission after resuscitated cardiac arrest	N/a	12676	15
Quality of life (QALY)	0.88	0.88	9

Table 1. *Continued*

Model input	ICD strategy	No ICD strategy	Reference
Disutility of ICD implantation	3 days 0.5 QALY	N/a	22, Assumption
Disutility of non-fatal event	10 days 0.5 QALY	10 days 0.5 QALY	22, Assumption
Disutility of ICD revision	20 days 0.5 QALY	N/a	22, Assumption
Disutility of de-implant/re-implant following primary implantation	3 days 0.5 QALY	N/a	22, Assumption
Disutility of late de-implant/re-implant following primary implantation	21 days 0.5 QALY	N/a	22, Assumption
Discount rate costs	4% per annum	4% per annum	24
Discount rate utilities	1.5% per annum	1.5% per annum	24

Abbreviations: ICD = implantable cardioverter-defibrillator; QALY = quality-adjusted life-year; N/a = not applicable.

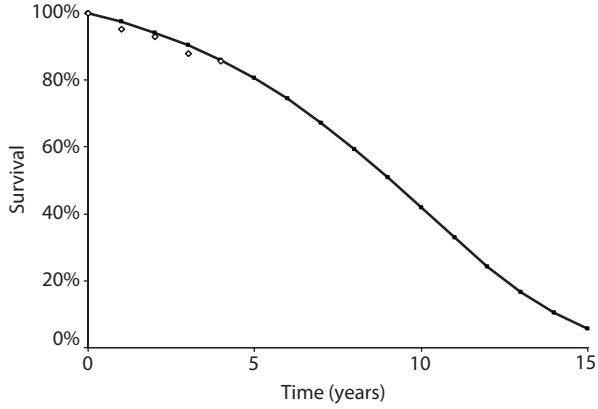

Figure 2. Survival function used in the model.

The short-term survival (until 5 years) was based on the Erasmus MC ICD registry (open diamonds), the long-term follow-up was based on literature (black dots).

Data analysis

The decision was analyzed from the societal perspective. Model-based calculations were made using a cycle length of one month. We modeled a lifetime horizon. A willingness-to-pay (WTP) threshold of €80000/QALY was used, as recommended by the Dutch Council for Public Health.[24] If the incremental cost-effectiveness ratio (ICER) (i.e. difference in costs divided by the difference in effectiveness of strategy A, compared with strategy B) is lower than the WTP threshold, we conclude that strategy A is a cost-effective alternative compared with strategy B. In deterministic one- and two-way sensitivity analysis we assessed the

effect of varying each parameter across its distribution. The Net Health Benefit (NHB) can be interpreted as the net benefit of investing in a certain strategy compared with the minimal net benefit that society would want in return for this investment. Mathematically, this can be expressed as NHB= E – (C / WTP), where NHB is the Net Health Benefit of a certain strategy, E is the effect of the strategy (QALY's associated with the strategy), C the lifetime costs of the strategy and WTP the societal willingness-to-pay threshold level. The strategy with the highest NHB can be considered as the most favourable strategy.

Probabilistic sensitivity analysis was performed using the outcome distributions of 100000 Monte Carlo simulations.[25,26] We calculated the probability that the 'ICD strategy' was cost-effective compared with the 'no ICD strategy' for varying willingness-to-pay thresholds, which yielded an acceptability curve. To quantify the value of obtaining more information through future research, we estimated the expected value of perfect information (EVPI) per individual.[27]

RESULTS

Reference-case analysis

The reference-case analysis showed that ICD therapy was associated with a lifetime cost of €86759 and an effectiveness of 7.08 QALY's. Patients in the control strategy accumulated a lifetime cost of €50685 and 6.26 QALY's. The ICER was €43993/QALY gained.

Deterministic sensitivity analysis

The model was sensitive to variations in the effectiveness of the primary prophylactic ICD therapy, the price of the ICD, the longevity of the ICD, the quality-of-life of patients in the 'ICD strategy' and in the 'no ICD strategy', and the follow-up costs of patients in the 'ICD strategy'. One-way sensitivity analysis demonstrated that the ICER remains under the WTP ratio of €80000/QALY gained under the reference-case assumptions, if:

- The hazard rate ratio (HRR) for ICD therapy in reducing all-cause mortality, compared with the 'no ICD strategy' is ≤ 0.85 (Figure 3);
- The price of the ICD is ≤ 160% of the reference-case price (Figure 4);
- The longevity of the ICD is ≥ 3 years;
- The quality-of-life of ICD patients is ≥ 0.83 QALY's;
- The quality-of-life of patients in the 'no ICD strategy' is ≤ 0.90 QALY's;
- The follow-up costs of patients in the 'ICD strategy' remain lower than 4.5 times the cost assumed in the reference-case.

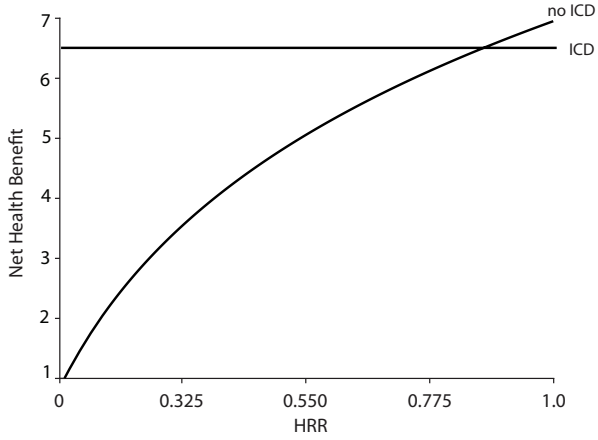

Figure 3A. Deterministic sensitivity analysis: one-way sensitivity analysis on the effectiveness of ICD therapy.

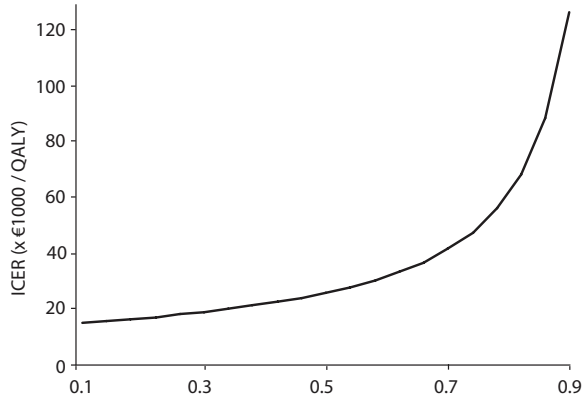

Figure 3B. One-way sensitivity analysis on the effectiveness of ICD therapy: ICER as a function of the HRR of primary ICD therapy compared with the 'no ICD' strategy'.

Net health benefit (NHB) as a function of the hazard rate ratio (HRR) of primary prophylactic ICD therapy compared with the 'no ICD' strategy. The NHB can be interpreted as the net benefit of investing in a certain strategy compared with the minimal net benefit that society would want to return for this investment. Mathematically, this can be expressed as NHB = E – (C / WTP), where NHB is the Net Health Benefit of a certain strategy, E is the effect of the strategy (QALY's associated with the strategy), C the lifetime costs of the strategy, and WTP the societal willingness-to-pay threshold level. The strategy with the highest NHB can be considered as the most favorable strategy.

Abbreviations: ICD = implantable cardioverter-defibrillator; ICER = incremental cost-effectiveness ratio; HRR = hazard rate ratio; QALY = quality-adjusted life-year.

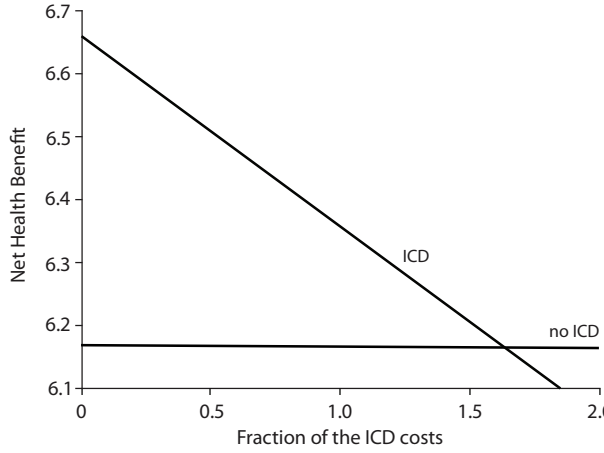

Figure 4A. Deterministic sensitivity analysis: one-way sensitivity analysis on the cost of the ICD device.
Abbreviations: ICD = implantable cardioverter-defibrillator.

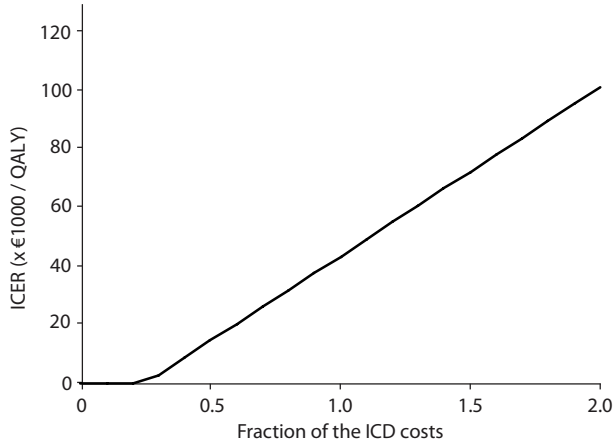

Figure 4B. One-way sensitivity analysis on the cost of the ICD device: ICER as a function of the fraction of the price of the device (where 1 represents the reference-case input variable).

Net health benefit (NHB) as a function of the fraction of the price of the device (where 1 represents the reference-case input variable). See legend of figure 3 for explanation of NHB.
Abbreviations: ICD = implantable cardioverter-defibrillator; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

The effect of variation of both the price of the ICD and the effectiveness of primary prophylactic ICD therapy is illustrated in Figure 5. This graph shows that the 'ICD strategy' becomes more attractive when the effectiveness of primary prophylactic ICD therapy is high, and when its price is low.

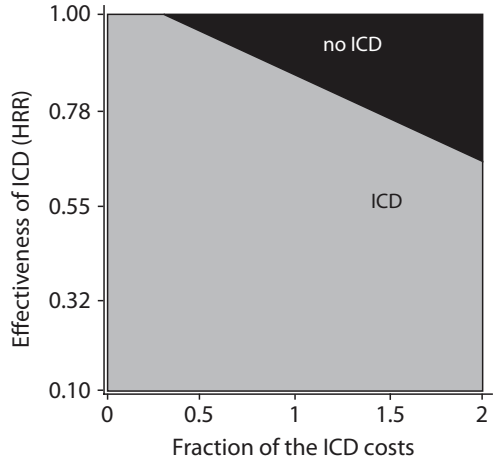

Figure 5. Two-way deterministic sensitivity analysis.

Two-way sensitivity analysis of the cost of the ICD and the effectiveness of primary prophylactic ICD therapy (expressed as the hazard rate ratio (HRR) of ICD therapy compared with optimal medical therapy). At high values of the fraction of the price of the ICD (i.e. expensive ICD's) and at values of the HRR closer to 1 (i.e. low effectiveness of ICD therapy in reducing all-cause mortality), the 'no ICD strategy' yields the highest effectiveness and lowest costs.
Abbreviations: HRR = hazard rate ratio; ICD = implantable cardioverter-defibrillator.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis, using a Monte Carlo simulation of 100000 samples, estimated that the 'ICD strategy' was associated with a lifetime cost of €86759 ± €3343 and an effectiveness of 7.08 ± 0.71 QALY's. Patients in the 'no ICD strategy' accumulated €50685 ± €4604 and 6.26 ± 0.64 QALY's, yielding an incremental cost-effectiveness ratio (ICER) of €43993/QALY gained. Using a willingness-to-pay threshold of €80000/QALY, the 'ICD strategy' was cost-effective compared with the 'no ICD strategy' in 65% of simulations (Figure 6). The expected value of perfect information (EVPI) was estimated at €18175 per patient.

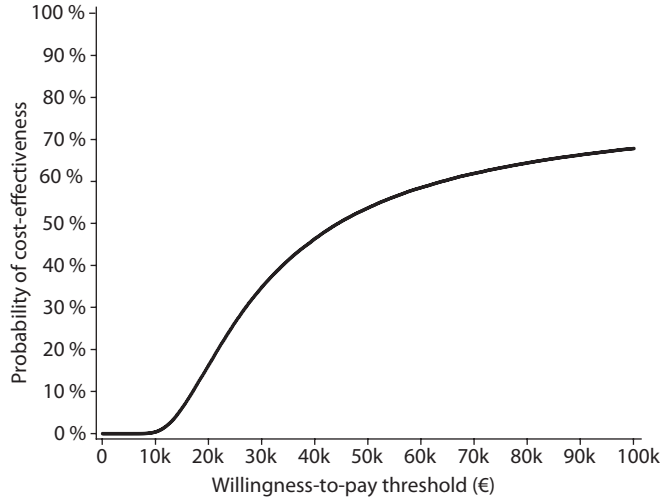

Figure 6. Probabilistic sensitivity analysis: acceptability curve for 'ICD strategy'.

The acceptability curve plots the probability that a certain strategy is cost-effective given a particular WTP threshold level. We ran 100000 Monte Carlo probabilistic simulations that used random draws from distributions that represent uncertainty around parameter estimates. We used a WTP threshold level of €80000/QALY. In 65% of simulations, the 'ICD strategy' was cost-effective compared with the 'no ICD strategy', which corresponds with a 65% probability of cost-effectiveness.

DISCUSSION

The present study addresses the cost-effectiveness of primary prophylactic ICD therapy in patients with ischemic or non-ischemic heart disease in a European country. The major finding of this study is that primary prophylactic ICD-only therapy, applied according to the European guidelines, is cost-effective under the reference case assumptions. Probabilistic sensitivity analysis showed that the probability of cost-effectiveness is 65% at a WTP threshold of €80000/QALY gained, which is a fairly high threshold but nevertheless an accepted threshold in several Western European countries.

Cost-effectiveness of primary prophylactic ICD therapy in the USA

The cost-effectiveness of primary prophylactic ICD therapy was evaluated in the milestone randomized clinical trials on primary prophylactic ICD therapy.[10,11] The ICER's calculated from these studies range from €30300 to €348000 per QALY gained, considering the duration of the trial as time horizon. Model based studies showed a wide spread of ICER's ranging from $34900/QALY gained for the second Multicenter Automatic Defibrillator Implantation Trial (MADIT II), to $70200/QALY gained for the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) when a lifetime horizon was applied.[9] In spite of the differences between the USA and Europe in costs of procedures and follow-up, the findings from the latter study (taking the dollar-to-euro exchange rate of 2010 (0.755) into account) are in line with our results.

Cost-effectiveness of primary prophylactic ICD therapy in Europe

Published data on the cost-effectiveness of primary prophylactic ICD therapy in Europe is scarce. A recent cost-effectiveness analysis of primary prophylactic ICD therapy in Belgium, with contributors of the device industry, reported an ICER of €31717/QALY gained, projected over a lifetime horizon.[12] Remarkably, the Belgian Healthcare Knowledge Center (KCE) performed an evaluation of the cost-effectiveness of primary prevention ICD therapy in Belgium in the same era, and presented an ICER of €71428/QALY gained over a lifetime horizon.[13] This difference may be explained by several factors as unrepresentative costs of ICD therapy, the optimistic device longevity, and different long-term survival extrapolations.[28,29]

Current analysis in the context of prior studies

The present study shows an ICER of €43993/QALY gained, with a probability of cost-effectiveness of 65%. These results suggest that primary prophylactic ICD therapy in patients with ischemic or non-ischemic heart disease and a LVEF <40% is cost-effective in Europe. In order to reflect the current clinical practice in Europe, we used evidence from all RCT's that did not incorporate function-improving therapy (e.g. cardiac resynchronization therapy, or coronary revascularization procedures) in their design.[5] This may have caused an underestimate of the effectiveness of ICD therapy, and prevents the additive effect of the concomitant function-improving therapies being counted towards the effect of the ICD therapy.[30-32] Neyt et al. used data from the SCD-HeFT trial as the only source for effectiveness, which does not reflect the current evidence that led to the guidelines on the indication of primary prophylactic ICD's.[13] Furthermore, recent real-world European data on the incidence of mortality, ICD interventions, and hospitalizations were incorporated in our model in order to represent the current clinical situation more accurately.

