Improvements in Implantable Cardioverter Defibrillator patient stratification

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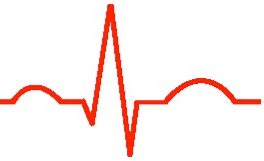
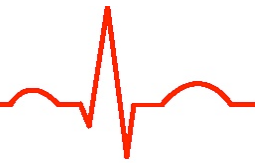


Chapter 1

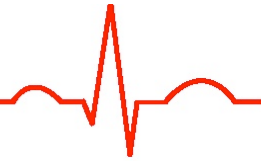
General introduction, aim and outline of the thesis



General introduction

Sudden cardiac death, mainly caused by ventricular arrhythmias (VA) in a population with coronary artery disease, is a major cause of mortality in the western world. In the United States alone, the annual incidence of sudden cardiac death varies from 200.000 to 450.000 of which most fatal events occur outside the hospital.[1] Since the prevention of these events has always been difficult, Mirowski and co-workers developed the implantable cardioverter defibrillator (ICD) and in 1980 the first ICD was implanted in a human.[2] Initially, the ICD was thought to be a treatment of last resort for the prevention of sudden cardiac death. Soon it became clear that, if it would be possible to identify patients at risk, it would be the treatment of choice for patients at high risk for life-threatening arrhythmias.[3] In 1984, 4 years after the first human implant, the first ICD was implanted in the Netherlands at the University Medical Centre Utrecht.

The first ICDs were large (8 cm x 11.5 cm, 170 cm^3) and heavy (280 g). These devices required open chest surgery and the device was implanted in the abdomen. Needless to say that these procedures were associated with a high rate of complications.[4] Algorithms for the detection of potentially life-threatening VA were limited and the occurrence of inappropriate device therapy was frequent.[5] At that time, ICD therapy was not generally accepted and considered unethical and even in-human by many. Despite the high failure rate of drug therapy, many physicians preferred treating their patients with antiarrhythmic drugs. Large secondary and primary prevention trials demonstrating the efficacy of ICD therapy were necessary to stimulate a wider use and to increase patient's acceptance. Furthermore, first generation devices were rather bulky and many improvements in size and weight, arrhythmia discrimination, battery technology, shock waveform and output, monitoring capabilities, and defibrillator electrode technology were necessary to allow the current large scale yearly implantations. However, the first human implants marked the start of a new way of treating patients at risk of dying suddenly. In other words, the era of ICD therapy had begun.



Major secondary and primary prevention trials

Initially, to be eligible for ICD treatment, patients had to survive at least one episode of life-threatening VA such as ventricular fibrillation (VF) or ventricular tachycardia (VT) (secondary prevention). In other words, all patients treated with ICD therapy were out of hospital cardiac arrest survivors. In the 1990s three large trials proved the effectiveness of ICD therapy for the secondary prevention of arrhythmic death: the Antiarrhythmics Versus Implantable Defibrillator study (AVID),[6] the Canadian Implantable Defibrillator Study (CIDS)[7] and the Cardiac Arrest Study Hamburg (CASH) (Table 1).[8] The AVID trial enrolled patients who had survived a cardiac arrest or with documented sustained VAs. Patients were randomized to either amiodarone therapy or ICD treatment and the primary endpoint was all-cause mortality. The results showed a reduction in all-cause mortality of 28% in the defibrillator group.[6] The CIDS trial had a similar design and showed a 20% reduction in mortality in the ICD group, compared with amiodarone treatment.[7] Finally, the CASH trial enrolled patients who survived an episode of cardiac arrest and randomized to either ICD therapy or antiarrhythmic drug therapy, showing a mortality reduction of 23% in the ICD group.[8] A meta-analysis of these three trials by Connolly et al., demonstrated a significant 28% reduction in all-cause mortality in the ICD treated group. The results of these studies led to the acceptance of ICD therapy for the secondary prevention of sudden arrhythmic death.[9] However, acceptance rate in Europe was much lower than in the United States.

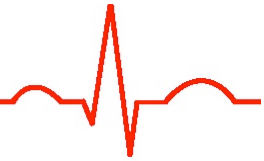
Since the survival rate of an episode of cardiac arrest is at best only 8%, the impact of secondary prevention ICD therapy on population mortality will be low.[10] Therefore focus shifted from secondary prevention to the identification of patients at risk of life-threatening VAs without a prior arrhythmic event. Large randomized trials tested the hypothesis that ICD treatment was beneficial in selected patients, prior to cardiac arrest or sustained VT (primary prevention) (Table 2). The first primary prevention trial was the Multicenter Automatic Defibrillator Implantation

Table 1. Clinical features and results of 3 major secondary prevention ICD trials

Trials	AVID[6]	CIDS[7]	CASH[8]
Sample size	1016	659	288
Design	ICD vs antiarrhythmic drugs	ICD vs amiodarone	ICD vs amiodarone vs metoprolol
Patients	Resuscitated from near-fatal VF or postcardioversion from sustained VT	Resuscitated VF or VT or with unmonitored syncope	Survivors of cardiac arrest secondary to documented ventricular arrhythmias
Follow-up (months)	18	36	57
Primary end point	All-cause mortality	All-cause mortality	All-cause mortality
Results			
Risk reduction with ICD	28% (P = .0.02)	20% (P = .14)	23% (P = .08)

AVID = Antiarrhythmics versus Implantable Defibrillators; CASH = Cardiac Arrest Study Hamburg; CIDS = Canadian Implantable Defibrillator Study; ICD = implantable cardioverter defibrillator; VF = ventricular fibrillation; VT = ventricular tachycardia.

Trial (MADIT). This study enrolled patients with a prior myocardial infarction, left ventricular ejection fraction (LVEF) less than 35%, documented nonsustained VT and inducible, non-suppressible VT on electrophysiological study. Patients were randomized to receive either amiodarone therapy or an ICD and, after the inclusion of 196 patients and with 27 months follow-up, the study demonstrated a 54% reduction in mortality in the ICD group.[11] Despite these findings, controversy about the study design remains. There was no registry of screened patients as in AVID, a high percentage discontinued taking amiodarone and the ICD treated population showed a disproportionately higher use of β-blockers. The prevailing consensus was that more data were needed to support the MADIT findings. Therefore, the results of this study were not adopted in the guidelines until the results of the Multicenter Unsustained Tachycardia Trial (MUSTT) were published.[12] MUSTT enrolled patients with coronary artery disease, LVEF less than 40%, documented nonsustained VT and inducible, non-suppressible VT on electrophysiological study and the survival rate was comparable with MADIT. Further analysis of the survival benefit in the MADIT showed that the highest benefit was observed in patients with



an LVEF of less than 26%.[13] These and other observations from the MADIT trial resulted in a simplified design and a new study. The MADIT II trial randomized patients with a history of myocardial infarction and an LVEF less than 30% to either ICD therapy or no ICD without the requirement of additional electrophysiological testing and reported a 31% reduction for mortality in patients treated with an ICD.[14] A meta-analysis of 10 primary prevention trials by Nanthakumar et al., demonstrated a significant 25% reduction in all-cause mortality in the ICD treated patients. Consequently, these findings led to the inclusion of primary prevention ICD treatment in the current guidelines (Table 3).

Table 2. Clinical features and results of 4 primary prevention ICD trials

Trials	MADIT[11]	MUSTT[12]	MADIT II[14]	SCD-HeFT[37]
Sample size	196	704	1232	2521
Design	ICD vs antiarrhythmic drugs as conventional therapy	EP-guided therapy vs placebo	ICD vs optimal pharmacologic therapy	ICD vs optimal pharmacologic therapy vs optimal pharmacologic therapy + amiodarone
Patients	Previous MI, EF ≤0.35, nsVT, positive findings on electrophysiologic study	Coronary disease, EF ≤0.40, nonsustained VT, inducible VT at EPS	Prior MI, EF ≤0.30	Ischemic and nonischemic cardiomyopathy, EF ≤0.35
Follow-up (months)	27	39	20	46
Results				
Risk reduction with ICD	54% (P = .001)	51% (P = .001)	31% (P = .02)	23% (P = .007)

EP = electrophysiology; EPS = electrophysiology study; ICD = implantable cardioverter defibrillator; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MI = myocardial infarction; MUSTT = Multicenter Unsustained Tachycardia Trial; nsVT = nonsustained ventricular tachycardia; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial; VT = ventricular tachycardia.

Table 3. Guidelines for implementation of implantable cardioverter defibrillators.

	Class 1	
1.	ICD therapy is indicated in patients who are survivors of cardiac arrest due to VF or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes.	*LoE: A*
2.	ICD therapy is indicated in patients with structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable.	*LoE: B*
3.	ICD therapy is indicated in patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiological study.	*LoE: B*
4.	ICD therapy is indicated in patients with LVEF less than or equal to 35% due to prior MI who are at least 40 days post-MI and are in NYHA functional Class II or III.	*LoE: A*
5.	ICD therapy is indicated in patients with nonischemic DCM who have an LVEF less than or equal to 35% and who are in NYHA functional Class II or III.	*LoE: B*
6.	ICD therapy is indicated in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF less than or equal to 30%, and are in NYHA functional Class I.	*LoE: A*
7.	ICD therapy is indicated in patients with nonsustained VT due to prior MI, LVEF less than or equal to 40%, and inducible VF or sustained VT at electrophysiological study.	*LoE: B*

ARVD/C = arrhythmogenic right ventricular dysplasia/cardiomyopathy; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter defibrillator; LoE = Level of Evidence; LVEF = left ventricular ejection fraction; LV = left ventricular; MI = myocardial infarction; NYHA = New York Heart Association; SCD = sudden cardiac death; VT = ventricular tachycardia; VF = ventricular fibrillation.

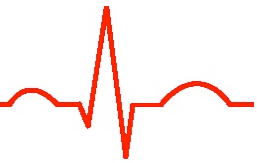
Table 3. Guidelines for implementation of implantable cardioverter defibrillators.

	Class IIa	
1.	ICD implantation is reasonable for patients with unexplained syncope, significant LV dysfunction, and nonischemic DCM.	*LoE: C*
2.	ICD implantation is reasonable for patients with sustained VT and normal or near-normal ventricular function.	*LoE: C*
3.	ICD implantation is reasonable for patients with HCM who have 1 or more major† risk factors for SCD.	*LoE: C*
4.	ICD implantation is reasonable for the prevention of SCD in patients with ARVD/C who have 1 or more risk factors for SCD.	*LoE: C*
5.	ICD implantation is reasonable to reduce SCD in patients with long-QT syndrome who are experiencing syncope and/or VT while receiving beta blockers.	*LoE: B*
6.	ICD implantation is reasonable for non hospitalized patients awaiting transplantation.	*LoE: C*
7.	ICD implantation is reasonable for patients with Brugada syndrome who have had syncope.	*LoE: C*
8.	ICD implantation is reasonable for patients with Brugada syndrome who have documented VT that has not resulted in cardiac arrest.	*LoE: C*
9.	ICD implantation is reasonable for patients with catecholaminergic polymorphic VT who have syncope and/or documented sustained VT while receiving beta blockers.	*LoE: C*
10.	ICD implantation is reasonable for patients with cardiac sarcoidosis, giant cell myocarditis, or Chagas disease.	*LoE: C*

ARVD/C = arrhythmogenic right ventricular dysplasia/cardiomyopathy; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter defibrillator; LoE = Level of Evidence; LVEF = left ventricular ejection fraction; LV = left ventricular; MI = myocardial infarction; NYHA = New York Heart Association; SCD = sudden cardiac death; VT = ventricular tachycardia; VF = ventricular fibrillation.

Cardiac Resynchronization Therapy-Defibrillator

Congestive heart failure (CHF) is associated with decreased hemodynamic function, exercise tolerance and quality of life due to poor left ventricular systolic or diastolic function. Furthermore, patients with CHF are at increased risk for sudden cardiac death (SCD). As already discussed, ICD treatment in CHF patients resulted in improved outcome and a reduction in all-cause mortality.[15] In a significant number of patients, left ventricular failure is associated with conduction disturbances causing mechanical dyssynchrony. Ventricular dyssynchrony further contributes to the already impaired left ventricular function. Electrical cardiac resynchronization therapy (CRT) is a technique which corrects dyssynchrony caused by ventricular dilatation and



electrical disturbance. Recent years, numerous randomized and observational studies demonstrated that CRT may improve functional status, quality of life and may even lower mortality.[16] It was therefore a logical step to combine CRT with ICD therapy (CRT-D). The first CRT implantations in the Netherlands were performed in Utrecht by thoracic surgeon Dr. Bakker and her team. In 1994, Cazeau et al were the first to report on the benefit from CRT in CHF patient. This study tested the safety and efficacy of multisite pacing in patients with heart failure. Significant improvements in exercise tolerance, New York Heart Association (NYHA) class and quality of life were noted. In 2003, the COMPANION trial was the first to randomize between optimal medical therapy, optimal medical therapy and CRT and optimal medical therapy and CRT-D. CRT-D reduced mortality with 36% in comparison with standard therapy, whereas CRT alone resulted in a 20% reduction in mortality.[15] Other studies (CARE-HF) demonstrated that CRT alone had the same effect on mortality as CRT-D in the COMPANION trial. Recently, the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT) enrolled patients with NYHA class I or II, QRS duration ≥ 130 ms and LVEF ≤ 30%. Patients were randomized to ICD therapy alone or to ICD therapy with CRT. The primary end-point was a composite of all-cause mortality and nonfatal heart failure and during follow-up 17% in the CRT-D group and 25% in the ICD group reached the primary end-point. It was concluded, that the incidence of all-cause mortality and nonfatal heart failure was significantly reduced when CRT was added to ICD therapy.[16]

The Device

The first ICD, developed in the 1970s, was large and heavy, could not be programmed, used epicardial patch electrodes, had no telemetry capabilities and required a thoracotomy for the implantation of the epicardial lead system. ICD implantation procedures were major surgical intervention, associated with significant morbidity and mortality. Fortunately, during the last 29

years, many improvements have been made. Current devices are relatively small, can be implanted subcutaneously in the majority of cases and are connected to an endocardial lead system. Furthermore, more and more functions became available and most modern devices can be connected to a telemonitoring system allowing remote follow-up. Nevertheless, the basic components of current generation ICDs do not differ from the first generation ICDs. Improvements were made in battery, capacitor, leads, microprocessors and resulted in a rapid evolution of ICD technology.[17] Furthermore, reductions in size and weight were made, whereas former devices were large and heavy, current devices are small and light (about 113 gr, < 5 cm wide and a thickness of 1,25 cm) (Figure 1 and 2).

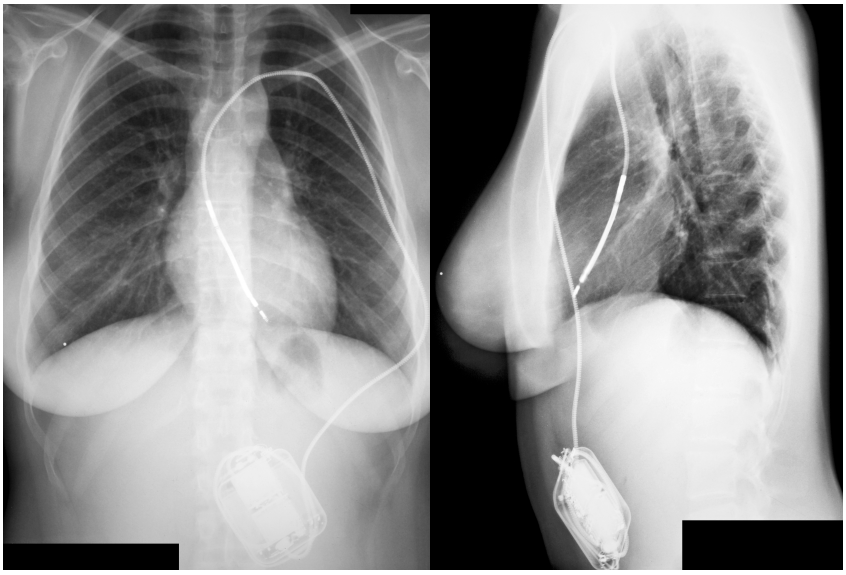


Figure 1: Example of abdominal implanted ICD system in 15-year old female

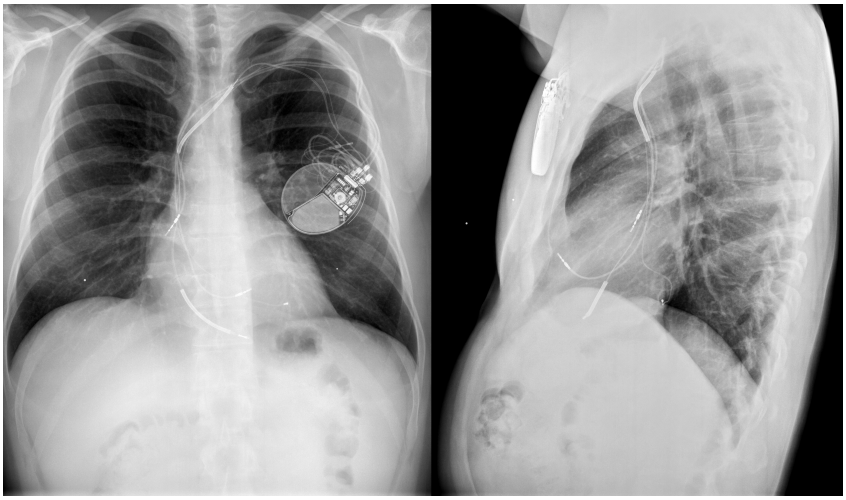


Figure 2: Example of pectoral implanted CRT-D system in 42-year old male

Components and function

An ICD contains a battery, a capacitor to store and deliver charges, a microprocessor and integrated circuits for electrogram sensing, data capture, storage and control of therapy delivery, a header to connect the endocardial leads used for sensing-, pacing, and defibrillation (Figure 3). Furthermore, the devices have extensive telemetry function for device programming and data retrieval. All these components together are called a pulse generator and are encased in a titanium can. The collaboration of these components results in the essential features of ICD function, including sensing, detecting and classification of tachyarrhythmias, delivering therapy (ventricular defibrillation or antitachycardia pacing), monitoring heart rhythm after therapy, and storage of episodes. In this process, the sensing function determines the depolarization sequences of each atrial and ventricular depolarization and the detecting function classifies the rhythm by an algorithm and determines if therapy should be delivered.[18]