Results from sensitivity analysis

Deterministic sensitivity analysis showed that the effectiveness of ICD therapy in preventing mortality, the costs and longevity of the ICD, the quality-of-life of patients in the 'ICD strategy' and in the 'no ICD strategy', and the follow-up costs of patients in the 'ICD strategy' are parameters that have significant impact on the cost-effectiveness. ICD therapy was to be preferred over the 'no ICD strategy' as long as the HRR for preventing all-cause mortality remains ≤0.85. A recent meta-analysis, used to estimate the effectiveness in the present study, showed a HRR = 0.74 (95% CI, 0.59 – 0.93) for ICD therapy in patients with ischemic or non-ischemic heart disease.[5] To appreciate this threshold value of HRR ≤0.85 in its context, one should keep the results of the second Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) in mind. These two landmark randomized controlled trials that led to the current guidelines, revealed a hazard ratio of 0.65 (95% CI, 0.51 – 0.93), and a hazard ratio of 0.77 (95% CI, 0.62 – 0.96) for MADIT-II and SCD-HeFT, respectively. More extensive risk stratification could increase the effectiveness even further. In MADIT-II eligible subjects, using sophisticated

electrocardiographic parameters improved the cost-effectiveness of primary prophylactic ICD therapy, as was also suggested in more recent studies.[33-35] Furthermore, additional diseases affect long-term prognosis, and may limit the effectiveness of the ICD. It may therefore be justifiable not to use this therapy in patients with extensive comorbidity. [36-38]

It is intuitive that ICD therapy becomes economically more attractive as ICD prices decline, and as ICD longevity increases. This was confirmed in the deterministic sensitivity analysis. The fact that the costs of ICD therapy vary widely between European countries complicates the judgment of cost-effectiveness in Europe as a whole. Different cost-effectiveness studies used different QOL estimates for ICD patients. Sensitivity analysis showed that the 'ICD strategy' is to be preferred over the 'no ICD strategy', if QOL of ICD patients is ≥0.83 QALY's, or ≤0.90 QALY's for similar patients without ICD. These results show that the difference in QOL estimates between cost-effectiveness studies does not solely drive the different conclusions.

Follow-up costs of ICD patients in a non-trial setting in Europe are difficult to estimate, as no complete registry of all healthcare usage of these patients is available. In order to obtain the most realistic estimate of the cost-effectiveness of defibrillator therapy in Europe, we conducted a healthcare utilization survey among the general practitioners of all ICD patients included in the prospectively collected Erasmus MC ICD registry and among general practitioners of patients from the Academic Medical Center (AMC), Amsterdam.[22] A limitation of this approach is the potential of underestimation of the incidence of health-care utilization because of under-reporting. However, it seems unlikely that the actual healthcare utilization would be more than 450% of the reported utilization. Deterministic sensitivity analysis showed that if this were not the case, the ICER would stay under the WTP threshold. Probabilistic sensitivity analysis was performed using Monte Carlo simulation. In contrast to 'Markov cohort simulation' (i.e. the technique used in the 'reference-case analysis'), which uses the point estimate of each model parameter, probabilistic (Monte Carlo) sensitivity analysis uses random draws from distributions that represent uncertainty around each of the parameter estimates. This analysis showed that in 65% of all simulations, the ICD strategy' was cost-effective compared with the 'no ICD strategy', which corresponds to a 65% probability of cost-effectiveness when considering all known uncertainty.[25,26]

The expected value of perfect information represents the monetary price that one would be willing to pay in order to gain perfect information. We estimated the EVPI at €18175 per patient. This is a large amount and implies that the uncertainty in the current analysis justifies pursuing this topic in future research in order to obtain more information.[27]

Cost-effectiveness in Europe as a whole?

In the present study, we included European source data to the extent possible, in an attempt to obtain a representative estimate of the cost-effectiveness of primary prophylactic ICD therapy in Europe. However, no universally accepted WTP threshold exists among European countries. Therefore, although the outcomes of our analysis are likely to be generalizable, one

can question whether the conclusion is generalizable to all European countries. The World Health Organization (WHO) provides a simple rule-of-thumb: all interventions with ICER's below three times the Gross Domestic Product (WHO-WTP) per capita can be considered cost-effective.[39] In 2010, the WHO-WTP threshold exceeded €80000 for all countries in the European Economic Area, except for France, Italy, Portugal, Spain, and the United Kingdom. Nevertheless, the WHO-WTP threshold was above €50000 in all countries, supporting the generalizability of the conclusion from our reference-case analysis. Nowadays, appropriate allocation of healthcare resources is becoming more and more complex as a result of increasing life expectancy of patients and increasing healthcare costs per patient, coupled with diminishing resources due to the global financial crisis. In this perspective, it can be questioned whether the WTP threshold used in the present study is still valid in the current financial situation. We feel that this question reaches beyond the scope of this article.

Limitations

This analysis has several limitations. The frequency of ICD interventions as observed in a large tertiary hospital was extrapolated to a lifetime time horizon. Whereas limiting the analysis to the time frame of the observed data underestimates the (cost-)effectiveness of ICD therapy, extrapolating the data may have overestimated it. The estimates of health-care costs during follow-up were based on a questionnaire with a limited response rate. Therefore, selection bias cannot be excluded. This could have caused an underestimation of the incidence of healthcare utilization and thereby overestimation of the cost-effectiveness of ICD therapy. However, since this questionnaire was sent to general practitioners instead of patients, selection due to unreported mortality or inability to respond because of severe illness is unlikely. Finally, we did not distinguish between ischemic and non-ischemic heart disease patients. According to the meta-analysis of pooled RCT's, the hazard rate ratio's for all-cause mortality with an ICD were very similar in these two groups, which would lead to similar cost-effectiveness results, justifying our approach in using a weighed pooled hazard rate ratio.

Conclusions

Primary prophylactic ICD therapy in patients with a left ventricular ejection fraction <40% and ischemic or non-ischemic heart disease, if applied according to the international guidelines, given the current knowledge and best-available evidence appears a cost-effective therapy in Europe. There is, however, still a large degree of uncertainty and the cost-effectiveness depends on the effectiveness of ICD therapy in preventing mortality, the costs and longevity of the ICD, the quality-of-life of patients with and without ICD, and the follow-up costs of patients. Future research is necessary to clarify these issues and to improve risk stratification in order to target those patients that can benefit most from ICD therapy and therefore increase cost-effectiveness.

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CHAPTER 6

PERFORMANCE OF THE SEATTLE HEART FAILURE MODEL IN IMPLANTABLE DEFIBRILLATOR PATIENTS TREATED WITH CARDIAC RESYNCHRONIZATION THERAPY

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ABSTRACT

The Seattle Heart Failure Model (SHFM) is a validated multivariable risk prediction model for mortality in heart failure (HF) patients, using widely available clinical variables. We assessed the performance of the SHFM when applied to HF patients who received a cardiac resynchronization therapy device with defibrillation (CRT-D). We identified 413 patients from 2 prospective ICD registries who received a CRT-D for primary prevention of sudden death. Baseline laboratory and clinical data were entered in the SHFM to calculate the predicted survival. The endpoint was all-cause mortality. During a median follow-up of 2.8 years, 78 patients died and 9 underwent heart transplantation. Observed versus predicted 5-year mortality rates were 11.6% vs. 11.4%, 21.5% vs. 22.1%, and 41.4% vs. 46.1% by ascending tertile of Seattle Heart Failure Score (SHFS), respectively. No systematic or substantial errors of risk estimation were observed. Discrimination was excellent; the *c*-statistic ranged from 0.78 at 1-year follow-up to 0.70 at 5-year follow-up; the Hosmer-Lemeshow χ^2 was 0.87 ($P = 0.65$). In conclusion, in HF patients who received a CRT-D, the SHFM offers adequate discrimination of risk for all-cause mortality, and estimation of mortality risk without substantial or systematic errors.

INTRODUCTION

Appropriate risk prediction in heart failure (HF) patients is of high importance, both to decide whether the potential benefits of an intervention additional to medical therapy for a certain patient outweighs its risks, and to be able to inform the patient about prognosis. The Seattle Heart Failure Model (SHFM) is a validated multivariable risk prediction model for mortality in HF patients.[1,2] The utility of this model was recently evaluated in patients enrolled in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT).[3] Because not all required SHFM covariates were registered in the SCD-HeFT study, a modified version of the SHFM (i.e. SHFM-D, differential ICD benefit) was developed. The performance of the SHFM-D was excellent in predicting survival among primary prevention ICD patients. However, the performance of the SHFM-D in HF patients who received an ICD combined with cardiac resynchronization therapy (CRT-D) is unknown. The purpose of this study was to assess the predictive value (i.e. calibration and discrimination) of the SHFM when applied to a real-world cohort of primary prevention CRT-D patients.

METHODS

We used data from prospective ICD registries of the Cardiology Departments of the Erasmus MC, Rotterdam, the Netherlands and the University Hospital of Basel, Switzerland. We identified all patients who received a first implantation of a CRT-D for primary prevention of sudden cardiac death between January 2000 and October 2009. The following selection criteria for CRT were applied: symptomatic HF despite optimal drug therapy, impaired LV ejection fraction (LVEF ≤35%), and the presence of an inter- or intraventricular conduction delay (QRS duration ≥120 ms). Primary prevention as indication for ICD therapy was defined as the presence of LVEF ≤35% with ischemic or non-ischemic cardiomyopathy without a history of cardiac arrest or sustained ventricular arrhythmia. The administrative censoring date was the end of October 2010 for all patients alive until that date.

Demographic and clinical data were obtained prior to CRT-D implantation. If multiple laboratory data were available, values from the date closest to the date of implantation were used; all laboratory values obtained up to 7 days prior to CRT-D implantation were accepted.

The SHFM is a validated risk prediction model that uses widely available clinical variables to predict both prognosis and impact of therapy on survival.[1,2] The original SHFM was derived from the Prospective Randomized Amlodipine Survival Evaluation (PRAISE I) database, and prospectively validated in 3 populations from clinical trials and in 2 outpatient practice settings. The recent SHFM-D model[3] included the original SHFM variables age, gender, weight, systolic blood pressure, NYHA class, LVEF, etiology of LV dysfunction, medication

use (angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker, beta-blocker, statin), daily diuretic dose (furosemide, bumetanide, torsemide, metolazone, and hydrochlorothiazide), and the laboratory values of serum sodium, as well as the new variables of digoxin use, carvedilol use, and serum creatinine. As haemoglobin, a variable in the original SHFM, was available in all patients, this variable was also added to the SHFM-D using the original dataset (10.038 patients) to derive the beta coefficient. The effectiveness of CRT-D in reducing mortality was estimated by using a fixed hazard ratio of 0.64 across the SHFM-D risk spectrum, as in the original SHFM (personal communication, WC Levy). For simplicity, we use the term SHFM instead of SHFM-D throughout the manuscript.

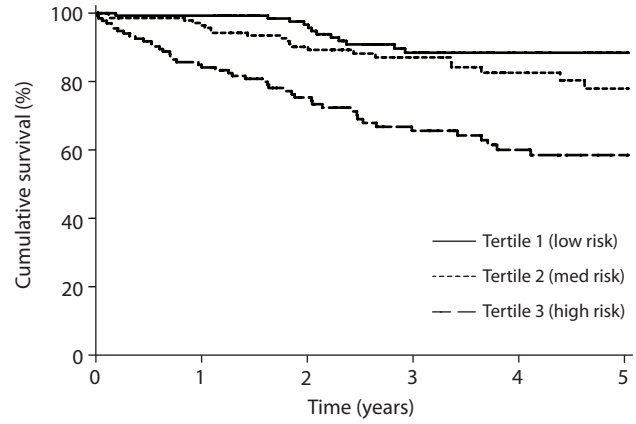
Follow-up started at the time of CRT-D implantation. In Rotterdam, patients were seen at 10 days, 3, 6, 9, and 12 months after implantation and at 6-monthly intervals thereafter. In Basel, patients were seen at 1, 3, and 6 months after implantation, and also at 6-monthly intervals thereafter. The follow-up visits included clinical assessment and device interrogation. The endpoint for this study was all-cause mortality; patients who underwent heart transplantation were censored alive on the day of transplant. Deaths were classified according to a modified Hinkle-Thaler system.[4,5]

Continuous variables are presented as mean ± SD for, if normally distributed, or otherwise by median and interquartile range (IQR). Data were compared with the Student's T-test or the Mann-Whitney U test, where appropriate. Categorical data were expressed as percentages and compared with Fisher's exact test. For all patients, the Seattle Heart Failure Score (SHFS) was calculated as previously described by Levy et. al.[1] In case of missing data, the covariate was imputed with the cohort mean of the respective continuous variables. Subsequently, the SHFS was converted to event-free survival probabilities up to 5 years for each individual patient (i.e. predicted survival). The observed survival rates were calculated according to the Kaplan-Meier method, and differences were evaluated by the log rank test. Calibration of SHFM was assessed by: 1) the SHFM-predicted survival plotted against observed survival at 1 and 5 years; and 2) the Hosmer-Lemeshow goodness-of-fit test. Discrimination was assessed by; 1) the *c*-statistic for time-to-event data; and 2) the 1- and 5-year receiver operating characteristic area under the curve (ROC AUC). The ROC AUC and *c*-statistic can range from 0.5 (no discrimination) to 1.0 (perfect discrimination).

Cox proportional hazards models were used to analyze the relations between SHFS and mortality. The proportional hazards assumption was tested by assessing log-log survival curves and by Schoenfeld residuals. Hazard ratios (HR's) are presented with corresponding 95% confidence intervals (CI's). Statistical analysis was performed using Stata version 11 SE for Windows (StataCorp, College Station, TX) and PASW version 18 (IBM Corp., Somers, NY). Statistical significance was defined as $P < 0.05$ (two-tailed).

RESULTS

The study cohort consisted of 413 HF patients who underwent a first implantation of a CRT-D for primary prevention of sudden cardiac death (299 (72%) from Rotterdam, 114 (28%) from Basel). The baseline characteristics of the study population are presented in Table 1. During a median follow-up of 2.8 years (IQR, 1.7 – 4.6 years), 78 patients (19%) died and 9 patients (2%) underwent heart transplantation. Of the 78 deaths, 61 (78%) were classified as cardiac (9 sudden and 52 non-sudden), and 9 (12%) as non-cardiac. The cause of death was unknown in 8 cases. The median interval from device implantation to death was 1.7 years (IQR, 0.7 – 2.4 years). The observed cumulative incidence of mortality was 6.6%, 13.1%, and 25.3%, at 1, 2, and 5 years, respectively. The median SHFS was higher for patients who died compared with those who survived (0.66 [IQR, 0.04 – 1.06] versus -0.06 [IQR, -0.51 – 0.47]; $P < 0.001$). Subsequently, the study population was stratified by ascending risk tertiles of SHFS (i.e. low to high risk). The baseline characteristics according to SHFS tertiles are presented in Table 1. Total mortality by ascending risk tertile of SHFS was 8.8% (n=12), 14.5% (n=20) and 33.3% (n=46), $P < 0.001$. The observed cumulative incidence of mortality stratified by SHFS tertiles is shown in Figure 1.



Patients at risk

——	137	136	101	68	43	12
------	138	132	100	64	40	20
— —	138	111	80	57	40	25

Figure 1. Cumulative survival for heart patients stratified by tertiles of the Seattle Heart Failure Score.

Table 1. Baseline characteristics among patients by quartiles of Seattle Heart Failure Score.

Variable	Total (n = 413)	Tertile 1 (n = 137)	Tertile 2 (n = 138)	Tertile 3 (n = 138)	*P*-value
Demographics					
Age (years)	61 ± 12	55 ± 13	63 ± 9	66 ± 9	< 0.001
Men	314 (76%)	101 (74%)	101 (73%)	112 (81%)	0.32
Weight (kg)	81 ± 16	83 ± 18	82 ± 15	79 ± 14	0.05
Heart failure characteristics					
NYHA class II	139 (34%)	82 (40%)	38 (27%)	19 (13%)	< 0.001
NYHA class III	264 (64%)	55 (60%)	95 (69%)	114 (83%)	< 0.001
NYHA class IV	10 (2%)	0 (0%)	5 (7%)	5 (4%)	< 0.001
Ejection fraction (%)	24 ± 7	25 ± 7	23 ± 7	23 ± 7	0.01
QRS duration (ms)	165 ± 30	163 ± 29	163 ± 30	168 ± 30	0.23
Ischemic etiology	194 (47%)	40 (29%)	74 (54%)	80 (58%)	< 0.001
Persistent atrial fibrillation	52 (13%)	6 (4%)	25 (18%)	21 (15%)	< 0.001
Systolic blood pressure (mmHg)	117 ± 19	125 ± 18	117 ± 16	108 ± 19	< 0.001
Haemoglobin (g/dL)	13.4 ± 1.8	14.1 ± 1.4	13.7 ± 1.8	12.7 ± 1.9	< 0.001
Serum sodium (mmol/L)	138 ± 4	139 ± 4	139 ± 4	137 ± 4	< 0.001
Serum BUN (mg/dL)	24.4*	19.6*	23.8*	33.9*	< 0.001
Serum creatinine (mg/dL)	1.2*	1.0*	1.1*	1.5*	< 0.001
Medications					
ACE inhibitor	343 (83%)	115 (83%)	109 (79%)	121 (88%)	0.15
ARB	104 (25%)	37 (27%)	38 (28%)	29 (21%)	0.38
Betablocker	324 (79%)	125 (91%)	110 (80%)	89 (65%)	< 0.001
Carvedilol	136 (33%)	53 (38%)	51 (36%)	32 (24%)	0.02
Digoxin	112 (27%)	17 (12%)	34 (25%)	61 (44%)	< 0.001
Diuretic	357 (86%)	98 (72%)	127 (92%)	132 (96%)	< 0.001
Spironolacton	189 (46%)	48 (35%)	75 (54%)	66 (48%)	0.005
Allopurinol	41 (10%)	7 (5%)	10 (7%)	24 (17%)	0.001
Statin	232 (56%)	78 (57%)	82 (59%)	72 (52%)	0.47

Continuous data are presented as mean ± SD or median *. Categorical data are presented as n(%).
Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BUN = blood urea nitrogen; NYHA = New York Heart Association.

The SHFM predicted a cumulative incidence of mortality of 5.7%, 11.2%, and 26.6%, at 1, 2, and 5 years, respectively. The difference between predicted and observed mortality was less than 3% for each year of follow-up. Calibration of the SHFM was assessed by plotting the predicted survival versus the observed survival by quartiles of SHFS (Figure 2). At 5 years, the observed mortality rates and the SHFM predicted mortality rates were closely related

(11.6% vs. 11.4%, 21.5% vs. 22.1%, and 41.4% vs. 46.1% by ascending tertile). There was no evidence of lack-of-fit as assessed by the Hosmer-Lemeshow test ($\chi^2 = 0.87$, $P = 0.65$). The SHFS was a predictor of mortality (HR 2.24, 95% CI, 1.72 – 2.93; $P < 0.001$). Model discrimination as assessed by the *c*-statistic is shown in Table 2. The *c*-statistic ranges from 0.78 at 1-year follow-up to 0.70 at 5-year follow-up. Figure 3 shows the ROC curve for 1- and 5-year mortality. The ROC AUC was 0.79 (95% CI, 0.72 – 0.86) and 0.71 (95% CI, 0.64 – 0.77), at 1 and 5 years, respectively.

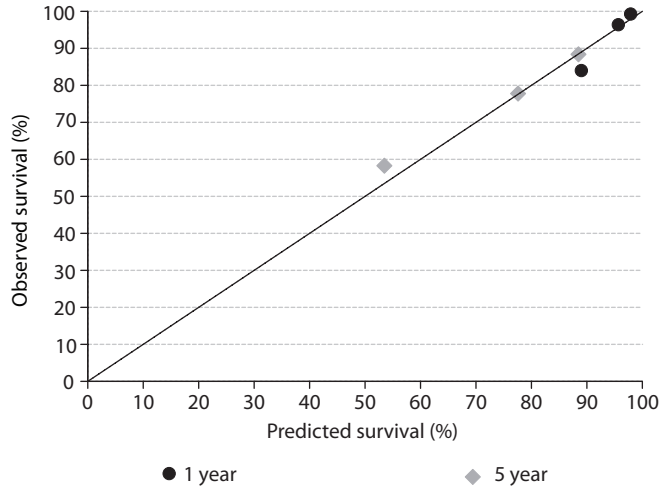


Figure 2. Model calibration.

Predicted survival by the Seattle Heart Failure Model versus observed survival (Kaplan-Meier) is shown for tertiles of the Seattle Heart Failure Score, at 1 and 5 years, respectively. The diagonal line is the line of identity.

Table 2. Performance of the Seattle Heart Failure Model for mortality prediction.

	Mortality Rate		
Year	**Predicted**	**Observed (95% CI)**	**c-statistic**
1	5.7	6.6 (4.6 – 9.5)	0.78
2	11.2	12.9 (9.9 – 16.7)	0.75
3	16.4	19.3 (15.5 – 23.9)	0.70
4	21.6	22.8 (18.5 – 28.1)	0.70
5	26.6	25.9 (20.7 – 31.8)	0.70

Abbreviations: 95% CI = 95% confidence interval.

To assess the validity of the assumed effectiveness of CRT-D in reducing mortality, the hypothetical survival without CRT-D was estimated by the SHFM for each patient (i.e. estimated survival based on the baseline characteristics with the effectiveness of CRT-D set to 0). This estimated survival without CRT-D was compared with the observed survival (i.e. with CRT-D). At 5 years follow-up, the estimated survival without CRT-D was 63.2%. For the total study population, the CRT-D decreased the risk of mortality by 36% (HR 0.64; 95% CI, 0.52 – 0.80; $P < 0.0001$). The estimated risk reduction in mortality appeared uniform across all tertiles of baseline risk estimated by SHFM; 35% in the lowest and middle risk tertile, and 44% in the highest risk tertile.

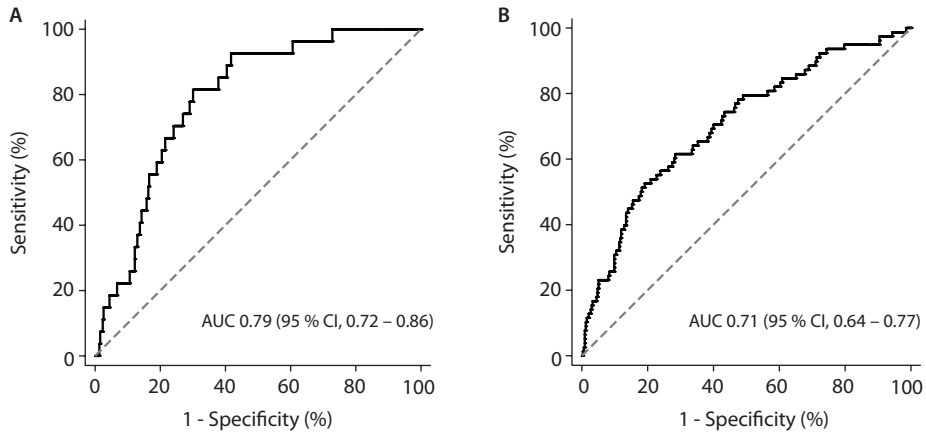


Figure 3. Receiver-operator characteristics curves.

The sensitivity of prediction of 1-year mortality (Panel A) and 5-year mortality (Panel B) versus 1-specificity for the Seattle Heart Failure Score are plotted. The diagonal line represents the absence of discrimination.
Abbreviations: AUC = area under the curve; CI = confidence interval.

DISCUSSION

In the present study, we evaluated the performance of the SHFM in HF patients who received a CRT-D as primary prevention of sudden cardiac death. The main findings of our study are 1) the calibration of the SHFM is excellent for risk prediction in CRT-D patients; 2) the ability of the SHFM to discriminate between patients with a high risk and a low risk of mortality was excellent at 1-year follow-up (*c*-statistic 0.78), and adequate during longer follow-up (*c*-statistic ranges from 0.70 – 0.75). In additional analyses, we confirmed the assumed effectiveness of CRT-D in reducing mortality as applied in the SHFM, which was

pre-specified at 36% and did not vary by the SHFM estimated baseline mortality risk. When the estimated survival based on medical therapy only was compared with the observed survival (i.e. with CRT-D), the observed effect of CRT-D was a 36% reduction in mortality.

The original SHFM has been validated in several hospital-based populations and was found to be predictive of short- and long-term survival (*c*-statistic ranges from 0.66 to 0.79).[6-8] Recently, a modified version of the SHFM was used to identify a subset of patients who did not benefit from ICD therapy.[3] In this study, the *c*-statistic for all-cause mortality was 0.71 in both the derivation and validation cohorts. In the present study, we applied the modified SHFM to HF patients who received a CRT-D as primary prevention of sudden cardiac death, yielding a ROC AUC of 0.79. Recently, a cohort study applying also the modified SHFM in 1141 ambulatory HF patients found a ROC AUC of 0.81.[9] In contrast to previous studies demonstrating underestimation of risk by the SHFM,[7,8] we found no substantial or systematic estimation errors. This difference might be explained by the applied baseline functions in the original and modified SHFM. The modified SHFM utilized an observed baseline function at 5 years, while the original SHFM utilized a mono-exponential equation over 3 years to predict survival at 5 years. It appears that the change in the baseline function at 5 years in the modified SHFM may have corrected the underestimation of mortality risk at 5 years as observed in the original SHFM. Comorbid conditions, such as cerebrovascular disease, chronic obstructive pulmonary disease, diabetes, peripheral vascular disease and malignancy also affect survival in heart failure patients.[10-13] The presence of comorbidities might be another possible explanation for the observed differences between estimated and observed mortality, as comorbidities are not incorporated in the SHFM.

The Cardiac Resynchronization in Heart Failure (CARE-HF) study showed a 36% reduction in mortality risk by CRT compared with medical therapy only.[14] In addition, the Comparison of Medical Therapy, Pacing and Defibrillators in Chronic Heart Failure (COMPANION) trial showed a 36% mortality risk reduction by CRT-D, and a 24% risk reduction by CRT pacing compared with medical therapy only.[15] The recently published Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy (MADIT-CRT), which was conducted in NYHA class I and II patients, demonstrated only a reduction in HF events, but no reduction in mortality.[16] However, the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT) showed that CRT-D had an additional benefit of 25% in reducing mortality compared with ICD only.[17] In the SHFM, the assumed effectiveness of CRT-D in reducing mortality was estimated from published literature data only. Our study results confirm the validity of the assumed effectiveness of CRT-D in reducing mortality. At 5-years follow-up, the hypothetical survival without CRT-D was 63.2% and the observed survival (i.e. with CRT-D) was 74.7%, yielding a 36% mortality risk reduction. In addition, the benefit of the CRT-D in reducing mortality appeared uniform across all quartiles. In contrast, the benefit of ICD only therapy was not uniform in the SCD-HeFT analysis, with no benefit in the highest quintile.[3]

The present study has some limitations. First, the design of the study was a retrospective analysis of data. However, most other studies validating the SHFM were retrospective of design. In addition, data in both ICD registries are prospectively collected. Another limitation might be the imputation of missing data. However, we had few missing data with 98% of patients with either all data or missing only one variable. As haemoglobin, a variable in the original SHFM, was available in all patients, this variable was also added to the SHFM-D using the original dataset. Therefore, the model in the present study is slightly different from the published SHFM-D.

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CHAPTER 7

MORTALITY WITHOUT PRIOR APPROPRIATE IMPLANTABLE DEFIBRILLATOR INTERVENTION IN PATIENTS TREATED WITH CARDIAC RESYNCHRONIZATION THERAPY: A COMPETING RISK ANALYSIS

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Submitted

ABSTRACT

Introduction: Cardiac resynchronization therapy (CRT) aims to relief heart failure symptoms and decrease heart failure mortality. Patients who die prior to receiving appropriate implantable cardioverter-defibrillator (ICD) interventions have no benefit of the defibrillation option of the device, but are exposed to the potential drawbacks of this modality. It would be of interest to be able to quantify and identify those CRT-D patients who die prior to receiving ICD interventions. Further, we aimed to analyze the value of the Seattle Heart Failure Model (SHFM) for the prediction of mortality without prior ICD therapy.

Methods: We identified 413 patients from 2 prospective ICD registries who received a CRT-D for treatment of heart failure and primary prevention of sudden death. The primary endpoint was mortality without prior appropriate ICD interventions (i.e. antitachycardia pacing or shock). Cumulative incidence functions were computed. We used the subdistribution proportion hazards model to estimate subdistribution hazard ratio's (SHR's), to assess the influence of baseline characteristics on the outcome. Baseline laboratory and clinical data were used to calculate the SHFM. Subsequently, we analyzed the value of the SHFM for prediction of mortality without prior ICD interventions.

Results: During a median follow-up of 34 months (IQR 20 – 56 months), 78 patients (19%) died, and 48 patients (i.e. 62% of all deaths, 12% of the study population) died without prior appropriate ICD intervention. Competing risk analysis identified advanced age, renal dysfunction, diabetes, and NYHA class > II heart failure symptoms as predictors of mortality without prior ICD interventions. The SHFM was positively correlated with both the risk of mortality without prior ICD interventions and with the risk of appropriate ICD interventions.

Conclusion: A significant proportion of the deceased CRT-D patients died without prior ICD interventions. The SHFM is able to identify patients at high risk of mortality without prior ICD interventions. Paradoxically, this subgroup of patients is also at highest risk of receiving appropriate ICD interventions.

INTRODUCTION

Cardiac resynchronization therapy (CRT) aims to relief heart failure (HF) symptoms and decrease HF mortality. Cardiac resynchronization therapy is recommended for HF patients in New York Heart Association (NYHA) Class II to ambulatory IV, with severe systolic dysfunction, and intra-ventricular conduction delay. Most patients, who are eligible for CRT, also qualify for implantable defibrillator (ICD) therapy for the primary prevention of sudden cardiac death.[1] After a long period of on going debate about the pro's and con's of CRT combined with ICD therapy (i.e. CRT-D), cumulating evidence is clearly in favour of the addition of ICD therapy to CRT for the reduction of mortality and symptoms among heart failure patients.[2-4] However, the addition of ICD therapy to CRT is not without potential drawbacks, both in terms of complications (e.g. inappropriate ICD interventions), and in economical terms.[5,6] Therefore, both from a clinical and from a scientific point-of-view, it would be relevant to prospectively identify patients at high risk of mortality without prior ICD intervention. In theory, the benefit of ICD therapy is determined by two mutually exclusive and competing processes: 1) appropriate ICD interventions, and 2) mortality without prior appropriate ICD interventions. Specific statistical methods are available for the analysis of 'competing risk' questions.[7-9] Competing risk analysis has been used for years in prosthetic heart valve research,[10-12] and has also been applied to ICD-only patients.[13] However, despite its many advantages over classical survival analysis methodology (as the Kaplan-Meier method, and Cox proportional hazards regression), this method is still not widely adopted in cardiovascular research and have to our best knowledge never been applied to CRT-D patients.

Recently, we demonstrated that the Seattle Heart Failure Model (SHFM) is predictive of all-cause mortality in CRT-D patients.[14] Therefore, we aimed 1) to quantify the cumulative incidence of mortality without prior ICD interventions in primary prevention CRT-D patients, 2) to perform a competing risk analysis to identify predictors of high-risk of death without prior appropriate ICD therapy, and 3) to study the value of the SHFM for the prediction of mortality without prior ICD interventions in CRT-D patients.

It has to be noted that the competing risk problem in CRT-D patients is more complex than in ICD-only patients; the benefit of this therapy is determined by both the 'ICD part' of the therapy (which aims to prevent arrhythmic mortality), and by the 'CRT part' of the therapy (which aims to relief cardiac failure symptoms/hospitalizations and prevent heart failure death). We explicitly did not aim to study the benefit of CRT in CRT-D patients in this manuscript.