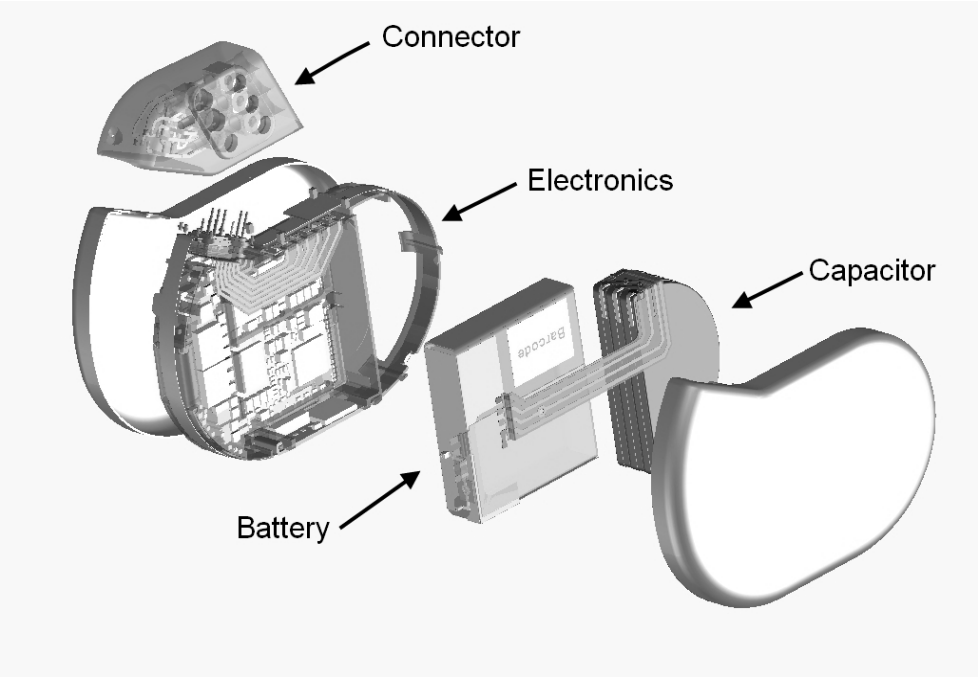
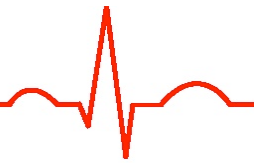


Figure 3: Exploded view of an ICD.

The device implanted in the 1980s, called the automatic implantable cardiac defibrillator, was designed only to recognize and terminate VF by delivering a high energy shock.[2] These early devices could not detect unstable VTs which could degenerate into VF, and because these devices lacked programmability, separate pacemakers were required to allow backup bradycardia pacing, leading to dangerous interactions.[18] Development of second generation devices facilitated bradycardia pacing capabilities and were (minimally) programmable. Especially the bradycardia pacing capability was important as it ended the need for separate pacemakers. Additionally, these devices had a limited telemetry function used to test battery strength and simply note the number of delivered shocks. For this telemetry function, an external monitoring device was needed. In the next decade, many improvements were made and in the early 1990s the first so-called third generation devices were introduced. In these devices, antitachycardia pacing was introduced as



well as low energy shocks for terminating VTs, extensive programmability and telemetry functions.[19] Current devices can be programmed into 3 or even 4 different cycle length related zones and different schemes of antitachycardia pacing, shock or a combination of both can be programmed. With these advancements in third generation devices programmability, current devices exhibited improved arrhythmia discrimination.

Battery and capacitor

First generation devices used capacitor and battery technology originally developed for camera flashes. The device contained cylindrical aluminum electrolytic capacitors and silver vanadium pentoxide batteries for rapid charge time and the delivery of high voltage shocks.[17] Nowadays, Lithium-silver vanadium manganese oxide batteries are used which resulted in an increase of the service life of an ICD. Some models use two batteries connected in series to minimize the time between arrhythmia detection and therapy and thereby reducing the charge time by a few seconds and improving patient safety. However, this reduction in charge time is accompanied with an undesirable increase in ICD size, since the sizes of the battery and capacitor are the major determinants of the size of the ICD. Additionally, the capacitor charge time will expand and worsen during service life. Therefore, it is important to develop capacitors which require a minimum of stored energy but still deliver enough energy for defibrillation without affecting the ICD service life.[20]

Leads

The large first generation devices were implanted abdominally and needed thoracotomy to place the lead system. The lead system which was used contained a spring patch and apical cup. The second generation devices eliminated thoracotomy by the introduction of transvenous leads in 1988. With the introduction of these transvenous leads, the implantation procedure was

transformed from open chest surgery to a procedure performed in the electrophysiology laboratory.[21] Further research evaluated the safety and efficacy of subcutaneous ICD implantation performed entirely by electrophysiologists and demonstrated a high success rate, low complication occurrence, and short implantation time and made subcutaneous ICD implantation in the electrophysiology laboratory the method of choice.

Besides improvements in the implantation procedures, improvements were made in the construction of the leads. Technical improvements in the construction are important for the efficient detection and termination of arrhythmias. Two different kind of leads are implanted, the coaxial lead design (Figure 4, left) in the first and second generation devices and the multilumen lead design (Figure 4, right) in third generation devices.[22] The coaxial lead has a layered design composed of a tip conductor, ring conductor and defibrillation conductor and an insulation layer between each conductor. The multilumen lead construction is based on parallel running conductors through a single insulating body. Tip and ring conductors are used for pacing and sensing, a defibrillation conductor for the coil located in the right ventricle and a defibrillation conductor for the coil located in the superior vena cava. The insulating body contains extra lumens to increase lead's resistance to compression forces. The major advantage of multilumen over coaxial leads is the fact that more conductors will fit into overall smaller leads.[22]

Besides improvements in the implantation procedures and in the construction of leads, lead failure occurs frequently. Due to the different design and materials which are used, longevity of current implanted leads may differ significantly. Borleffs et al. evaluated the survival and failure rate in a large number of defibrillation leads implanted over a 16-year period.[23] The implanted leads were produced by different manufacturers and different lead diameters were used. Defibrillation leads characterized by a small diameter body have several alleged advantages: it simplifies the implantation procedure, it maintains the venous blood flow and reduces subclavian crush syndrome. Borleffs et al. demonstrated major differences in failure rates

among different groups and showed an overall 10 years lead survival rate of 73%. Based on these findings it is important to carefully select the type of leads which are used for each patient and to optimize future lead performance.[23]

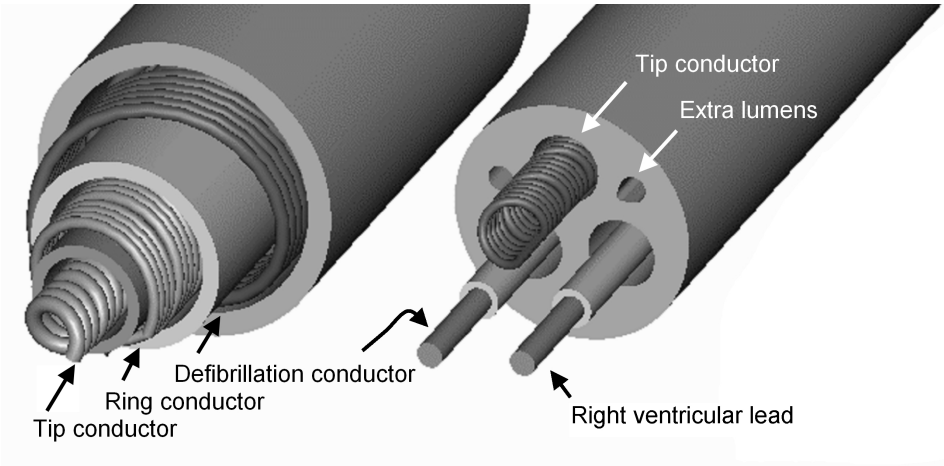


Figure 4: Cross section of coaxial lead construction of a single coil defibrillation lead with true bipolar sensing and pacing (left) and cross section of multilumen lead construction (right).