METHODS

Study population

Two prospective ICD registries of the Cardiology departments of the Erasmus MC, Rotterdam, the Netherlands and the University Hospital Basel, Switzerland were the basis for this study. From these registries, all patients who received a first implantation of a CRT-D for the primary prevention of sudden cardiac death were identified. Primary prevention as indication for ICD therapy was defined as the presence of left ventricular ejection fraction (LVEF) ≤35% with ischemic or non-ischemic cardiomyopathy without a history of cardiac arrest or sustained ventricular arrhythmia. The administrative censoring date was November 2010 for all patients alive until that date. The CRT-D devices were implanted according to local practice in the two centers. A 2-zone configuration for arrhythmia detection was programmed in the majority of patients. The rate cut-off for detection of ventricular tachycardia (VT) was set at 170 – 180 beats per minute (bpm) for primary prevention. The rate cut-off for detection of ventricular fibrillation (VF) was set at 210 bpm. For all devices, anti-tachycardia pacing (ATP) in combination with cardioversion/defibrillation therapy features was activated.

Seattle Heart Failure Model

The SHFM is a validated risk prediction model based on routinely collected clinical and laboratory data.[15] In the present study we used the SHFM-D model which includes the original SHFM variables age, gender, weight, systolic blood pressure, NYHA class, left ventricular ejection fraction, etiology of ventricular dysfunction, medication use (angiotensin-converting enzyme (ACE) inhibitor/ angiotensin receptor blocker, aldosterone blocker, beta-blocker, statin, allopurinol), daily diuretic dose (furosemide, bumetanide, torsemide, metolazone, and hydrochlorothiazide), and the laboratory values of serum sodium, as well as the new variables digoxin use, carvedilol use, and serum creatinine.[16] Because hemoglobin, a variable in the original SHFM, was available in all patients, this variable was also added to the SHFM-D using the original dataset (10038 patients) to derive the β-coefficient. Ninety-eight percent of patients had 1 or no missing SHFM variables. In case of missing data, the covariate was imputed with the cohort mean of the respective continuous variables. For each individual patient, the Seattle Heart Failure Score (SHFS) was calculated based on the original equation as previously described by Levy et al.[16]

Event classification

Arrhythmic events triggering defibrillator therapies were retrieved from the device's memory at regular follow-up visits in each center. Two experienced physicians per center analyzed all stored intracardiac electrograms to classify the arrhythmia responsible for triggering ICD therapy. Ventricular tachyarrhythmias were defined as events with a sudden increase in rate combined with a change in ventricular electrogram morphology from the baseline

rhythm. As an atrial electrogram is present in CRT-D devices, the presence of atrioventricular dissociation was used to diagnose ventricular tachyarrhythmia. Appropriate ICD therapy was defined as ATP or shock for an arrhythmia determined to be either VT or VF.

Deaths were classified according to a modified Hinkle-Thaler system.[17,18] Total mortality was divided into cardiac and non-cardiac mortality. Patients who underwent cardiac transplantation were censored alive on the day of transplant.

Competing risk analysis and endpoints

In survival analysis, the effect of a variable (e.g. an intervention) is evaluated by the time to occurrence of a certain endpoint. The occurrence of the event of interest (e.g. death) is known as 'failure'. When there is only one event (e.g. all-cause mortality), appropriate statistical methods are the Kaplan-Meier method, the Log-rank test, and Cox proportional hazard regression models. However, if there is a type of failure that is not inevitable (e.g. appropriate ICD intervention), but can be precluded by another event (e.g. death), this problem is referred to as a 'competing risk problem'.[12] The probability of such a competing risk is given by the cumulative incidence function (CIF).

The primary endpoint in the present analysis is time from CRT-D implantation until first delivered appropriate ICD therapy (ATP or shock) or death resulting from any cause. Death without prior appropriate ICD interventions excludes the delivery of appropriate ICD therapy during follow-up (i.e. presumed prevention of arrhythmic death). In competing risk terms, any appropriate ICD intervention is the primary event, death without prior appropriate ICD interventions is the competing event. In case of tied events (i.e. appropriate ICD intervention and death on the same day), the event was classified as death.

The secondary endpoint was appropriate ICD shocks, where the shock was delivered as primary therapy. Thus, shock delivered as secondary therapy after ineffective ATP was excluded for the analysis of the secondary endpoint.

Statistical analysis

Continuous variables were expressed as the mean ± SD, if normally distributed, and compared with the Student's T-test for independent samples. In case of non-normal distribution of data, medians and interquartile ranges (IQR) were reported and the Mann-Whitney U test was used for data comparison. Categorical data were expressed as percentages and compared with the Chi-square test or Fisher's exact test when appropriate.

For competing risk analysis, we used CIF's, representing the probability of occurrence of a particular event by time *t* in the presence of competing events. The associated CIF plots were constructed. To analyze the effect of baseline characteristics on the outcome, we used the proportional subdistribution hazard model proposed by Fine and Gray.[7] Subhazard ratios (SHR's) with corresponding 95% confidence intervals (CI's) are reported. Statistical analysis was performed using Stata version 12 SE for Windows (StataCorp, College Station,

TX) and PASW version 18 (IBM Corp., Somers, NY). Statistical significance was defined as $P < 0.05$ (two-tailed).

RESULTS

Study population and mortality

The study cohort consisted of 413 patients. The population was predominantly male (76%), with a mean age of 61 ± 12 years. Ischemic etiology of left ventricular dysfunction was present in 47% of patients. The mean LVEF was 24 ± 7%. Further baseline characteristics of the study population are presented in Table 1.

During a median follow-up of 34 months (IQR 20 – 56 months), 78 patients (19%) died and 9 patients (2%) underwent heart transplantation. Of the 78 deaths, 61 (78%) were classified as cardiac (9 sudden and 52 non-sudden), and 9 (12%) as non-cardiac. The cause of death was unknown in 8 cases. The median interval from device implantation to death was 22 months (IQR 9 – 32 months). The crude mortality rates were 6.6% (95% CI, 4.6% – 9.5%) and 25.3% (95% CI, 20.3% – 30.9%), at 1 and 5 years, respectively. Univariate associations of baseline variables and all-cause mortality are also presented in Table 1.

Appropriate ICD therapy and death without prior ICD therapy

At 5 years follow-up, a total of 98 patients (24%) had experienced appropriate ICD interventions (ATP or shock). The majority of first delivered appropriate ICD interventions was ATP (63%). The median interval between implantation and first appropriate ICD intervention was 11 months (IQR 3 – 21 months). At 5-years follow-up, the cumulative incidence of a ventricular event triggering ICD intervention was 32.6% (95% CI, 26.9% – 39.1%). Univariate analysis showed that appropriate ICD interventions were more frequently observed in patients with atrial fibrillation compared with patients without atrial fibrillation (33% vs. 21%, $P = 0.01$) The median SHFS was higher for patients experiencing appropriate ICD intervention compared with those without appropriate ICD interventions (0.27 vs. -0.04; $P = 0.001$). During follow-up, 35 patients (8%) received an appropriate ICD shock. At 5-years follow-up, the cumulative incidence of appropriate ICD shocks was 19.8% (95% CI, 15.5% – 25.1%).

Competing risk analysis

Of the 78 patients who died, 48 patients (62%) died without prior appropriate ICD intervention. This represents 12% of the total study population. The median interval between implantation and mortality was 16 months (IQR 6 – 25 months). At 1-year follow-up, the cumulative mortality of these patients was 41.7% (95% CI, 29.2% – 56.8%), and

91.7% (95% CI, 81.8% – 97.3%) at 3-year follow-up. The median SFHS for patients who died without prior appropriate ICD intervention was 0.55 (IQR 0.07 – 1.17).

Table 1. Baseline characteristics.

Characteristic	Total n = 413 (100%)	Deceased n = 78 (19%)	Survivors n = 335 (81%)	*P*-value
Demographics				
Age, years	61 ± 12	63 ± 12	61 ± 11	0.08
Male gender	314 (76%)	63 (81%)	251 (75%)	0.31
Heart failure characteristics				
NYHA class II	139 (34%)	20 (26%)	116 (34%)	
NYHA class III	264 (64%)	55 (71%)	209 (62%)	0.55
NYHA class IV	10 (2%)	3 (4%)	7 (2%)	
Ejection fraction, %	24 ± 7	22 ± 6	24 ± 7	0.02
Ischemic etiology	194 (47%)	43 (55%)	151 (45%)	0.13
Systolic blood pressure, mmHg	117 ± 19	112 ± 20	118 ± 19	0.01
Laboratory values				
Hemoglobin, g/dL	13.4 ± 1.8	13.1 ± 1.9	13.6 ± 1.8	< 0.05
Serum sodium, mmol/L	138 ± 4	136 ± 4	139 ± 4	< 0.001
Serum ureum, mg/dL	24.4 (19.0 – 33.6)	29.4 (20.2 – 41.3)	23.2 (18.8 – 31.4)	0.003
Serum creatinine, mg/dL	1.2 (1.0 – 1.5)	1.4 (1.1 – 1.9)	1.1 (0.9 – 1.4)	< 0.001
Medications				
ACE inhibitor	343 (83%)	65 (83%)	278 (83%)	0.99
Angiotensin receptor blocker	104 (25%)	18 (23%)	86 (26%)	0.77
Betablocker	324 (79%)	52 (67%)	272 (81%)	0.009
Carvedilol	136 (33%)	22 (28%)	114 (34%)	0.35
Digoxin	112 (27%)	26 (33%)	86 (26%)	0.20
Diuretic	357 (86%)	65 (83%)	292 (87%)	0.36
Furosemide equivalent daily dose, mg/kg	0.53 (0.28 – 0.96)	0.76 (0.32 – 1.36)	0.51 (0.27 – 0.85)	0.008
Spironolactone	189 (46%)	37 (47%)	152 (45%)	0.80
Allopurinol	41 (10%)	10 (13%)	31 (9%)	0.40
Statin	232 (56%)	40 (51%)	192 (57%)	0.38

Continuous data are presented as mean ± SD or median (25^{th}, 75^{th} percentiles). Categorical data are presented as n(%).
Abbreviations: ACE = angiotensin-converting enzyme; NYHA = New York Heart Association.

Univariate competing risk analysis demonstrated that the SHFS was a significant predictor of mortality without prior ICD intervention (SHR 2.15, 95% CI, 1.57 – 2.96; $P < 0.001$), and was also associated with appropriate ICD interventions (SHR 1.47, 95% CI, 1.16 – 1.86; $P = 0.001$). Figure 1 shows the univariate effects of ascending SHFS tertiles on the cumulative incidence

functions of death without prior appropriate ICD intervention. The SHFS was positively correlated with both the risk of appropriate ICD therapy, and with the risk of death without prior appropriate ICD therapy. Death without prior appropriate therapy was almost four times more frequently observed in patients in the highest SHFS tertile compared with patients in the lowest tertile (SHR 3.78, 95% CI, 1.73 - 8.27, $P = 0.001$). The SHR for death without prior appropriate therapy was 1.67 (95% CI, 0.70 - 4.00, $P = 0.25$) for patients in tertile 2 compared with patients in tertile 1. Also, the risk of appropriate ICD interventions increased with increasing SHFS: the SHR's for appropriate ICD interventions were 2.21 (95% CI, 1.26 - 3.87, $P = 0.005$), and 2.82 (95% CI, 1.63 - 4.89, $P < 0.0001$), for patient in SHFS tertile 2 compared with SHFS tertile 1, and for patients in SHFS tertile 3 compared with SHFS tertile 1, respectively (Figure 2).

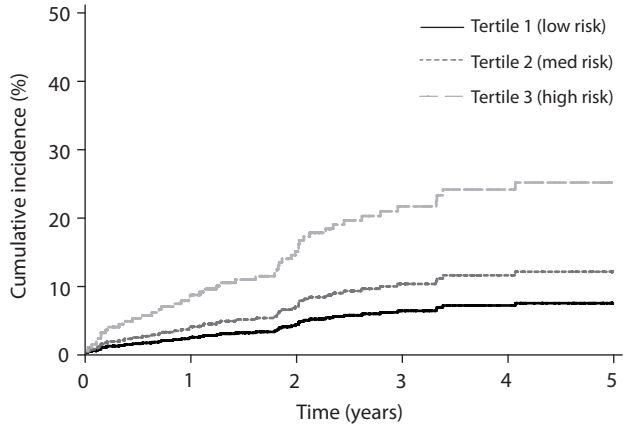

Figure 1. Cumulative incidence functions of death without prior appropriate ICD intervention, stratified by ascending tertiles of the Seattle Heart Failure Score.

tertile 3 vs. tertile 1, $P = 0.25$
tertile 2 vs. tertile 1, $P = 0.001$

Table 2 presents the univariate SHR's for mortality without prior appropriate ICD interventions, and for appropriate ICD interventions as determined by competing risk analysis. Patients with atrial fibrillation and patients in NYHA class III had a significantly increased risk of appropriate ICD interventions. Competing risk analysis showed that patients at advanced age, patients with renal dysfunction, diabetes, and patients in NYHA class > II had an increased risk of mortality without prior ICD interventions.

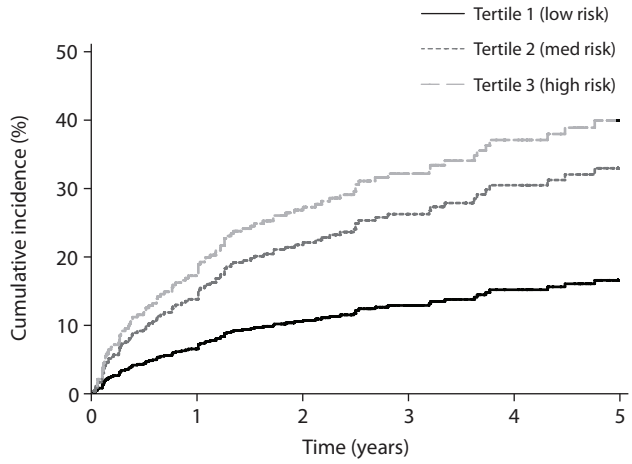

Figure 2. Cumulative incidence functions of appropriate ICD interventions, stratified by ascending tertiles of the Seattle Heart Failure Score.

tertile 3 vs. tertile 1, $P = 0.005$
tertile 2 vs. tertile 1, $P < 0.0001$

Table 2. Univariate competing risk analysis for individual components of the SHFM.

	SHR (95% CI)	
Variable	**Appropriate ICD therapy**	**Prior Death**
Age (years)	1.01 (0.98 – 1.02)	1.04 (1.01 – 1.07)
Atrial fibrillation	1.80 (1.20 – 2.69)	0.57 (0.31 – 1.05)
Serum creatinine (mg/dl)	1.06 (0.79 – 1.43)	2.10 (1.46 – 2.94)
Serum sodium (mmol/L)	0.95 (0.90 – 0.99)	0.91 (0.86 – 0.97)
Diabetes	0.92 (0.58 – 1.46)	1.81 (1.01 – 3.23)
NYHA class*		
NYHA II (ref)	1.0	1.0
NYHA III	1.87 (1.16 – 3.00)	1.18 (0.63 – 2.21)

Of note * NYHA IV was excluded from analysis because of small numbers.
Abbreviations: CI = confidence interval, NYHA = New York Heart Association, ref = reference, SHR = subhazard ratio.

DISCUSSION

Main findings

In the present study, we evaluated the incidence of mortality without prior appropriate ICD interventions among primary prevention CRT-D patients. Further, we aimed to identify predictors of mortality without prior ICD interventions, and to evaluate the predictive value of the SHFM for this competing risk question. The main findings of the present study are: 1) Sixty-two percent of all deceased patients died without prior appropriate ICD intervention. This represents 12% of the total study population. 2) Advanced age, renal dysfunction, diabetes, and heart failure symptoms in NYHA class III were predictors of mortality without prior ICD interventions, and 3) The SHFS is positively and significantly correlated with the risk of mortality without prior ICD interventions, and is also positively and significantly correlated with the risk of appropriate ICD interventions.

Relation to other CRT-D studies

Competing risk regression analysis showed that patients with renal dysfunction had an increased risk of mortality without prior ICD interventions. It is well-known that ICD patients with renal dysfunction are at high risk of mortality. Furthermore, a recent analysis of the Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy (MADIT-CRT) showed that increased levels of creatinine, and of blood urea nitrogen, were both and independently associated with an increased risk of mortality and heart failure in the total study population. However, the benefit of CRT-D in MADIT-CRT was similar between patients with and without kidney disease.[19] Combined assessment of the two renal markers showed to identify a significant differential clinical and echocardiographic response, also suggesting that cardiorenal interactions relate to the benefit of CRT-D.