Longevity

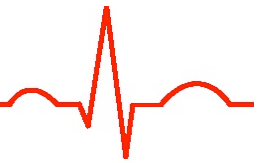
Since the first implantation in 1980, worldwide implantation rates have increased and, therefore, the number of ICD replacements is expected to increase dramatically. Most of the replacements are due to end of service life (battery depletion) and every implantation or replacement brings a substantial risk of complications and negatively influences patients' quality of life. The major determinant of ICD longevity is the capacitor and therefore the ICD size. Hauser compared the cumulative survival of patients implanted with an ICD with ICD longevity. The probability of a patient living 4, 5 and 6 years after implantation was 79%, 75% and 68% respectively. Furthermore, the study suggested that if an ICD had 10 service years, the majority of patients would not need a replacement.[24] A feasible solution is to produce larger pulse generators with

batteries with longer service life. However, this will impact patients acceptance and possibly cause more pocket related problems due to the larger volume of the devices. Furthermore, because of the fast development of new ICD features it will sometimes be questionable if it is really desirable to implant devices with a projected longevity of 10 or more years. Replacement of the currently used Lithium-silver vanadium oxide batteries with large-capacity batteries can increase service life by 2.3 years.[24] These large-capacity batteries increase the size and weight of the device and are in conflict with downsizing the device as the market forces.

Algorithms and rhythm discrimination

First generation devices were designed to detect VF only by wave-form analyses. The standard wave-form analyses used to identify cardiac rhythm was the rate of R waves. Due to the limitations of wave-form analyses only, inappropriate therapy occurred frequently, since episodes of supraventricular tachycardia with fast ventricular response could be classified as VT or VF and cause inappropriate shocks.[5] The first detection criterion in all current devices is the signal rate recorded by the right ventricular lead. In order to confirm a ventricular tachyarrhythmia, a specified number of sensed events must occur at a higher rate than the cut-off rate.

To improve specificity in discriminating between VT or supraventricular tachycardia, various algorithms have been developed. As mentioned previously, current ICDs can be programmed into 3 different cycle length related zones and the discriminative detection algorithms can be programmed in the 2 lowest zones. The highest programmable zone is meant for detection of fast VT or VF without any further discrimination to avoid unnecessary therapy delivery delay. Single chamber devices use algorithms to discriminate rhythms, comparing morphology of the arrhythmia with the morphology of baseline sinus rhythm, the rate of onset of arrhythmia and rhythm regularity. Dual chamber devices can use additional information retrieved from the atrial lead for discriminating between rhythms.



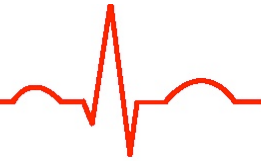
All currently available algorithms have some known limitations like false positive and false negative therapy delivery decisions but by combining some of these algorithms, the amount of inappropriate inhibition or therapy delivery can be further reduced. The complexity and combination of algorithms which can be used depends on power requirements of the ICD. Since downsizing the ICD is an important goal, larger batteries which can provide the power requirements for complex algorithms are not used. These constraints reduce the use of more complex algorithms and despite advances in algorithms, inappropriate therapy still occurs.[25]

Future developments

Many marked improvements were made since the first implantation in 1980.[2] Despite developments in sophisticated algorithms the inappropriate shock rate is still high. Patients with inappropriate shocks experience diminished quality of life, can even develop symptoms such as "phantom shocks", and inappropriate therapy can initiate new arrhythmias which may even be life threatening.[26] Technologies that eradicate the occurrence of inappropriate shocks are not developed yet.

Need for clinical follow-up

Normally, patients are clinically followed-up every 3 to 6 months, although the majority of these visits involve data collection only and do not require any further action to be undertaken. To decrease office time, a mechanism for intensive device surveillance without the consequent increase in office time was desired. To this purpose, telemonitoring was introduced in 2001.[27] Telemonitoring provides everyday wireless information about device function and diagnostic data, and facilitates potentially dangerous events to be sent to the physician without patient intervention. Telemonitoring may reduce hospitalization by early detection of potentially dangerous events and increases patients' convenience by reducing hospital visits.[27, 28]



Subcutaneous ICD system

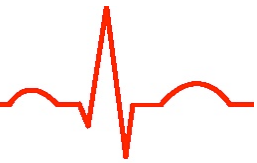
In January 2005, the subcutaneous implantable defibrillator system was tested. A device that can be implanted entirely subcutaneously and positioned based on anatomical markings. The absence of leads in the heart might decrease implantation procedural time and risk for complications.[29] Besides these advantages, disadvantages are the positioning in the axilla of the pulse generator with a subcutaneous lead tunneled into a parasternal position, a higher amount of shock energy and the lack of pacing capabilities. The question is whether these advantages will counterbalance the disadvantages.

Four-pole ICD connector

Another improvement in device technology is the four-pole ICD connector, with high voltage and low voltage connectors inline, thus eliminating the bulky bipod or tripod of pace/sense connector and the connector(s) of the shock coil(s). The four-pole ICD connector uses a smaller pulse generator and thinner leads and, therefore, may simplify the implantation procedure and reduce complications. The device is attractive for patients who require CRT-D which uses three leads and requires multiple electrical contacts.[30]

ICD cost-effectiveness

With the inclusion of primary prevention ICD treatment in the current guidelines, worldwide implantation rates have increased significantly. With the increasing implantation rates of these expensive devices, high costs burdens are put on the health care systems, therefore warranting assessment of cost-effectiveness of ICD therapy. Sanders et al. assessed the cost-effectiveness of ICD therapy in 8 large primary prevention trials (MADIT, MADIT II, MUSTT, DEFINITE, COMPANION, SCD-HeFT, DINAMIT, CABG patch trial). The study demonstrated that prophylactic single-chamber ICD implantation added between 1.01 and 2.99 quality-adjusted life

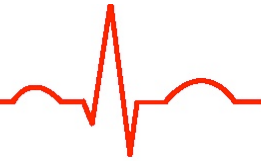


years (QALY) and the cost-effectiveness ranged from $34.000 to $70.200 per gained QALY. The upper limit of the cost-effectiveness was relatively high because of the inclusion of two negative trials (DINAMIT the CABG patch trial).[31] Cowie et al. also analyzed the cost-effectiveness of ICD therapy in 6 large primary prevention trials (AMIOVERT, CAT, DEFINITE, MADIT, MADIT II, SCD-HeFT). In this analysis, prophylactic single-chamber ICD implantation added 1.88 QALY and the incremental cost-effectiveness was $29.530 per gained QALY.[32] Smulders et al. demonstrated that a cost-effectiveness ratio below €40.000 per gained QALY was assumed acceptable according to the current Dutch economic threshold.[33] In both studies the mean costs per gained QALY was below the acceptable cost-effectiveness ratio and therefore indicating that ICDs are cost-effective in primary prevention.

Another way of evaluating the cost-effectiveness of ICD therapy is by evaluating the number needed to treat (NNT). Camm et al. evaluated the NNT in 4 major primary prevention trials and in 1 secondary prevention trial. The evaluated primary prevention trials were MUSTT, MADIT, MADIT II, SCD-HeFT and a NNT of 3 at 5 year follow-up, 4 at 2.4 year follow-up, 11 at 3 year follow-up and 14 at 5 year follow-up were found, respectively. The NNT in the secondary prevention trial (AVID) was 9 at 3 year follow-up. Additionally, the NNT for optimal medical therapy was ranging between 20 and 37.[34] The review clearly demonstrates a higher NNT for optimal medical therapy compared with the primary and secondary trials. However, since the NNT is dependent on the time window over which the benefit is assessed, it is difficult to compare different trials and medications with different follow-up durations.

Current risk stratification for SCD

Although the beneficial effect of ICD treatment has been proven in selected patients, the majority of cases of SCD occurs in patients who are still not eligible for ICD implantation.[35] In other words, the problem lies in identifying patients at risk for SCD prior to the first, often fatal,



ventricular arrhythmia. Primary prevention trials have established depressed LVEF as the single most important risk stratification tool to identify individuals at high-risk for SCD. The Maastricht circulatory arrest registry clearly shows that LVEF alone will not adequately identify high-risk patients of SCD. In the circulatory arrest registry 57% of the SCD victims had an LVEF >30% and 20% had an LVEF >50% showing the poor sensitivity of LVEF.[10] Additionally, the MUSST trial demonstrated that approximately half of mortality occurred suddenly in patients with an LVEF <30% and the other half in patients with an LVEF >30%, hereby suggesting that the degree of left ventricular systolic failure did not predict the mode of death.[36] As a perfect risk stratification tool should have a good sensitivity and specificity, one could say that LVEF as the single most important risk stratification tool alone is not the optimal tool to identify individuals at risk of SCD nor to identify patients at low risk.

Aim and outline of the thesis

Although the beneficial effect of ICD treatment has been proven in selected patients, the population assessed in large clinical trials does not reflect the population with ICDs in the real world. The aim of the current thesis is to give better insight in these patients at risk for life-threatening arrhythmias by studying a large population of patients treated with an ICD, outside the setting of a clinical trial.

In part I, the actual need for defibrillator backup during long-term follow-up is evaluated. Chapter 2 describes differences in mortality and the occurrence of ventricular arrhythmia between patients receiving an ICD as primary vs. secondary prevention of SCD. The actual need for device replacement after an event-free first battery service-life is studied in Chapter 3.