Further, we showed that CRT-D patients with diabetes were at increased risk of mortality without prior ICD interventions. Although analysis of MADIT-CRT data showed that diabetic patients had significantly more primary endpoints compared with non-diabetic patients (26.6% vs. 18%, $P < 0.001$), no differences in the effectiveness of CRT-D in reducing the primary endpoint were observed (diabetic patients, hazard ratio (HR) = 0.56, non-diabetic patients, HR = 0.67).[20] The effectiveness of CRT-D in diabetic patients was also consistently found in subgroup analyses of patients with ischemic cardiomyopathy vs. non-ischemic cardiomyopathy, and between patients with a wide QRS complex.[20] The question remains how our study findings relate to these findings of MADIT-CRT. Large differences in baseline characteristics between our study population and the MADIT-CRT (with 66% of patient in NYHA class III-IV in our study population, vs. none in MADIT-CRT) make head-to-head comparison impossible.

The finding that patients with heart failure symptoms in NYHA class III had an increased risk of mortality without prior ICD interventions could be in line with recent literature.

Since MADIT-CRT excluded patients in NYHA class III of IV, no direct comparison is possible. However, a recent post-hoc analysis of the MADIT-CRT showed that patients with a poor functional capacity at baseline – assessed by a 6-minute walk test – are at a 2.4-fold increased risk for all-cause mortality.[21] In contrast, analysis of the Comparison Of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial showed that patient in NYHA class III had a reduced risk of appropriate ICD shocks compared with patients in NYHA class IV. Also, NYHA IV patients in the CRT-arm of the trial had twice the risk of sudden cardiac death compared with NYHA III patients (HR = 2.62, 95% CI, 1.61 – 4.26).[22] The relative underrepresentation of NYHA IV patients in our study cohort can be a possible explanation for this: since only 2% of patients were in NYHA IV, statistical power is insufficient to show differences in the risk of mortality without prior ICD therapy between patients in NYHA III and NYHA IV. However, a clear trend towards a higher risk of mortality without prior ICD interventions in patients with more severe heart failure symptoms was observed.

Advantages of the competing risks methodology

To the best of our knowledge, this is the first application of competing risk methodology to a CRT-D population. When applied to competing risk data, this methodology has several important advantages over classical statistical methods used for the analysis of survival data, as the Kaplan-Meier method, and Cox proportion hazards regression models. First, the Kaplan-Meier model assumes that patients who are still alive will ultimately die in the future, and that they will die at similar rates as those who have already failed. This assumption is also known as 'non-informative censoring', and poses no problems as long as the endpoint of interest is all-cause mortality. However, when the probability of the event of interest is not inevitable (e.g. ICD interventions), but can be precluded by other events (e.g. death), the Kaplan-Meier method is not adequate: in this situation, the Kaplan-Meier estimator overestimates the probability of appropriate ICD interventions, because deceased patients (who are censored), are treated as if they could fail (i.e. experience appropriate ICD interventions). The 'real' probability of mortality without prior appropriate ICD interventions is given by the cumulative incidence.[12,13] This estimator is also known as the 'actual' probability in cardiovascular literature, because it estimates the probability that a patient will fail from one of the competing events. Although this methodology is applied to several cardiovascular disease entities (e.g. heart valve replacement research, and coronary artery bypass re-operations)[10-12] it has not been widely adopted in ICD research,[13] and not in CRT-D research yet. Also, the use of subdistribution hazard regression, in contrast to cause-specific Cox proportional hazards models, allows intuitive direct quantification of effect of covariates on the CIF.

Conclusion

Patients treated with CRT-D have no benefit from the defibrillation capacity of their device, if they die without prior ICD interventions. In this real-world cohort of primary prevention CRT-D patients, death without prior ICD interventions represented 62% of all deaths. The risk of mortality without prior ICD interventions seems increased in patients with renal dysfunction, in diabetic patients, and in patients with severe heart failure symptoms and advanced age. Further research is needed to clarify these complex relations. This study may be an example of how competing risk methodology can be applied to CRT-D patients. Awareness among clinicians about the need for specialized statistical methods for this type of competing risk type of questions is needed, as classic statistical methods as the Kaplan Meier method may overestimate the risk of the competing event of interest.

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CHAPTER 8

PROGNOSTIC ROLE OF HIGH-SENSITIVE C-REACTIVE PROTEIN IN IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR PATIENTS TO PREDICT VENTRICULAR ARRHYTHMIAS

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ABSTRACT

Background: High-sensitivity C-reactive protein (hs-CRP) and B-type natriuretic peptide (BNP) are useful biomarkers for cardiovascular risk stratification. Little data are available regarding the prognostic value of hs-CRP and BNP serum levels and future ventricular arrhythmic events triggering implantable cardioverter-defibrillator (ICD) therapy.

Methods: A total of 100 patients eligible for ICD implantation were enrolled in a prospective cohort study. Serum levels of hs-CRP and BNP were obtained the day before ICD implantation and at scheduled follow-up visits. For risk analysis, the study cohort was dichotomized based on serum level of hs-CRP using a cut-off value of 3 mg/L. The endpoint was appropriate ICD therapy triggered by ventricular arrhythmias during a follow-up of 24 months.

Results: Appropriate ICD therapy was delivered in 20% of patients. Median baseline serum level of hs-CRP was significantly higher in patients with appropriate ICD therapy than in those without appropriate ICD therapy (5.33 mg/L vs. 2.19 mg/L; $P = 0.002$). The same was true for median serum levels of hs-CRP and BNP during follow-up (5.43 mg/L vs. 2.61 mg/L, $P = 0.001$ and 261.0 pg/mL vs. 80.1 pg/mL, $P = 0.01$, respectively). Multivariate analysis demonstrated that baseline hs-CRP level >3 mg/L was independently associated with appropriate ICD therapy (odds ratio 4.0, 95% CI, 1.1 – 14.2; $P = 0.03$).

Conclusion: Elevated pre-implantation hs-CRP serum level is independently associated with increased risk for appropriate ICD therapy. Monitoring for elevated BNP levels during follow-up adds to the assessment of risk for future arrhythmias.

INTRODUCTION

The implantable cardioverter-defibrillator (ICD) has become the standard therapy in patients who have survived life-threatening ventricular tachyarrhythmias or who are at high risk for ventricular arrhythmias.[1-3] However, a significant proportion of ICD recipients will never receive appropriate device therapy for ventricular tachyarrhythmias.[4] Therefore, means to better identify patients who will benefit most from ICD implantation remains of great interest. During the last few years, serum levels of biomarkers have emerged as a feasible method to identify patients at high risk for various cardiac events. In particular, serum levels of B-type natriuretic peptide (BNP) have prognostic significance in patients with congestive heart failure. Elevated serum levels of BNP not only independently predict mortality in patients with or without heart failure, but also have been associated with sudden death.[5-7] Serum levels of high-sensitivity C-reactive protein (hs-CRP) have been associated with increased risk for cardiovascular events (myocardial infarction, stroke, and peripheral arterial disease).[8-10] However, the association between elevated serum levels of BNP or hs-CRP and the occurrence of tachyarrhythmias is less clear. Elevated serum levels of hs-CRP have been associated with recurrence of atrial fibrillation.[11,12] Little is known about the role of hs-CRP in patients who are at risk of experiencing spontaneous ventricular arrhythmic events. The purpose of our study was to assess whether serum levels of BNP and hs-CRP could predict future ventricular tachyarrhythmias in ICD patients at baseline and during follow-up.

METHODS

Study population

The study cohort consisted of 100 consecutive patients who were prospectively enrolled. All patients eligible for the study had a standard indication for ICD implantation either for secondary or primary prevention of sudden cardiac death. Exclusion criteria were an acute coronary syndrome during the month prior to enrollment, acute or chronic inflammatory or infective disease known to increase hs-CRP levels, and the presence of a channelopathy (i.e., long QT syndrome or Brugada syndrome). The study complied with the World Medical Association Declaration of Helsinki, and was approved by the local institutional ethics committee. Written informed consent was obtained from all patients prior to enrollment in the study.

Device settings

All implanted devices were capable of storing intracardiac electrograms. A single-chamber device was the most common implanted device (64%). For all patients, ICD programming was intended to avoid inappropriate therapy and tailored according to the clinical presentation.

A two-zone configuration was programmed in 90% of patients. The programmed mean cycle length for ventricular tachycardia detection was 354 ± 24 ms and for ventricular fibrillation detection 289 ± 12 ms. For all patients, except two, primary antitachycardia pacing therapy (ATP) followed by shocks was activated in the lowest detection zone.

Follow-up

Follow-up started at the time of ICD implantation. Every 3 months, patients were seen for routine ICD interrogation. In case of a symptomatic event, patients were advised to contact our outpatient clinic as soon as possible. All spontaneous episodes with stored electrograms that resulted in device therapies (ATP and/or shock) were reviewed and classified by two experienced electrophysiologists. Ventricular tachyarrhythmias were defined as events with a sudden increase in rate with a stable ventricular response combined with a change in electrogram morphology from the baseline rhythm. If an atrial electrogram was present, the presence of atrioventricular dissociation was used to confirm a ventricular tachyarrhythmia.

Blood sampling and laboratory methods

Venous blood samples were drawn the day before implantation and at the scheduled follow-up visits. High-sensitivity CRP concentrations were determined by immunonephelometry (Beckman Coulter Inc. Fullerton, CA, USA) on non-EDTA serum-separated samples. Measurement of BNP plasma concentrations was performed using a fluorescence immunoassay method (Biosite Diagnostics, San Diego, CA, USA) on samples collected in EDTA tubes. The sensitivity (ie. lowest concentration different from zero) was 0.02 mg/dL for hs-CRP and 5 pg/mL for BNP. For the evaluation of renal function, serum creatinine levels were determined and glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation.[13]

Statistical analysis

High-sensitivity CRP will be considered as a binary parameter with respect to the specified cut-off value (0 = hs-CRP ≤3 mg/L, 1 = hs-CRP >3 mg/L). The cut-off level of 3 mg/L is justified by the statement of the American Heart Association, which considers serum levels of hs-CRP of >3 mg/L as high risk for cardiovascular events (e.g., death, myocardial infarction, stroke).[14] Continuous data are expressed as mean ± standard deviation if normally distributed, or otherwise by median and interquartile range (IQR). Continuous data were analyzed with Student's T-test or Mann-Whitney U test, when appropriate. Categorical data are summarized as percentage. The Chi-square test was used for analysis of categorical data. Receiver operating characteristic (ROC) curves were generated for graphical representation of sensitivity and specificity of hs-CRP and BNP regarding ventricular tachyarrhythmias. The generated ROC curves were compared using the method of DeLong et al.[15] Logistic regression analysis was performed to identify independent factors for the occurrence of

ventricular tachyarrhythmias as all patients had a follow-up of 24 months. The Hosmer-Lemeshow test was used to examine the models' goodness-of-fit.[16] Odds ratios (OR's) with corresponding 95% confidence intervals (CI's) are reported. A two-sided *P*-value <0.05 was used for declaring statistical significance. All statistics were performed using SPSS 16.0 for Windows (SPSS Inc, Chicago, IL, USA) and STATA 11 SE for Windows (StataCorp LP, College Station, TX, USA).

RESULTS

Study population

The study cohort included 79 men and 21 women, with a mean age of 60 ± 13 years (range 18 – 80 years). The mean left ventricular ejection fraction (LVEF) was 27 ± 12%; LVEF was 35% or less in 65% of patients. The indication for ICD therapy was primary prophylactic in 60% of patients. Twenty-four patients received an ICD for aborted sudden death, and 16 patients had documented sustained ventricular tachycardia. The prevalence of diabetes was 18%, and hypertension was present in 11% of patients. A GFR ≥60 mL / min / 1.73 m^2 was recorded in 75% of patients. A GFR between 45 and 59.9 mL / min / 1.73 m^2 in 16%, and a GFR <45 mL / min / 1.73 m^2 in 9% of patients was recorded. The mean total cholesterol level was 4.3 ± 1.2 mmol/L, and the prevalence of total cholesterol >6.5 mmol/L was 5%. During a follow-up of 24 months, nine patients died: seven deaths were considered cardiac, and in two cases the cause of death was unknown.

Ventricular arrhythmias and cardiac markers

All patients underwent their scheduled follow-up examination. At 2-year follow-up, 86 ventricular arrhythmias were treated by the ICD in 20 patients (20%), with ATP in 51, ATP followed by shock in 10, and shocks alone in 25 cases. The median number of treated ventricular arrhythmias per patient was two, with a median inter-event interval of 3 days. For subsequent episodes, the number of patients with inter-event interval >30 days is low (n = 6). Based on this low number, analysis is performed only to first occurrence of ventricular arrhythmia. The median time to first appropriate ICD therapy was 181 days (IQR 52 – 345 days). The mean cycle length of the ventricular tachyarrhythmia was 302 ± 61 ms, with cycle length <350 ms in 79% of patients.

Table 1 presents the baseline characteristics of patients with and without appropriate ICD therapy. No differences were observed between the two groups with regard to age, gender, LVEF, New York Heart Association (NYHA) class, indication for ICD therapy, underlying cardiac disease, pharmacological treatment, or to the presence of diabetes mellitus and renal failure. Previously documented atrial fibrillation was more prevalent among patients with appropriate ICD therapy compared with those without (65% vs. 19%,

P < 0.001). The baseline serum level of BNP for patients with and without appropriate ICD therapy is presented in Figure 1. No significant difference in median serum level of BNP was observed between patients with and without appropriate ICD therapy (190.0 vs. 125.0 pg/mL; *P* = 0.26). This finding was confirmed by ROC analysis to determine the diagnostic power of baseline BNP and appropriate ICD therapy (area under the curve = 0.58 [95% CI, 0.45 – 0.71]). In Figure 2, the baseline serum levels of hs-CRP for patients with and without appropriate ICD therapy are presented. Median serum level of hs-CRP was significantly higher in patients who received appropriate ICD therapy than in those without appropriate ICD therapy (5.33 vs. 2.19 mg/ L; *P* = 0.002). A baseline serum level of hs-CRP >3 mg/L was recorded in 49% of patients (median 5.80 mg/L, IQR 4.06 – 9.07 mg/L). Appropriate ICD therapy occurred in 33% of patients with hs-CRP >3 mg/L versus 8% of patients with hs-CRP ≤3 mg/L (*P* = 0.002). In 80% of patients receiving appropriate ICD therapy, baseline serum level of hs-CRP was >3 mg/L (median 6.58 mg/L, IQR 4.21 – 8.01 mg/L). We performed ROC analysis to determine sensitivity and specificity of hs-CRP (Figure 3). The area under the curve was 0.73 (95% CI, 0.62 – 0.84). The cut-off level of 3 mg/L for hs-CRP was found to be 80% sensitive and 59% specific with a negative predictive value of 92% for the prediction of ventricular arrhythmias triggering device therapy.

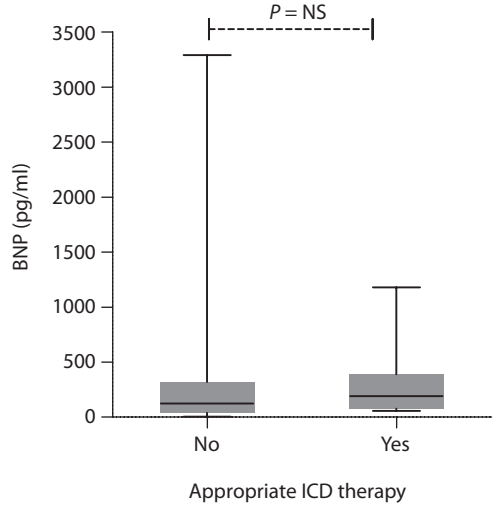

Figure 1. Baseline serum levels of BNP (pg/mL) for patients with appropriate ICD therapy and patients without appropriate ICD therapy.

The error bars extend down to the minimum value and up to the maximum value. The box extends from the 25th percentile to 75th percentile, with a black box at the median (50th percentile).

Abbreviations: BNP = brain-natriuretic peptide; ICD = implantable cardioverter-defibrillator; NS = not significant.

Table 1. Baseline clinical characteristics of patients who did and did not receive appropriate ICD therapy.

Variable	ICD therapy (n=20)	No ICD therapy (n=80)	*P*-Value
Age, yrs	64 ± 10	58 ± 14	0.10
Male gender	15 (75%)	64 (80%)	0.76
Ejection fraction, %	25 ± 9	28 ± 13	0.44
QRS duration, ms	133 ± 28	129 ± 34	0.59
NYHA class I – II	16 (80%)	62 (78%)	0.99
Primary prevention indication ICD therapy	11 (55%)	49 (61%)	0.62
Underlying cardiac disease			
Coronary artery disease	13 (63%)	49 (61%)	0.80
Myocardial infarction	12 (60%)	38 (48%)	0.45
Dilated cardiomyopathy	5 (25%)	18 (23%)	0.78
History of atrial fibrillation	13 (65%)	15 (19%)	< 0.001
Diabetes mellitus	3 (15%)	15 (19%)	0.99
Renal failure	8 (40%)	17 (22%)	0.15
Cardiac medication			
Amiodarone	5 (25%)	13 (17%)	0.35
Betablockade	16 (80%)	59 (75%)	0.77
Digoxin	4 (20%)	10 (13%)	0.47
ACE/ARB	15 (75%)	56 (71%)	0.79
Diuretic	12 (60%)	45 (57%)	0.99
Statin	12 (60%)	45 (57%)	0.99

Data are expressed as mean ± SD, or n (%), unless otherwise noted.
Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association.

In addition, we analyzed the serum levels of hs-CRP and BNP obtained at the scheduled follow-up visit prior to the ventricular arrhythmia triggering ICD therapy. For patients without ventricular arrhythmias, the serum levels of hs-CRP and BNP obtained at the last scheduled follow-up during study were used for comparison. Follow-up serum level of hs-CRP >3 mg/L was recorded in 95% of patients experiencing appropriate ICD therapy. The median serum level of hs-CRP was significantly higher in patients who had appropriate ICD therapy than in those who had no appropriate ICD therapy (5.43 mg/L vs. 2.61 mg/L, $P = 0.001$) (Figure 4A). The same was true for follow-up BNP (261.0 pg/mL vs. 80.1 pg/mL, $P = 0.01$) (Figure 4B). In Figure 5, the calculated areas under the curve by ROC analysis for hs-CRP and BNP during follow-up are presented. These calculated areas under the curve for hs-CRP and BNP were 0.75 (95% CI, 0.65 – 0.84) and 0.69 (95% CI, 0.58 – 0.79), respectively.

Comparison of these calculated area under the curves showed no statistical difference ($\chi^2 = 0.92$; $P = 0.34$).

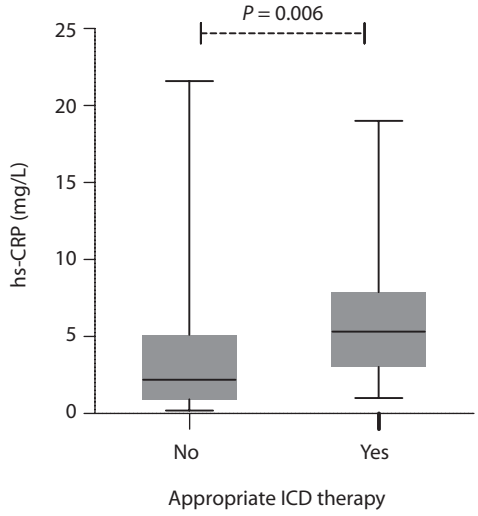

Figure 2. Baseline serum levels of hs-CRP (mg/L) for patients with appropriate ICD therapy and patients without appropriate ICD therapy.

The error bars extend down to the minimum value and up to the maximum value. The box extends from the 25th percentile to 75th percentile, with a black box at the median (50th percentile).
Abbreviations: hs-CRP = high sensitivity C-reactive protein; ICD = implantable cardioverter-defibrillator.

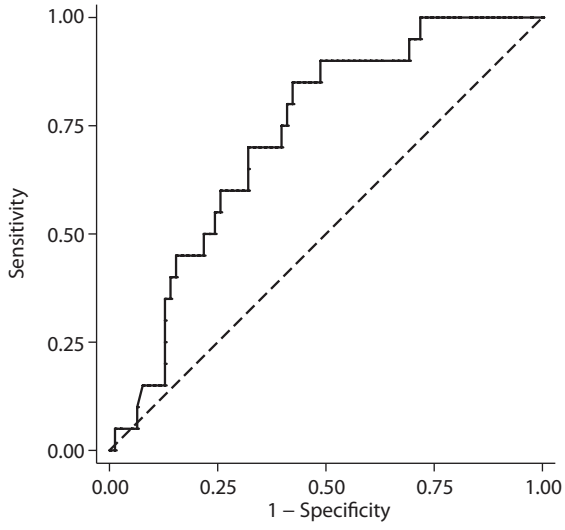

Figure 3. Receiver operating characteristic analysis representing the diagnostic power of hs-CRP (mg/L) for appropriate ICD therapy.

The diagnonal line represents the line of identity. Area under the curve = 0.73.

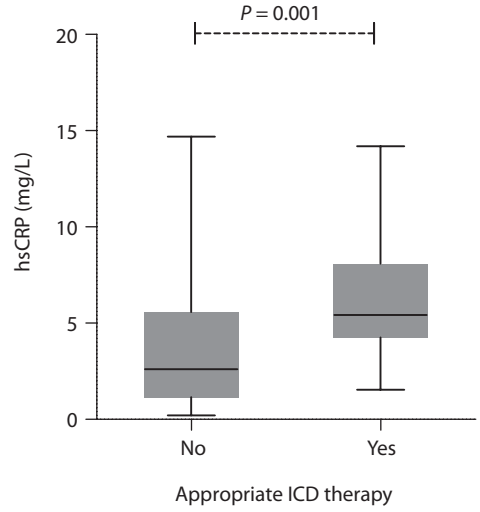

Figure 4A. Follow-up serum levels of hs-CRP for patients with appropriate ICD therapy and patients without appropriate ICD therapy.

The error bars extend down to the minimum value and up to the maximum value. The box extends from the 25th percentile to 75th percentile, with a black box at the median (50th percentile).
Abbreviations: hs-CRP = high sensitivity C-reactive protein; ICD = implantable cardioverter-defibrillator.

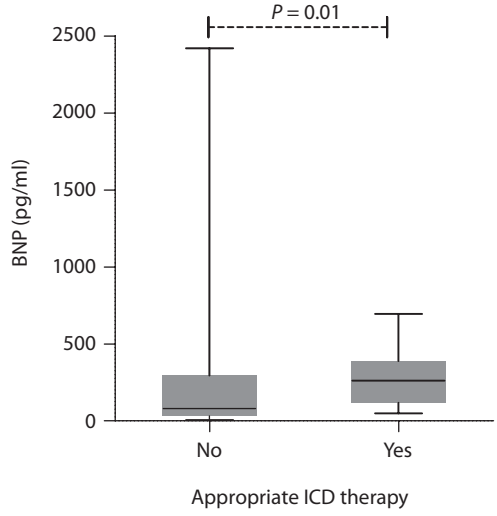

Figure 4B. Follow-up serum levels of BNP for patients with appropriate ICD therapy and patients without appropriate ICD therapy.

The error bars extend down to the minimum value and up to the maximum value. The box extends from the 25th percentile to 75th percentile, with a black box at the median (50th percentile).

Abbreviations: BNP = brain natriuretic peptide; ICD = implantable cardioverter-defibrillator.

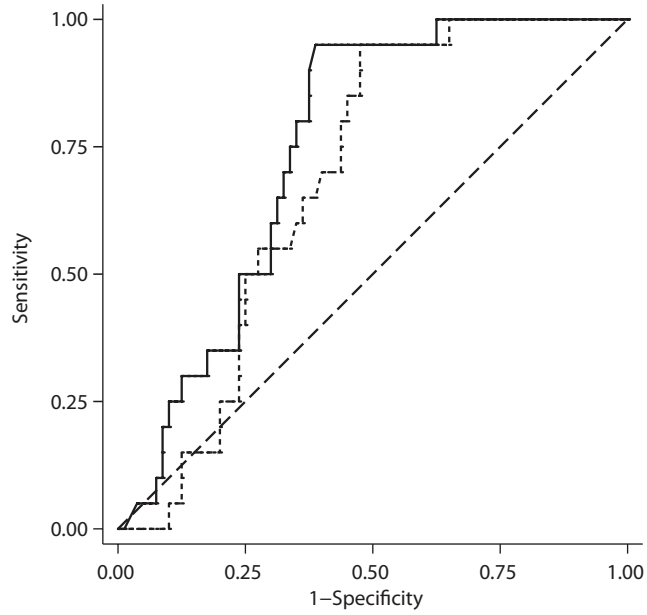

Figure 5. Receiver operating characteristic analysis representing the diagnostic power of follow-up serum levels of hs-CRP (mg/L) and BNP (pg/mL) for appropriate ICD therapy.
Area under the curve: 0.69 for BNP (dashed line), and 0.75 for hs-CRP (solid line).

Multiple logistic regression analysis was performed to determine independent predictors for appropriate ICD therapy. Next to baseline hs-CRP >3 mg/L and documented AF that were univariately significant, the prespecified variables age and indication for ICD therapy were entered into the model. The results indicate that a serum level of hs-CRP >3 mg/L obtained at baseline (OR = 4.0, 95% CI, 1.1 – 14.2; $P = 0.03$) and documented AF (OR = 5.7, 95% CI, 1.8 – 18.1; $P = 0.003$) are independently associated with ventricular arrhythmias triggering appropriate ICD therapy.

DISCUSSION

In this prospective cohort study of ICD recipients, a baseline serum level of hs-CRP >3 mg/L was positively associated with the occurrence of ventricular arrhythmias triggering appropriate ICD therapy. This relationship was consistent during follow-up, as serum level of hs-CRP remained elevated in patients who received appropriate ICD therapy. In contrast, baseline level of BNP was not significantly associated with the occurrence of ventricular

arrhythmias. However, elevation of BNP during follow-up was significantly associated with the delivery of appropriate ICD therapy.

Previous studies have examined risk factors that predict appropriate ICD therapy. Traditional clinical risk factors include low LVEF, higher NYHA functional class, atrial fibrillation, lack of β-blocker use, and secondary prevention indication.[17-22] Despite the fact that each of these factors may have some predictive accuracy, it is still not clear how the identification of patients could be optimized. During the last years, serum levels of biomarkers have emerged as a feasible method to identify patients at high risk for various cardiac events. An association between serum biomarkers and ventricular tachyarrhythmias may be helpful to identify patients at high risk developing arrhythmias. There is cumulating evidence that elevated serum levels of inflammatory markers are associated with the genesis and perpetuation of atrial fibrillation.[11,12,23-25] However, little is known about the association of inflammation and the occurrence of ventricular tachyarrhythmias. Elevation of inflammatory markers has been associated with sudden cardiac death in patients with heart failure,[26,27] with coronary artery disease,[28] and even in apparently healthy men.[29] Some studies failed to demonstrate an association between inflammatory markers and ventricular tachyarrhythmias.[30,31] Other studies have indicated that elevated serum levels of inflammatory markers at baseline are associated with the occurrence with ventricular tachyarrhythmias.[32-34] Biasucci et al. observed an association between CRP levels >3 mg/L and ventricular arrhythmias in ICD patients who had active ischemia.[32] Ventricular arrhythmias occurred in 48% of patients with CRP >3 mg/L versus 11% of those with CRP ≤3 mg/L. In our study, we observed a similar association between hs-CRP levels >3 mg/L and the occurrence of ventricular tachyarrrhythmias in a nonselected study cohort of ICD recipients (33% vs. 8%). Moreover, serum level of hs-CRP was persistently elevated in patients who received appropriate ICD therapy during follow-up. What are possible explanations of the association between inflammation and ventricular tachyarrhythmias? C-reactive protein levels have been consistently associated with atherosclerosis.[8,10,29,35] Apart from the clear evidence in atherosclerosis, inflammation also plays a role in the pathophysiology of heart failure progression.[36,37] The study by Albert et al. reported that in cases without acute ischemia as evidence of sudden death, isolated areas of myocardial fibrosis and inflammation were found.[29] These areas constitute an ideal substrate for reentry predisposing an individual to sudden cardiac death. The use of statins was associated with a reduced risk of cardiac death and with a reduction in ventricular tachyarrhythmias.[38-40] The findings of these studies suggest that the antiarrhythmic properties of statins are possibly also attributed to their anti-inflammatory properties.

Recent published studies demonstrated an association between baseline BNP levels and appropriate ICD therapy in patients with chronic heart failure and different types of cardiomyopathy.[30,33,41,42] However, we only found an association between elevated BNP levels during follow-up and appropriate ICD therapy, which must not be confused with

causality. Brain natriuretic peptide is largely released in the ventricles as response to increases in intraventricular pressure and myocardial stretch. These increases in pressure and myocardial stretch may lead to enhanced arrhythmogenesis.[43,44] Monitoring of BNP levels during follow-up can help to identify which patient has an increased likelihood to receive appropriate ICD therapy.

Limitations

Several limitations of the present study warrant consideration. First, our cohort consisted of a limited number of patients and a relatively low ventricular tachycardia occurrence rate. In addition, our study population was heterogeneous as this prospective study was planned to be a pilot study. Therefore, a larger prospective study in a homogeneous study population is needed to confirm the results of this study. A possible homogenous study population consists of patients with ischemic heart disease and a primary prevention indication for ICD therapy, investigating serial measurements of pro-inflammatory cytokines (interleukin-6 and tumor necrosis factor-alpha), and hs-CRP. Second, hs-CRP is a sensitive but nonspecific marker for cardiovascular disease. However, the fact that a serum level of hs-CRP >3 mg/L obtained at baseline proved to be an independent predictor of appropriate ICD therapy seems to imply that hs-CRP has a potential role for risk stratifying. This fact is underlined as patients with appropriate ICD therapy had serum levels of hs-CRP >3 mg/L during follow-up.

Conclusion

Elevated pre-implantation hs-CRP serum level is independently associated with increased risk for appropriate ICD therapy. Monitoring for elevated BNP levels during follow-up add to the assessment of risk for appropriate ICD therapy. The utility of serum biomarkers in identifying patients who might benefit the most from ICD therapy needs further exploration.

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CHAPTER 9

SURVIVORS OF VENTRICULAR FIBRILLATION HAVE PERSISTENT CARDIOVASCULAR RISK FACTORS LATE IN FOLLOW-UP

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ABSTRACT

Objective: Implantable cardioverter-defibrillators (ICD's) prevent arrhythmic death, but do not modify disease progression. The prevalence of persistent cardiovascular risk factors in patients receiving an ICD and their adherence to optimal pharmacological therapy at late follow-up is unknown. The aim of this study was to assess the prevalence of cardiovascular and specific sudden cardiac arrest (SCA) risk factors, and the pharmacological treatment in ICD recipients who survived SCA caused by ventricular fibrillation (VF).

Design: Cross-sectional study. A total of 100 consecutive ICD patients who survived SCA due to documented VF, not due to a transient or reversible cause or an arrhythmogenic disease, were interviewed and examined at the routine outpatient clinic.

Results: The mean age of the patients was 60 ± 11 years, and they were analyzed at a median interval of 1092 days after SCA. The majority of patients had coronary artery disease. The New York Heart Association class at the time of implantation was ≥II in 62%. A single chamber device was used in 49% and a resynchronization device in 12%. At the routine control, the most prevalent risk factors were overweight or obesity (63%), hypertension (41%), and smoking (16%). Pharmacological therapy was suboptimal in 18 – 32% of the patients. Eight percent of the patients had known diabetes and 29% had elevated HbA1c levels. While only 7% had pre-existing overt heart failure, 43% had N-terminal pro-brain natriuretic peptide levels ≥100 pmol/l. High sensitivity C-reactive protein was ≥3 mg/l in 52% of the patients. Family history was positive for sudden cardiac death (SCD) in 46% of the patients.