In part II, an attempt is made to improve risk stratification by evaluating currently available parameters and the additive value of novel parameters. In Chapter 4 all classic baseline variables are combined to construct a clinically applicable mortality risk score in primary

prevention ICD recipients with ischemic heart disease. Chapter 5 demonstrates the importance of atrial fibrillation in patients with ICD or CRT-D. Chapter 6 shows that usage of a risk model can predict the risk of non-benefit (death, prior to first ventricular arrhythmia) which might have important clinical consequences. In Chapter 7 the spatial QRS-T angle is evaluated in the prediction of ventricular arrhythmia. Chapter 8 demonstrates the risk of lead failure in small diameter defibrillation leads compared with a benchmark cohort.

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Part I

The actual need for defibrillator backup during long-term follow-up

Chapter 2

Long-term follow-up of primary and secondary prevention implantable cardioverter defibrillator patients

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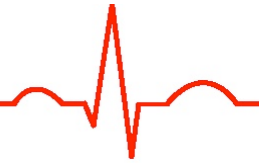
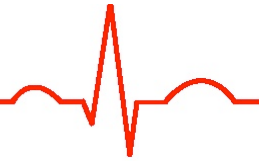


Abstract

Aims: The beneficial effects of implantable cardioverter defibrillators (ICDs) in primary and secondary prevention patients are well established. However, data on potential differences between both groups in mortality and ICD therapy rates during long-term follow-up are scarce. The aim of the study was to assess differences in mortality and ICD therapy between secondary and primary prevention ICD recipients.

Methods and results: With exception of patients with congenital monogenetic cardiac disease, all patients treated with an ICD, regardless of the underlying cardiac pathology, from 1996 to 2008 at the Leiden University Medical Center were included in the current analysis. The study population was grouped by type of prevention (secondary or primary) for sudden cardiac death. Primary end-point was all-cause mortality. Secondary end-point was the occurrence of device therapy (appropriate or inappropriate). A total of 2134 (80% men, mean age 63±12 years) ICD recipients were included. Thirteen-hundred-and-two (61%) patients received an ICD for primary prevention of sudden cardiac death and 832 (39%) patients for secondary prevention. During a mean follow-up of 3.4±2.8 years, 423 (20%) patients died. The 5-year cumulative incidence of mortality was 25% (95%CI 21-29%) for primary prevention patients and 23% (95%CI 20-26%) for secondary prevention patients. Secondary prevention patients exhibited a 74% increased risk for appropriate therapy as compared to primary prevention patients (HR 1.7, $p<0.001$). Comparable risk for inappropriate shocks was observed (HR 1.0, $p=0.9$).

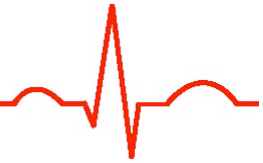
Conclusion: During long-term follow-up primary prevention patients exhibited a lower risk of appropriate therapy but comparable mortality rates were observed between both groups. Both groups showed similar occurrence of inappropriate shocks.



Introduction

Sudden cardiac death, mainly caused by ventricular arrhythmias (VA) in a population with coronary artery disease, is a major cause of mortality in the Western world. In the United States, the annual incidence of sudden cardiac death varies from 200.000 to 450.000 subjects.[1-4] Initially, large trials proved the effectiveness of implantable cardioverter defibrillator (ICD) treatment in survivors of life-threatening VAs such as ventricular fibrillation or ventricular tachycardia (secondary prevention).[5-7] Since survival rates of VA, prior to ICD implantation, are low, focus shifted to the identification of patients at risk of VA (primary prevention).[1] Randomized trials tested the hypothesis that ICD treatment was beneficial in a population characterized by depressed left ventricular ejection fraction (LVEF) without prior cardiac arrest and demonstrated a reduction in all-cause mortality.[8-11] Not only did the implementation of these results in the international guidelines dramatically increase the number of implantations worldwide, it also changed the ICD-treated population from VA survivors to patients characterized by decreased LVEF and symptomatic or asymptomatic heart failure.[12] It is therefore important in follow-up studies to clearly describe the population currently receiving ICD treatment and to assess differences between secondary and primary prevention ICD recipients. Previous studies have clearly shown a higher occurrence of VA, causing appropriate device therapy, in secondary prevention ICD patients as compared to primary prevention ICD patients. However, data on potential differences in mortality and inappropriate ICD shocks during long-term follow-up are scarce.

Since 1996, all ICD recipients in the Leiden University Medical Center have been assessed and followed-up. This cohort allows the evaluation of the long-term outcome in these two groups of patients.



Methods

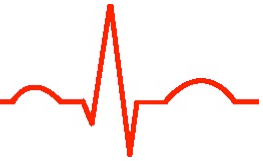
Patient population

Since 1996, all patients who received an ICD in the Leiden University Medical Center have been registered in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center). Characteristics at baseline and data of all follow-up visits are recorded. Eligibility for ICD implantation is based on the international guidelines which, due to evolving guidelines, may have changed over time.[4, 12] For the current study all ICD treated patients up to January 2008 were included. Patients with congenital monogenetic cardiac disease, such as hypertrophic obstructive cardiomyopathy, long-QT syndrome, Brugada syndrome and idiopathic ventricular fibrillation, related to an increased risk of cardiac arrhythmia were excluded.[13]

The study population was grouped by type of prevention (secondary or primary) for sudden cardiac death. Prevention was defined secondary after survival of an episode of cardiac arrest, occurrence of VA with loss of consciousness or VA lasting longer than 30 seconds.[5, 6] Prevention was considered primary in case of depressed LVEF without prior sustained VA.[8, 9, 11, 12]

Device implantation and programming

All implantations were carried out in the catheterization laboratory and all devices were implanted transvenously without thoracotomy. Ventricular and atrial (pacing and shock) leads were positioned conventionally. For implantation of a cardiac resynchronization therapy - defibrillator, a coronary sinus venogram was obtained using a balloon catheter, followed by insertion of the LV pacing lead into one of the posterolateral veins through an 8Fr guiding catheter. During implantation, sensing and pacing thresholds were tested and defibrillation threshold testing was performed. Implanted systems were manufactured by Biotronik (Berlin,



Germany), Medtronic (Minneapolis, MN, United States), Boston Scientific (Natick, MA, United States, formerly CPI, Guidant [St. Paul, MN, United States]) and St. Jude Medical/Ventritex (St. Paul, MN, United States). All devices were programmed with three consecutive zones: a monitor zone (150-188 bpm), an antitachycardia pacing (ATP) shock zone (188-210 bpm) and an initial shock zone (≥210 bpm). In the monitor zone, no therapy was programmed unless slow VA was detected during follow-up. In the ATP-shock zone, arrhythmias were initially attempted to be terminated by two bursts of ATP and, if arrhythmia continued, defibrillator shocks were used. In case of VA faster than 210 bpm, device shocks were the initial therapy. Furthermore, atrial arrhythmia detection was set to >170 bpm with supraventricular tachycardia discriminators enabled.

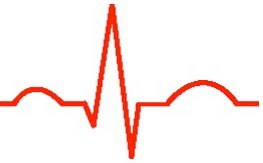
Follow-up and device interrogation

ICD treated patients were periodically seen at the outpatient clinic every 3-6 months, which included device interrogation. Printouts were checked for appropriate and inappropriate therapy (ATP and shocks). Adjudication of the delivered therapy was performed by a trained electrophysiologist. Unscheduled device interrogations were performed in case of symptomatic episodes of arrhythmia and during unplanned hospitalization.

Last follow-up data was acquired in February, 2009. Patients with more than six months of missing data were considered lost to follow-up.

End-points

All-cause mortality was considered the primary end-point. ICD therapies were classified appropriate when they occurred in response to ventricular tachycardia or ventricular fibrillation (secondary end-point) and inappropriate when triggered by sinus or supraventricular tachycardia, T-wave over sensing, or electrode dysfunction (tertiary end-point).



Furthermore the risk for subsequent VA after the first experienced VA was assessed and compared between both subgroups. By definition, secondary prevention patients have experienced a VA prior to ICD implantation and primary prevention patients have not. Therefore, to evaluate differences in the risk for subsequent VA, the risk of a first appropriate shock in secondary prevention patients was compared to the risk of a second appropriate shock in primary prevention patients.

Statistical analysis

Continuous data are expressed as mean ± standard deviation; categorical data are presented as numbers and percentages. Differences at baseline were evaluated with the independent-sample t-test for continuous variables, and Chi-square test for categorical variables. Cumulative incidences were analyzed by method of Kaplan-Meier and compared using the log rank test. The 95% confidence intervals (CI) were calculated as 1.96 times the standard error in each direction. The relation between baseline characteristics and end-points was assessed by using Cox regression analysis and described with hazard ratios (HR) and 95% CI. In the multivariate Cox regression analysis for all-cause mortality, adjustments were made for age, gender, QRS-duration, New York Heart Association (NYHA) functional class, renal function, LVEF, history of atrial fibrillation.[14, 15] For all tests a p-value <0.05 was considered significant.