Conclusions: Despite regular medical consultation, a large proportion of patients had persistent cardiovascular risk factors and was often suboptimally treated. Unexpectedly, latent heart failure and unrecognized diabetes are observed in a large proportion of patients, as well as elevated inflammatory markers. Genetic analysis may be rewarding, as 46% of patients had a family history of SCD. Full medical attention, optimizing drug therapy, and counseling of these patients is necessary.

INTRODUCTION

Sudden cardiac death (SCD) is a major health problem, with incidence rates up to 1/1000 inhabitants per year.[1] SCD is mostly due to ventricular tachyarrhythmias as ventricular fibrillation (VF) and subsequent hemodynamic collapse, on a background of coronary artery disease (CAD), or heart failure, with or without cardiomyopathy, and seldom primary electrical disease.[2-5] Population studies have shown that risk factors for SCD are mainly the same as those for atherosclerotic CAD.[6-9] Therefore, it is likely that cardiovascular risk factors contribute to a large extent to the risk of recurrent arrhythmia and death in patients who survive sudden cardiac arrest (SCA). Despite the effectiveness of the implantable cardioverter-defibrillator (ICD) in terminating VF, mortality in ICD recipients remains high.[10] ICD therapy may shift the cause of death towards non-arrhythmic death, giving rise to concerns about the cost-efficacy of these expensive devices.[11] Therefore, optimal pharmacological therapy including statins, beta-blockers, and angiotensin-converting enzyme inhibitors must be an integral part of the clinical management of these patients. New biomarkers associated with heart failure and chronic inflammation may help to guide this therapy.[12,13]

Surprisingly, the prevalence of risk factors in survivors of SCA is unknown.[14] Therefore, the aim of this study was to analyze the prevalence of classical clinical cardiovascular risk factors for SCD in a population of SCA survivors, who all had documented VF at the index event, during late follow-up.

METHODS

Study population

The study population consisted of 100 consecutive survivors of SCA who received an ICD in the Erasmus MC between June 1998 and December 2008. The selection process is shown in Figure 1. The goal was to collect a homogeneous group with a substrate for VF. In 283/672 patients, VF was the documented arrhythmia related to SCA. Patients with VF due to a transient or reversible cause (acute myocardial infarction (MI), electrolyte disturbances, or cardiac surgery less than 1 week before the SCA) were excluded.

Additionally, patients with congenital or acquired long QT syndrome, the Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy, and patients who experienced SCA after exacerbation of heart failure or with documented ventricular tachycardia degenerating to VF were not taken into account. Only 107/283 patients remained eligible for inclusion. Seven patients refused or were not able to participate. All patients at the ICD clinic were also followed and treated by their referring cardiologist, within the Erasmus MC or elsewhere.

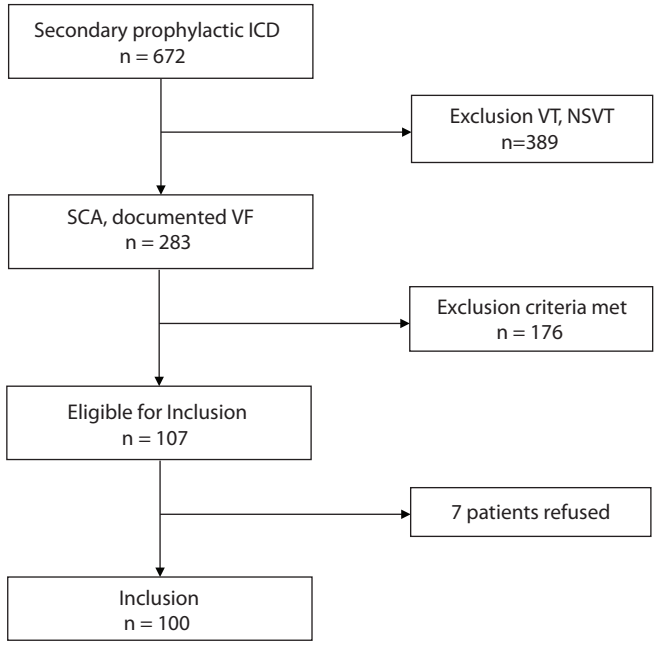

Figure 1. Selection process of the included patients.

Abbreviations: ICD = implantable cardioverter-defibrillator; NSVT = non-sustained ventricular tachycardia; SCA = sudden cardiac arrest; VF = ventricular fibrillation; VT = ventricular tachycardia.

Data collection

All patients gave written informed consent. The local ethics committee approved this study. Data collection covered age, gender, CAD, and MI history at time of ICD implantation. Coronary artery disease had to be documented either clinically by MI history, if coronary artery bypass grafting (CABG) or a percutaneous coronary intervention had been performed, or if significant coronary stenosis was documented. The clinical context of SCA, the functional status, and the renal function was assessed by reviewing the medical files. The renal function was assessed by estimating the baseline glomerular filtration rate (eGFR) with the abbreviated Modification of Diet in Renal Disease (MDRD) formula. Impaired renal function was defined as an eGFR <60ml / min / 1.73 m^2. All patients were interviewed during a routine technical follow-up visit between May 2007 and March 2009 at the outpatient clinic by a trained research assistant, using a standardized form. The interview assessed the presence of a history of hypertension, hypercholesterolemia, and diabetes mellitus and of a positive family history of SCD. Family history included data on the prevalence of SCD among parents and siblings, defined as acute death within 1 hour of onset of symptoms in persons younger than 80 years. Data on successfully resuscitated SCA among parents and siblings

and on SCA and SCD in second-degree relatives were collected. Smoking and alcohol habits were recorded, and height, weight, hip and waist circumferences, and blood pressure measured. Overweight was defined as body mass index (BMI) ≥25kg/m2 and obesity as BMI ≥30 kg/m^2.

Laboratory measurements

Non-fasting venous blood samples were drawn for routine measurements and glycosylated hemoglobin (HbA1c) and N-terminal pro-brain natriuretic peptide (NT-pro-BNP). A central laboratory performed biochemical and hematological analyses. Glucose levels were measured using hexokinase on a P-modular (Roche), glycosylated hemoglobin levels by high performance liquid chromatography and colorimetry on a HA-8160 analyser (Menarini). NT-pro-BNP levels were measured using an electrochemilumiscence immunoassay on an Elecsys 2010 analyser (Roche). High-sensitivity C-reactive protein (hs-CRP) levels were measured by nephelometry using an Immage 800 (Beckman Coulter). Values out of normal range were: glucose ≥11 mmol/L, HbA1c ≥6%, hs-CRP ≥3 mg/l, NT-pro-BNP ≥100 pg/ml, cholesterol ≥6.5 mmol/L, high-density lipoprotein (HDL) cholesterol ≤1.55 mmol/L, low-density lipoprotein (LDL) cholesterol ≥4.12 mmol/L, and cholesterol/HDL ratio ≥4.0.

Data analysis

Continuous variables are expressed as the mean ± standard deviation (SD) if normally distributed, or otherwise as the median and interquartile range (IQR). Categorical variables are expressed as frequency (percentage). All statistical analyses were performed with SPSS for Windows (release 17.0, SPSS, Chicago, Illinois, USA).

RESULTS

Study cohort

Table 1 presents baseline characteristics of the population. The majority of patients was male (77%) and had CAD (69%). The left ventricular ejection fraction (LVEF) was ≤35% in 39 of 67 (58%) of patients with the LVEF determined in our hospital. New York Heart Association functional class was missing in five patients, and was class I in 38%. QRS duration was ≥120ms in 40 patients and ≥150ms in 18 patients. A resynchronizing ICD was given to 12 patients, all with QRS duration ≥140ms. Serum creatinine was 98 ± 44 mmol / dl; the mean eGFR was 77 ± 24 ml / min / 1.73 m2. Renal failure was present in 25% of patients.

Table 1. Characteristics of the cohort at time of ICD implantation.

Characteristic	n = 100
Age (years)	60 ± 11
Male gender (n, %)	77 (77%)
Prior manifest heart failure (n, %)	7 (7%)
Documented VF (n, %)	100 (100%)
Chest pain preceding SCA (n, %)	46 (46%)
NYHA class	
NYHA I	36 (38%)
NYHA II	53 (56%)
NYHA III	6 (6%)
NYHA IV	0 (0%)
LVEF (%)	36 ± 15
QRS duration (ms)	117 ± 28
Ischemic heart disease (n, %)	
Coronary artery disease	69 (69%)
Prior myocardial infarction	59 (59%)
Prior CABG	20 (20%)
Non-ischemic dilated cardiomyopathy (n, %)	12 (12%)
Renal failure	25 (25%)
Implanted devices (n, %)	
Single chamber	49 (49%)
Dual chamber	39 (39%)
Resynchronization	12 (12%)

Data are presented as mean ± SD or total number (%). Abbreviations: CABG = coronary artery bypass grafting; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; SCA = sudden cardiac arrest; VF = ventricular fibrillation.

Follow-up

During follow up, 13 patients received at least one appropriate shock as primary therapy for ventricular arrhythmias (mean cycle length 216 ± 36 ms). The first occurred at a median interval of 299 days (IQR 73 – 1015) after ICD implantation.

Risk factors as assessed at follow-up

The interview at the time of routine technical control took place at a median interval of 1092 days (IQR 584 – 1982 days) after the index SCA. In Table 2, the prevalence of cardiovascular risk factors is presented: 41% of patients reported hypertension treatment, 8% diabetes mellitus, and 47% hypercholesterolemia. While 67% had quitted smoking, 16% continued, and 22% consumed ≥2 alcoholic units/day. A positive family history for SCD in first-degree

relatives (i.e. parents, siblings, and children) was present in 31%, and for SCD in first-or second-degree relatives in 46% of patients. Physical examination showed a systolic blood pressure ≥140mmHg in 29%, and a diastolic blood pressure ≥90 mmHg in 13%, and 31% had hypertension. BMI was <25kg/m^2 in 37%, between 25 and 29kg/m^2 (overweight) in 45% of patients, and ≥30 kg/m^2 (obesity) in 18%. Waist circumference was ≥102 cm in 44% of men and ≥88 cm in 61% of women.

Table 2. Risk factors as assessed at follow-up visit.

Risk factor	n = 100
History of hypertension	41 (41%)
History of diabetes	8 (8%)
History of hypercholesterolemia	47 (47%)
Overweight*	45 (45%)
Obesity*	18 (18%)
Smoking	
Past	67 (67%)
Current	16 (16%)
Alcohol consumption	
No	38 (38%)
<2 units/day	40 (40%)
2-4 units/day	22 (22%)
>4 units/day	0 (0%)
Family history of SCD	
Positive in 1st degree	31 (31%)
Positive in 1st or 2nd degree	46 (46%)

Of note * overweight is defined as as BMI≥25 kg/m2, obesity as BMI≥30 kg/m2. Abbreviations: SCD = sudden cardiac death.

Pharmacological treatment as assessed at follow-up

The proportion of patients not receiving optimal pharmacological therapy at follow-up visit is presented in Figure 2: 82% used beta-blockers, 69% statins, and 47% at least one diuretic. Of all diuretic users, 39% had potassium sparing diuretics, and 40% loop diuretics. Fifty-two per cent of patients used angiotensin-converting enzyme (ACE) inhibiting drugs and 18% angiotensin-2 receptor blockers, giving a total of 68% taking an angiotensin-2 receptor blocker and/or an ACE inhibitor. Aspirin was taken by 45% of the patients and oral anticoagulants by 39%. Twenty per cent of the patients used nitrates, 10% calcium antagonists, 11% digitalis, and 12% amiodarone.

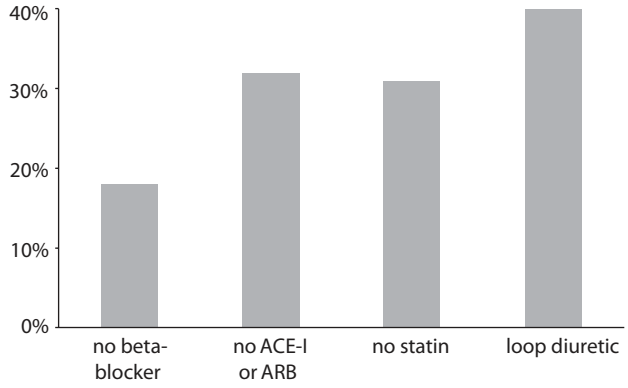

Figure 2. Percentages of patients not receiving recommended drug therapy or loop diuretics rather than potassium-sparing or thiazide diuretics.

Abbreviations: ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

Biochemical and hematological measurements at follow-up

Glucose levels were 5.7 ± 1.9 mmol/L, and HbA1c was 5.9 ± 0.9%. Hs-CRP was not normally distributed (median 4.72 mg/l, IQR 1.59 – 5.38). The median NT-pro-BNP level was 58.3 pg/ml (IQR 16.7 – 209.8). Total cholesterol (TC) was 4.50 ± 0.93 mmol/L, HDL cholesterol 1.18 ± 0.34 mmol/L, and LDL cholesterol 2.70 ± 0.84 mmol/L. The TC/HDL cholesterol ratio was 4.1 ± 1.4. The proportions of patients showing abnormal biochemical values at follow up are presented in Figure 3. A high proportion had an abnormal HbA1c (29%). High-sensitivity CRP, NT-pro-BNP, HDL, and TC/HDL ratio were abnormal in more than 33% of patients.

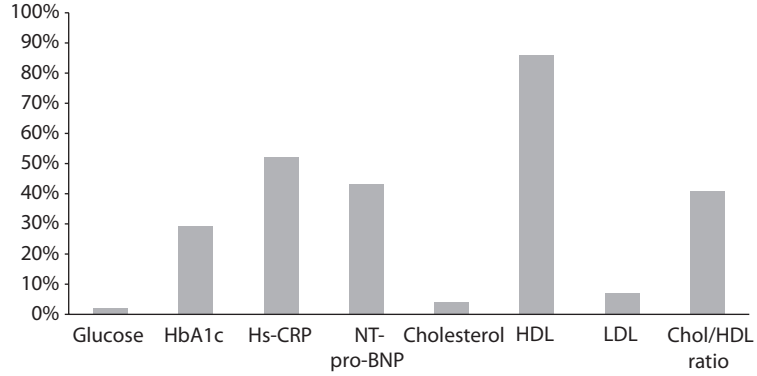

Figure 3. Percentages of patients with laboratory results outside normal range.

Abbreviations: HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; NT-pro-BNP = N-terminal pro-brain natriuretic peptide.

DISCUSSION

This cross-sectional study evaluated the prevalence of cardiovascular risk factors in survivors of SCA with documented VF, during routine follow-up at the ICD outpatient clinic after a median of three years. The results of our study show that the burden of conventional cardiovascular risk factors and the prevalence of markers of increased cardiovascular risk remain high.

General risk factors

In spite of regular medical consultation, treatment, and advice by both the general practitioner and the cardiologist, 63% of the patients were overweight or obese and one-third had a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90mmHg. Obesity is an important cause of the development of hyperglycaemia, dyslipidaemia, and hypertension, all of which promote further atherosclerotic coronary disease and therefore may increase the SCD risk. Hypertension, apart from its well-known role in CAD, seems to play a disproportionate role in increasing the risk of SCD.[15,16]

Smoking was continued by 16% of patients. Population studies showed that this is an independent risk factor for SCD.[7,9] Even more, persistent smoking is associated with a significantly higher risk of recurrent arrhythmias in ICD patients with CAD.[17]

Pharmacological treatment

The need for optimal pharmacological therapy in CAD with beta-blockers, diuretics, statins, ACE inhibitors, and aspirin is established. In our population, 82% used beta-blockers. Subanalysis of the AVID trial showed that beta-blocker use was independently associated with improved survival after symptomatic ventricular tachycardia or VF when not treated with an ICD.[18] Although this protective effect was less prominent in patients who were treated with an ICD, it is likely that beta-blockers are beneficial for SCA survivors, especially when we observe that the vast majority of these patients suffer from CAD. Statins are primarily used for lowering cholesterol, but are also known to reduce the incidence of arrhythmias, also because of the anti-inflammatory effect.[19,20] The guidelines recommend statin therapy as recommendation class I level of evidence A in all patients with CAD.[14] In this study, 87% of all CAD patients used a statin. Few patients received potassium-sparing diuretics, while loop diuretics which are known to be pro-arrhythmic, were used by 40%.[21] The fact that guidelines are not always followed and that patients are often not compliant to the prescribed therapy was documented in previous studies in the general population.[22]

Heart failure

Advanced heart failure predicts mortality after ICD implantation.[23] Therefore, it seems important to detect heart failure at an early stage. The present study revealed elevated

NT-pro-BNP levels in 43%, whereas only 7% of the patients had a prior episode of overt heart failure. This suggests latent heart failure in almost half of the patients. Data from the Framingham Heart Study showed a significant, multivariable-adjusted hazard ratio of 1.62 for death and 1.76 for major cardiovascular events at NT-pro-BNP levels much lower than those conventionally used for the diagnosis of heart failure.[12] If we apply the cut-off values as used in this study, the proportion of patients with high risk, based on the raised NT-pro-BNP levels becomes 69%. Optimal ACE inhibition is one of the cornerstones in heart failure treatment. ACE inhibitors and angiotensin receptor blockers are proven to slow disease progression and therefore prevent arrhythmias, also at the atrial level.[24] The present study shows that only 68% of the study population received an ACE inhibitor or angiotensin receptor blocker.