Results

Baseline

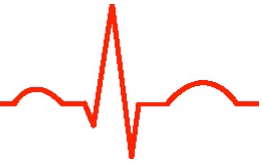
A total of 2471 patients received ICD treatment during the study period. Two-hundred-and-six (8%) patients were diagnosed with a congenital monogenetic cardiac disease. One-hundred-thirty-one (5%) patients were lost to follow-up, of whom 52 (40%) patients received an ICD for

secondary prevention and 79 (60%) patients for primary prevention. The remaining 2134 patients were considered the study population and had a mean follow-up duration of 3.4±2.8 years.

The study population was, as mentioned above, grouped by type of prevention (secondary or primary) for sudden cardiac death. Thirteen-hundred-and-two (61%) patients received an ICD for primary prevention and 832 (39%) patients for secondary prevention. Primary prevention patients had a mean follow-up duration of 2.5±2.0 years and secondary prevention patients a mean follow-up duration of 4.9±3.3 years. As can be seen in Table 1, comparison of the two groups revealed in the primary prevention group a higher NYHA functional class (mean NYHA: 2.3 ± 0.8 vs. 1.8 ± 0.8, p<0.001), a wider QRS complex (mean QRS: 130 ± 35 ms vs. 120 ± 32 ms, p<0.001) and a lower LVEF (mean LVEF: 29 ± 12% vs. 37 ± 15%, p<0.001).

All-cause mortality

During follow-up, 423 (20%) patients died. Cumulative incidence for all-cause mortality was 6% (95%CI 5-7%) at 1 year, 16% (95%CI 14-17%) at 3 years and 25% (95%CI 22-28%) at 5 years. Comparison between the two groups demonstrated a higher, but not statistically significant cumulative incidence for all-cause mortality for primary prevention patients as compared to secondary prevention patients during follow-up (Figure 1); at 5 years of follow-up the incidence was respectively 25% (95%CI 21-29%) versus 23% (95%CI 20-26%). As can be seen in Figure 1, during the first 3 years of follow-up, differences in mortality rates between both groups increased, whereas after 3 years the differences in mortality rates remained stable. The risk for all-cause mortality was higher for primary prevention patients than for secondary prevention patients, but did not reach significance (HR 1.2 95%CI 1.0-1.5) after 5 years of follow-up (p=0.05). Moreover, multivariate Cox regression analysis demonstrated that after adjustment for age, gender, QRS duration, NYHA functional class, renal function, LVEF and history of atrial



fibrillation primary prevention patients exhibited similar risk for death as compared to secondary prevention patients. (HR 1.1 95%CI 0.8-1.4, p=0.6).

Table 1. Baseline characteristics of primary vs. secondary prevention ICD patients.

	Primary (n=1302)	Secondary (n=832)	p-value
Clinical parameters			
Male gender	1035 (80%)	680 (82%)	0.204
Age (years)	63 ± 11	63 ± 13	0.459
Ischemic heart disease	881 (68%)	605 (73%)	0.020
NYHA functional class			<0.001
I	245 (19%)	372 (45%)	
II	486 (37%)	288 (34%)	
III	529 (41%)	158 (19%)	
IV	42 (3%)	14 (2%)	
QRS duration (ms)	130 ± 35	120 ± 32	<0.001
Renal clearance (ml/min)*	78 ± 36	79 ± 38	0.791
LVEF (%)	29 ± 12	37 ± 15	<0.001
History of atrial fibrillation	347 (27%)	173 (21%)	0.002
Type of device			<0.001
Single chamber	36 (5%)	219 (26%)	
Dual chamber	517 (40%)	487 (59%)	
CRT-D	722 (55%)	126 (15%)	
Medication			
Beta blockers	830 (64%)	337 (41%)	<0.001
ACE inhibitor / AT antagonist	1100 (85%)	569 (68%)	<0.001
Diuretics	975 (75%)	429 (52%)	<0.001
Amiodarone	117 (14%)	226 (27%)	<0.001
Statins	864 (66%)	436 (52%)	<0.001

**Renal clearance was determined with the formula of Cockcroft-Gault. ACE = angiotension-converting enzyme; AT = angiotensin; CRT-D = cardiac resynchronization therapy – defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.*

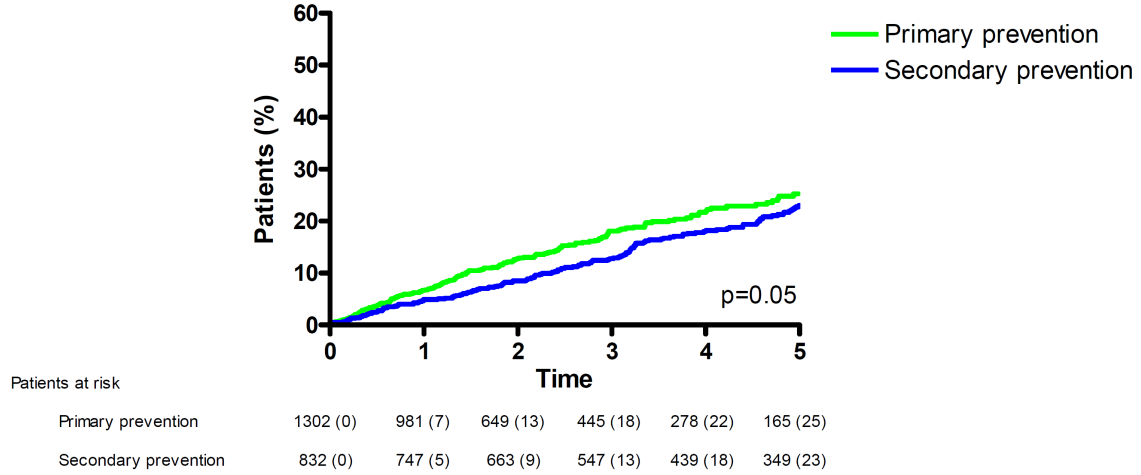


Figure 1: All-cause mortality. Kaplan-Meier curves of all-cause mortality for primary and secondary prevention ICD recipients. In the parenthesis, next to patients at risk, the yearly incidences (%) per corresponding time point are noted.

Appropriate therapy

Ventricular arrhythmia triggered appropriate therapy (ATP or shock) in 674 (32%) patients. A total of 1529 episodes of VA were terminated by ICD shocks in 423 (20%) patients. Appropriate ATP ended VA in 14006 episodes in 466 (22%) patients. Cumulative incidence for appropriate therapy was 18% (95%CI 16-19%) at 1 year, 33% (95%CI 31-35%) at 3 years and 43% (95%CI 40-46%) at 5 years. Comparison between the two study groups demonstrated a cumulative 5-year incidence for appropriate therapy of 37% (95%CI 33-42%) for primary prevention patients and 51% (95%CI 47-55%) for secondary prevention patients (Figure 2). Cox regression analysis demonstrated a 74% increased risk of appropriate therapy in the secondary prevention group as compared with the primary prevention group (HR 1.7, 95%CI 1.5-2.0, p<0.001).

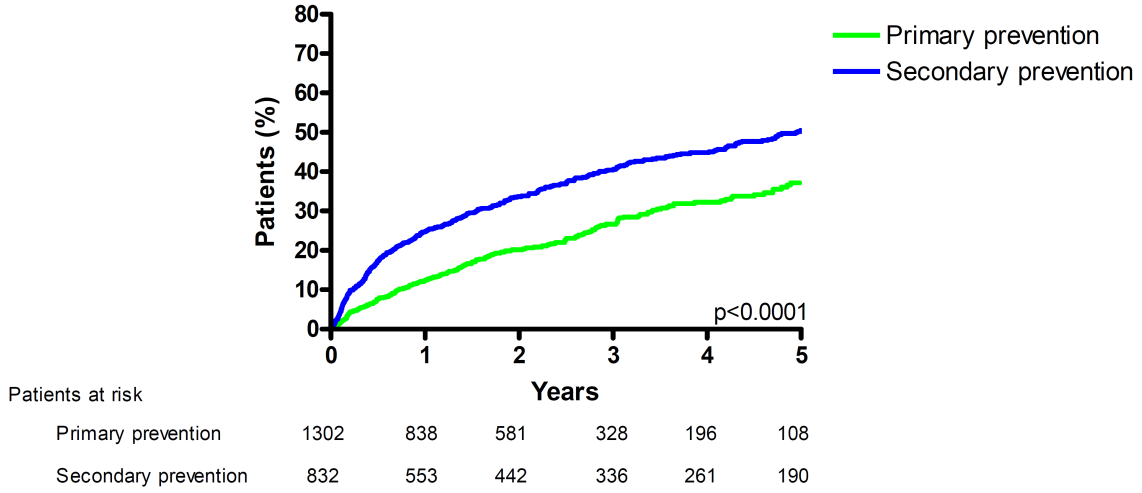


Figure 2: Appropriate therapy. Kaplan-Meier curves of appropriate therapy for primary and secondary prevention ICD recipients.

Cumulative incidence for appropriate shock only was 28% (95%CI 25 - 31%) at 5 years. For primary prevention patients, the 5-year cumulative incidence for appropriate shocks was 20% (95%CI 16 - 23%) as compared to 37% (95%CI 33 - 41%) for secondary prevention patients (Figure 3). Secondary prevention patients exhibited more than double the risk for appropriate shocks during long-term follow-up (HR 2.3, 95%CI 1.9 – 2.9, p<0.001).