Diabetes

We observed elevated HbA1c levels in 29% of patients, whereas only 8% reported to have diabetes. This suggests the presence of unrecognized diabetes in a large proportion. Diabetes is a risk factor for additional mortality due to progression of heart failure and neurological dysfunction. Diabetes is one of the variables predicting a high mortality in patients after ICD implantation.[23] It is associated with reduced heart rate variability, which predicts cardiac death.[25,26] Aggressive screening and early therapy can limit the effects. Prevention of overweight and obesity is a first step in this process.

Inflammation

Persistent inflammation as measured by CRP has been proposed as a risk factor for a variety of cardiovascular diseases, including SCD.[13] Recent studies indicated that CRP is also predictive for arrhythmias and shocks in ICD recipients.[27,28] Probably, the level of inflammation is an intermediate representing the status of disease progression. A large-scale study showed that CRP levels >3mg/l are indicating high cardiovascular risk.[29] In our study we observed such levels, measured with a high sensitive assay in 52% of the patients. In our opinion, this finding can only support the importance of early and intensive treatment of SCA survivors.

Familial history

A family history of SCD, either with MI or isolated, carries an increased risk for SCA, independently of traditional risk factors that can aggregate in families.[8,30] It was reported that the risk of primary VF in acute MI patients is increased if family history for SCD was positive.[31] In a large cohort, a prevalence of SCD in first degree relatives of 11% was detected in the control group, versus 19% in SCD cases.[8] Therefore, the high familial incidence of SCA of 31% in first-degree relatives in our group of SCA survivors due to documented VF is a surprise and suggests that further genetic analysis of this population may be rewarding.

Conclusion

SCA survivors, irrespective of a background of CAD, require full attention and optimal pharmacological treatment. The high prevalence of persistent cardiovascular risk factors at late follow up emphasizes the need for specialized care of these patients. Continued medical attention and counseling seems to be necessary and cannot be substituted by technical control alone or remote monitoring.[31] This could be provided in cardiac rehabilitation centres or by heart failure facilities or heart failure nurses. Heart failure should be detected early. Patients should be screened for diabetes, advice concerning smoking and obesity should be given, and pharmacological therapy should be optimized. Also, genetic research is needed to analyze the complex hereditary pattern of this disease entity.

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CHAPTER 10

SUMMARY

SUMMARY

The primary aim of this thesis was to study the effectiveness, the cost, and the cost-effectiveness of primary prevention implantable defibrillator therapy in patients with ischemic or non-ischemic heart disease in Europe. Secondly, we aimed to study the utility of new risk indicators and risk prediction and stratification models in ICD patients.

Chapter 1 gives an overview of the current knowledge on the epidemiology, the etiology, and the preventive therapy of sudden cardiac death. Also, the concept of cost-effectiveness analysis is introduced in this chapter.

Chapter 2 describes a meta-analysis of randomized controlled trials evaluating the effectiveness of ICD therapy in reducing all-cause mortality in patients with ischemic or non-ischemic heart disease. In this pooled analysis of eight trials, we demonstrated that ICD therapy (without cardiac resynchronization therapy) reduces the relative risk of all-cause mortality with 27%. We observed no statistical difference between the effectiveness of ICD therapy (without cardiac resynchronization therapy) between patients with ischemic and non-ischemic heart disease.

Chapter 3 describes a cohort study of primary prevention ICD patients, with complete long-term follow-up on mortality and ICD interventions. We demonstrated that the observed mortality and the incidence of ICD interventions were not significantly different between patients with ischemic and non-ischemic heart disease. Also, we performed multivariate regression analysis to identify predictors of mortality in these patients. Patients with advanced age and patients with heart failure symptoms in New York Heart Association (NYHA) class III to IV showed to have an increased risk of early mortality.

Chapter 4 describes a multicenter cohort study of ICD patients in two different academic medical centers. The objectives of this study were to study differences in mortality and in the incidence of ICD interventions between patients from two tertiary academic hospitals, and to estimate the incidence of hospitalizations and unscheduled consultations after ICD implantation for primary prevention. We showed that the mortality and the incidence of hospitalizations were comparable between patients from the two centers. Differences were observed in the incidence of appropriate ICD interventions. Further, it became clear that primary prevention ICD patients place a large burden on healthcare resources after the initial ICD implantation; frequent hospitalizations and outpatient clinic visits were registered. This may have important consequences for the cost-effectiveness of the therapy.

Chapter 5 describes a model-based cost-effectiveness analysis of primary prophylactic ICD therapy in the European healthcare setting. We used the evidence obtained in Chapters 2, 3, and 4 as input data to the decision model. Literature data was used to estimate the frequency of rare complications and quality-of-life after ICD implantation. This study demonstrated that primary preventive ICD therapy in Europe is cost-effective if applied according to the international guidelines. We performed extensive sensitivity analyses to investigate the uncertainty.

We studied the performance of the Seattle Heart Failure Model in ICD patients treated with cardiac resynchronization therapy (CRT-D) in **Chapter 6.** This model was developed in a pooled derivation dataset of several pharmacological heart failure trials and was validated and recalibrated in the Sudden Cardiac Death in Heart Failure trial (SCD-HeFT) dataset. It uses several clinically readily available parameters to obtain estimates on all-cause mortality. We demonstrated that the Seattle Heart Failure model has a good calibration for risk prediction in CRT-D. Also, the discriminative performance was excellent among CRT-D patients. This study adds to the current clinical knowledge and facilitates physicians with mortality estimates that can be used to inform patients about prognosis, and potentially to help guide treatment decisions.

In **Chapter 7**, the same population as in Chapter 6 was used to study the competing risks of appropriate ICD interventions on one hand, and of mortality without prior appropriate ICD interventions on the other hand. We showed that 62% of all patients who died, died without prior appropriate ICD interventions. This represents 12% of the total study population. The SHFM is showed to be able to identify patients at high risk of mortality without prior ICD interventions. Paradoxically, this subgroup of patients was also at highest risk of receiving appropriate ICD interventions.

Chapter 8 describes a prospective follow-up study of ICD patients in whom N-terminal pro-brain natriuretic peptide (NT-pro-BNP) and high-sensitivity C-reactive protein (hs-CRP) were measured serially. We demonstrated that the level of hs-CRP, which is a measure of systemic inflammatory status, is positively correlated with the incidence of appropriate ICD interventions. This study emphasizes the potential use of biomarkers for risk-stratification in ICD-patients.

Chapter 9 describes a cross-sectional study showing the persistence of both reversible and irreversible cardiovascular risk factors during late follow-up in ICD patients who survived cardiac arrest. This study underlines the need for specialized care of these patients.

SAMENVATTING

De onderzoeken die in dit proefschrift worden gepresenteerd, hebben als gemeenschappelijk doel de effectiviteit, de kosten, en de kosteneffectiviteit van implanteerbare defibrillatoren (ICD's) ter primaire preventie van plotse hartdood van patiënten met ischemische dan wel niet-ischemische hartziekten in Europa te onderzoeken. Een tweede doel was de waarde en de prestatie van nieuwe risico indicatoren en predictiemodellen voor vroege sterfte van ICD patiënten te onderzoeken.

In **Hoofdstuk 1** wordt een actueel overzicht van de epidemiologie en etiologie van plotse hartdood gegeven, en de preventieve maatregelen hiertegen. Tevens worden in dit hoofdstuk de beginselen van kosteneffectiviteitsonderzoek beschreven.

In **Hoofdstuk 2** wordt een meta-analyse gepresenteerd. In deze studie wordt de effectiviteit van ICD's ter preventie van plotse hartdood bestudeerd onder patiënten met een ischemische dan wel een niet-ischemische hartziekte. Implanteerbare defibrillatoren (zonder additionele re-synchronisatietherapie) blijken het relatieve risico op vroege sterfte met 27% te verlagen in deze patiëntengroep. Er werd geen statistisch significant verschil gevonden tussen in de effectiviteit van ICD's toegepast in patiënten met een ischemische hartziekte, in vergelijking met patiënten met een niet-ischemische hartziekte.

In **Hoofdstuk 3** wordt een cohort onderzoek van patiënten met een ICD ter primaire preventie van plotse hartdood gepresenteerd. Deze studie bestudeert de kans op vroege sterfte onder ICD patiënten met een ischemische hartziekte, vergeleken met patiënten met een niet-ischemische hartziekte; deze bleek niet verschillend. Daarnaast werd aangetoond dat de incidentie van ICD interventies niet verschillend was tussen deze twee groepen. Multivariate regressie analyse werd toegepast om predictoren van vroege dood in deze patiëntengroep te vinden; patiënten met een hoge leeftijd en patiënten met ernstige symptomen van hartfalen bleken een verhoogd risico op vroege mortaliteit te hebben.

In **Hoofdstuk 4** wordt een cohort onderzoek van ICD patiënten in twee verschillende academische medische centra gepresenteerd. Het doel van deze studie was de verschillen in mortaliteit en de incidentie van ICD interventies tussen de patiënten uit deze verschillende centra te onderzoeken. Het tweede doel was om de incidentie van ziekenhuisopnames en onverwachte polikliniekbezoeken te inventariseren. De sterfte en het voorkomen van ICD interventies bleek vergelijkbaar tussen de patiënten uit deze twee centra. Wel werd een verschil in de incidentie van terechte ICD interventies (i.e. interventies voor ventriculaire aritmieën) geobserveerd. Het werd duidelijk dat patiënten met een ICD ter primaire

preventie van plotse hartdood een significante zorgvraag hebben. Dit kan belangrijke consequenties voor de kosteneffectiviteit van deze vorm van therapie met zich meedragen.

In **Hoofdstuk 5** wordt een studie naar de kosteneffectiviteit van ICD's voor de primaire preventie van plotse hartdood in Europa beschreven. De informatie uit hoofdstuk 2, hoofdstuk 3 en hoofdstuk 4 werd gebruikt om een zogenaamd 'Markov model' te maken. Gegevens uit de literatuur werden gebruikt om de incidentie van zeldzame complicaties, en om een maat voor de kwaliteit van leven na ICD implantatie te bepalen. Deze studie toonde aan dat ICD therapie ter primaire preventie van plotse hartdood in Europa kosteneffectief is. Sensitiviteitsanalyse werd gebruikt om de onzekerheid rond de uitkomsten verder te exploreren.

In **Hoofdstuk 6** wordt een onderzoek naar de toepassing van het 'Seattle Heart Failure model' in ICD patiënten, die tevens behandeld worden met cardiale re-synchronisatietherapie, beschreven. Het 'Seattle Heart Failure model' is een predictiemodel dat ontwikkeld werd vanuit een samengevoegde database van meerdere studies naar de effectiviteit van verschillende farmacotherapeutische interventies bij hartfalen. Recentelijk werd dit model gevalideerd en gerecalibreerd voor toepassing in ICD patiënten, met behulp van de 'Sudden Cardiac Death in Heart Failure Trial' (SCD-HeFT) dataset. Het model bestaat uit verschillende, klinische parameters die gebruikt worden om een predictie van de kans op vroege sterfte te geven. In dit onderzoek werd de validiteit van het 'Seattle Heart Failure Model' aangetoond in de predictie van het risico op vroege sterfte van ICD patiënten die tevens worden behandeld met cardiale re-synchronisatietherapie (CRT-D). Het model blijkt goed te discrimineren tussen patiënten met een hoge kans op vroege mortaliteit, en patiënten met een lage kans hierop.

In **Hoofdstuk 7** werden de competitieve risico's van terechte ICD interventies enerzijds, en van sterfte zonder voorafgaande terechte ICD interventies anderzijds, bestudeerd. Hiervoor werd dezelfde studiegroep als in hoofdstuk 6 gebruikt. Daarnaast werd de waarde van het 'Seattle Heart Failure Model' voor de predictie van sterfte zonder voorafgaande terechte ICD interventies onderzocht. Tweeënzestig procent van alle patiënten bleek te sterven zonder voorafgaande terechte ICD interventie. Deze groep representeert 12% van de totale studiegroep. Het 'Seattle Heart Failure Model' bleek in staat om patiënten te identificeren met een hoge kans op sterfte zonder voorafgaande terechte ICD interventies

In **hoofdstuk 8** wordt een prospectieve cohort studie van ICD patiënten van wie zowel voor als na de ICD implantatie bepaling van serumspiegels van 'N-terminal pro-brain natriuretic peptide' (NT-pro-BNP) en 'high-sensitivitiy C-reactive protein' (hs-CRP) werd verricht, beschreven. De serumspiegel van hs-CRP bleek positief gecorreleerd met de incidentie

van terechte ICD interventies. Deze studie illustreert dat het mogelijk zinvol is om deze zogenaamde biomarkers te gebruiken voor risicostratificatie van ICD patiënten.

In **Hoofdstuk 9** wordt een cross-sectionele studie gepresenteerd, die aantoont dat zowel reversibele, als niet-reversibele risicofactoren onvoldoende behandeld blijven, ook lange tijd na de ICD implantatie. De resultaten van deze studie onderstrepen het belang van gespecialiseerde zorg voor deze patiëntencategorie.

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Tim Smith was born on September 30 1985 in Rotterdam. After finishing secondary school at the "Erasmiaans Gymnasium" in Rotterdam, he started medical school at the Erasmus University in 2004. In 2006, he enrolled in the Master of Science program in Clinical Research at the Netherlands Institute for Health Sciences (NIHES). In 2008, he attended the Summer Program at Harvard School of Public Health (Harvard University, Boston, Massachusetts). He wrote his master thesis under supervision of professor Luc Jordaens and professor Myriam Hunink. The research that he initiated during medical school formed the basis for this PhD thesis. In 2011, he graduated from the Master of Science program in Clinical Reseach, and also obtained his medical degree "cum laude" at Erasmus University, Rotterdam. The same year, he started a residency at the Cardiology department of the St. Antonius Hospital, Nieuwegein, the Netherlands (supervisor dr. J.M. Ten Berg). In 2012, he started as a resident in Cardio-Thoracic Surgery at the St. Antonius Hospital, Nieuwegein (supervisor dr. W.J. Morshuis).

LIST OF SCIENTIFIC PUBLICATIONS

T. Smith, L. Jordaens, D.A.M.J. Theuns, P.F. van Dessel, A.A. Wilde, M.G.M. Hunink. The cost-effectiveness of primary prophylactic implantable defibrillator therapy in patients with ischemic of non-ischemic heart disease: an European analysis. Eur Heart J 2012; May 14 (Epub ahead of print).

T. Smith, W.C. Levy, B.A. Schaer, A.H.M.M. Balk, C. Sticherling, L. Jordaens, D.A.M.J. Theuns. Performance of the Seattle Heart Failure Model in implantable defibrillator patients treated with cardiac resynchronization therapy. Am J Cardiol 2012; 110:398-402.

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M. Meine, **T. Smith**, R.N. Hauer. The economic challenge in the treatment of chronic heart failure: is primary prophylactic ICD implantation cost-effective in Europe? Europace 2009;11:689-691.

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