Risk for subsequent appropriate shock

In the primary prevention group, 141 (11%) patients received appropriate shocks. Of these 141 patients, 49 (35%) patients experienced a second appropriate device shock 275±455 days after the first episode. As can be seen in Figure 4, the 5-year cumulative incidence of a second appropriate device shock in primary prevention patients was 50% (95%CI 38-62%) and the cumulative incidence of a first appropriate shock in secondary prevention patients was 37% (95%CI 33-41%). Comparison of these groups demonstrated that primary prevention ICD recipients have

twice the risk for a subsequent appropriate shock as compared to a first appropriate shock in the secondary prevention group (HR 2.0, 95%CI 1.5-2.7, p<0.001).

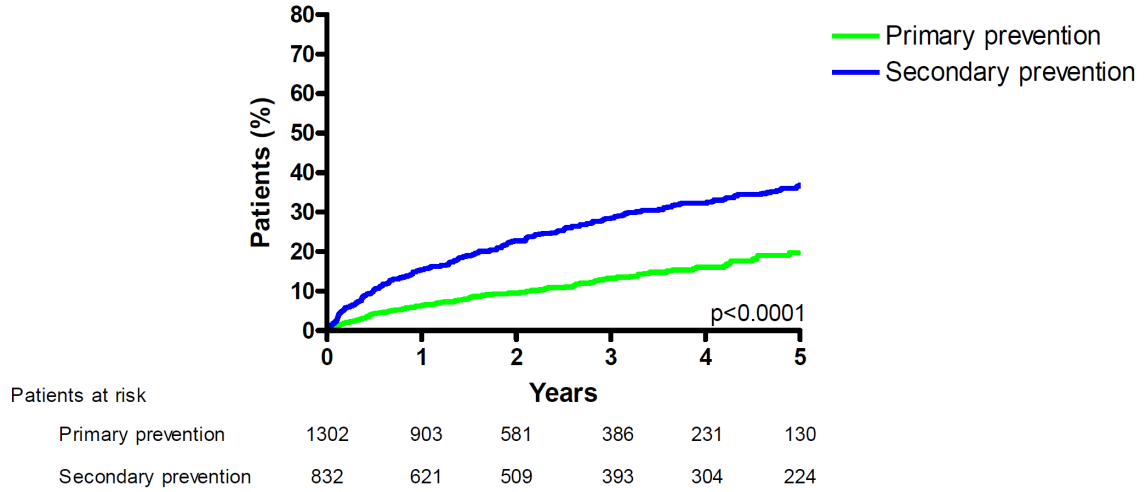


Figure 3: Appropriate shocks. Kaplan-Meier curves of appropriate shocks for primary and secondary prevention ICD recipients.

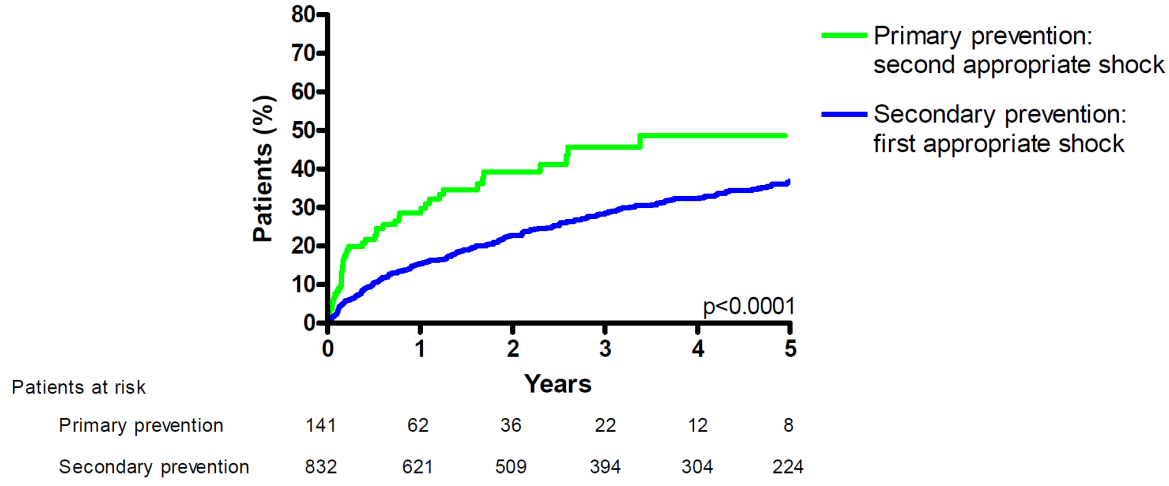


Figure 4: Subsequent risk for appropriate shock. Kaplan-Meier curves of appropriate shock for the second appropriate shock in primary prevention ICD recipients and the first appropriate shock in secondary prevention ICD recipients.

Inappropriate shocks

During follow-up, 241 (14%) patients experienced inappropriate device discharges with a mean number of 2.9 ± 4.5 shocks. Cumulative incidence for inappropriate shocks was 7% (95%CI 6-8%) at 1 year, 13% (95%CI 11-14%) at 3 years and 17% (95%CI 15-19%) at 5 years. As can be seen in Figure 5, the comparison between the two study groups demonstrated a cumulative 5-year incidence for inappropriate shocks of 18% (95%CI 14-21%) for primary prevention patients and 17% (95%CI 14-20%) for secondary prevention ICD patients. Cox regression analysis showed comparable risk of experiencing an inappropriate shock between the two groups (HR 1.0, 95%CI 0.8-1.3, p=0.9).

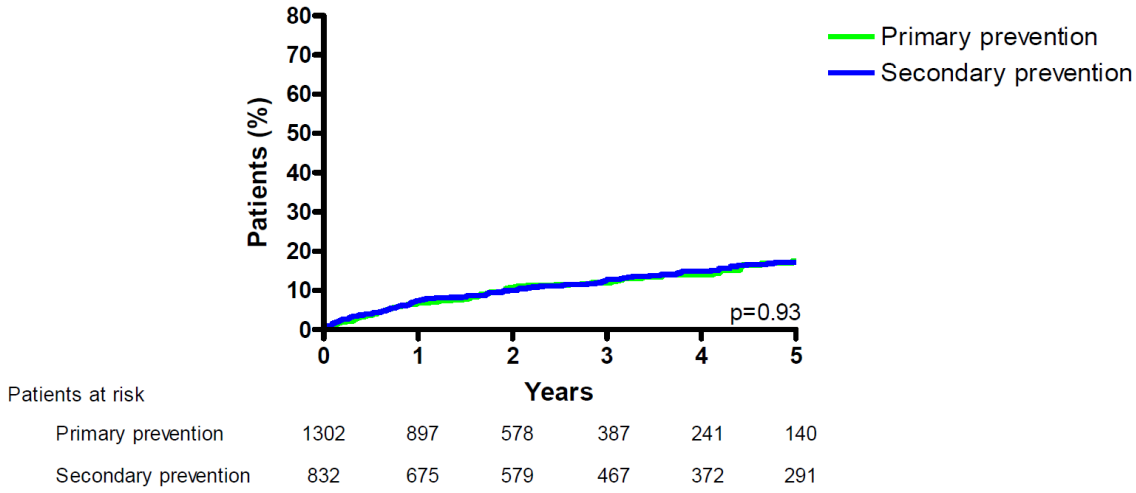
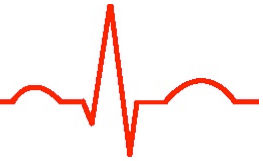


Figure 5: Inappropriate shocks. Kaplan-Meier curves of inappropriate shocks in primary and secondary prevention ICD recipients.

Discussion

The main findings of the current study on the 5 years outcome of primary and secondary prevention ICD patients can be summarized as follows: 1) Patients treated for secondary prevention experienced appropriate therapy more often; 2) The long-term risk for all-cause

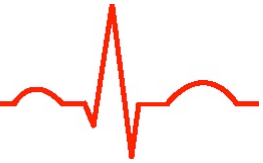


mortality was comparable for both groups; 3) Risk for subsequent VA was higher in primary prevention patients than in secondary prevention patients; 4) No differences were demonstrated in the incidence of inappropriate shocks.

Previously executed large randomized trials have proven the beneficial effect of ICD treatment for primary and secondary prevention of sudden cardiac death. These trials, however, required specific patient criteria for inclusion and might therefore not be representative for the overall population presently considered for ICD treatment. The current study is of additive value to current literature since it assesses long-term follow-up in a large population of primary and secondary prevention ICD recipients in general practice, outside the setting of a clinical trial.

Survival in ICD recipients

Large randomized clinical trials for primary and secondary prevention have demonstrated improved survival in patients treated with ICD therapy.[8-11, 16] The first trials on the secondary prevention of sudden cardiac death reported all-cause mortality rates ranging from 16% to 36% over 18 to 57 months, respectively.[5-7] Primary prevention trials, on the other hand, demonstrated mortality incidences ranging from 14% to 23% over 20 to 39 months follow-up, respectively.[8-11, 17] In the current study comparable mortality rates were observed. During long-term follow-up of 5 years, 23% of secondary prevention patients died as compared to 25% of primary prevention patients. Considering the different clinical characteristics at baseline, one should expect higher mortality rates for primary prevention ICD patients. After all, primary prevention ICD patients have more advanced heart disease and more coexisting comorbidity which is in line with previous clinical trials.[5, 7, 9-11, 16, 17] Undisputedly, these characteristics are related to an increased risk for nonarrhythmic death. In contrast, secondary prevention ICD recipients exhibited a higher risk of experiencing life-threatening arrhythmic events than primary prevention patients, as can be concluded from higher incidences of appropriate device therapy.[18] Since ICDs extend survival

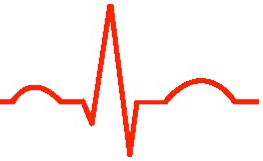


only in case of VA and not in case of nonarrhythmic events, one might expect higher all-cause mortality rates in primary prevention patients. It is therefore interesting that in the current study this thesis was not confirmed. Inaccuracy due to the smaller number of primary prevention patients with long-term follow-up could be an explanation, since initially the mortality curves were divergent (up to 3 years of follow-up). Another explanation could be the supposed negative impact of appropriate shocks on mortality (HR 2.2, $p<0.001$).[19] As demonstrated, secondary prevention patients exhibit a 74% increased risk for appropriate therapy and accordingly this might affect the mortality curve of the secondary prevention group more than it affects the curve of the primary prevention group.

Occurrence of appropriate and inappropriate ICD therapy

Germano and co-workers evaluated the incidence of appropriate therapy in 7 major primary and secondary prevention ICD trials and reported appropriate ICD therapy rates ranging from 54% during 45 months of follow-up to 64% during 36 months of follow-up in secondary prevention trials.[18] In primary prevention trials, lower incidences were reported ranging from 17% over 29 months of follow-up to 31% over 24 months of follow-up in primary prevention trials.[18] These results were in line with the observed cumulative incidences in the current study. As expected, the prevalence of appropriate ICD therapy was highest in survivors of life-threatening arrhythmias.

In the current study, inappropriate shocks were relatively common in both groups of ICD recipients, occurring in 18% of primary prevention patients and in 17% of secondary prevention patients after 5 years of follow-up. Comparable findings were observed in the review by Germano et al.[18] It should be noted that both groups had similar risk for experiencing inappropriate shocks. Previously reported studies in literature characterize patients who experience inappropriate shocks as younger patients with non-ischemic heart disease, and a history of atrial fibrillation and smoking.[20-23] Unlike with the occurrence of VA, for which poor cardiac function predicts well,



inappropriate shocks occur mainly due to erroneous discrimination of supraventricular arrhythmias or abnormal sensing by the algorithms within the ICD.[24, 25] Therefore, criteria for the classification of primary and secondary prevention (i.e. depressed LVEF or prior life-threatening VA) do not predispose for the occurrence of inappropriate shocks.

Limitations

This was a prospective observational study, performed to assess differences between primary and secondary prevention ICD patients. Since patients were collected over a long period of time, evolving guidelines could have created a heterogeneous population.

Conclusion

During long-term follow-up, compared to secondary prevention ICD patients, primary prevention ICD recipients exhibited a lower risk of VA which triggered appropriate ICD therapy but demonstrated comparable mortality rates. Both groups showed a similar occurrence of inappropriate shocks.

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Chapter 3

Primary prevention ICD recipients: the need for defibrillator back-up after an event-free first battery service-life

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Abstract

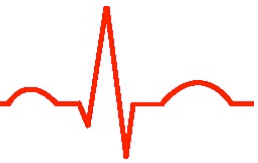
Background: In primary prevention implantable cardioverter defibrillator (ICD) patients, the relatively low incidence of ventricular arrhythmias (VA), combined with the limited battery service-life potentially results in a large group of patients who have had no benefit of the ICD during first service-life. Data on the occurrence of VA after device replacement remain scarce.

Objective: The purpose of this study was to give clinicians better insight in the dilemma whether or not to replace an ICD after an event-free first battery service-life.

Methods: All patients treated with an ICD for primary prevention who had a replacement because of battery depletion and who did not receive appropriate therapy before device replacement were included in the current analysis.

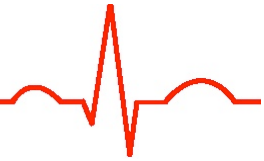
Results: Out of 154 primary prevention ICD patient needing replacement because of battery depletion, 114 (74%) patients (mean age 61 ± 11 years, 80% male) had not received appropriate ICD therapy for VA. Follow-up was 71 ± 24 months after the initial implantation and 25 ± 21 months after device replacement. Following replacement, three year cumulative incidence of appropriate therapy in response to ventricular tachycardia or ventricular fibrillation was 14% (95% CI 5-22%).

Conclusion: The majority of primary prevention ICD patients do not experience VA during first battery service-life. However, a substantial part of these patients does experience appropriate ICD therapy after replacement.



Introduction

Sudden cardiac death mainly caused by ventricular arrhythmias (VA) is a major cause of mortality in the western world.[1-4] Initially, patients were treated with implantable cardioverter defibrillator (ICD) therapy after survival of a life threatening VA (secondary prevention), but because of the low survival rate after experiencing a VA, focus shifted to the identification of patients at high risk for developing an arrhythmic event (primary prevention). Large randomized trials demonstrated a reduction in all-cause mortality in patients treated with ICD therapy, initially in patients treated for secondary prevention,[5-7] but later also in patients who are at risk for arrhythmic death, the primary prevention.[8-11] Findings of these trials led to the inclusion of primary prevention ICD treatment in the current guidelines. Not only did the implementation of these results change the ICD-treated population from VA survivors to patients, characterized by a low LVEF and symptomatic or asymptomatic heart failure, it also increased the number of implantations dramatically.[12] Hauser demonstrated that current ICD service-life is approximately 4.7 years for single-chamber devices and 4.0 years for dual-chamber devices and therefore, a large number of (mainly primary prevention) ICD replacements can be expected.[13] Although these primary prevention patients are at high risk for developing an arrhythmia, data from randomized studies showed that only 35% receives appropriate therapy for ventricular tachycardia (VT) or ventricular fibrillation (VF).[14] Data from observational clinical studies even showed a lower number of patients receiving appropriate therapy.[15] Therefore, a significant number of patients treated for primary prevention who are eligible for ICD replacement, have not developed a VA during the first ICD service-life, posing a dilemma whether or not the patient will receive potentially life saving ICD therapy after this replacement. In other words: do patients not experiencing a VA during the first ICD service life need a replacement?



Since 1996, all primary prevention ICD recipients in the Leiden University Medical Center have been assessed and followed-up. This large cohort offers possibilities for the evaluation of patient follow-up after a long event-free period.

Methods

Patient population

Since 1996, all patients who received an ICD in Leiden University Medical Center were registered in the departmental Cardiology Information System. Characteristics at baseline and data of all follow-up visits were recorded. Eligibility for ICD implantation was based on the international guidelines which, due to evolving guidelines, might have changed over time.[4, 12] For the current study, all ICD treated patients up to august 2008 with a primary indication for implantation, who had a replacement because of battery depletion and who did not receive appropriate therapy before device replacement were included. Prevention was considered primary in case of poor LVEF without prior sustained VA.[8, 9, 11, 12] Patients with a congenital structural or monogenetic heart disease (associated with increased risk of ventricular arrhythmias) were excluded.

Device implantation and programming

All implantations were carried out in the catheterization laboratory and all devices were implanted transvenously and without thoracotomy. During implantation, sensing and pacing thresholds were tested and defibrillation threshold testing was performed. Implanted devices included single-chamber, dual-chamber and cardiac resynchronization therapy-defibrillator (CRT-D) devices and were manufactured by Biotronik (Berlin, Germany), Medtronic (Minneapolis, MN, United States), Boston Scientific (Natick, MA, United States, formerly CPI,

Guidant [St. Paul, MN, United States]) and St. Jude Medical/Ventritex (St. Paul, MN, United States).

All devices were programmed with three consecutive zones: a monitor zone (150-188 bpm), an antitachycardia pacing (ATP) shock zone (188-210 bpm) and an initial shock zone (≥210 bpm). In the monitor zone, no therapy was programmed unless VA was detected during follow-up. In the ATP-shock zone, arrhythmias were initially attempted to be terminated by two bursts of ATP and, if arrhythmia continued, defibrillator shocks were used. In case of VA faster than 210 bpm, device shocks were the initial therapy. Furthermore, atrial arrhythmia detection was set to >170 bpm with supraventricular tachycardia discriminators enabled. In replaced devices, therapy settings were adopted from the initially implanted devices.

Follow-up and device interrogation

ICD treated patients were periodically followed-up every 3-6 months, which included device interrogation. Printouts were checked for appropriate and inappropriate therapy (ATP and shocks). Unscheduled device interrogations were performed in case of symptomatic episodes of arrhythmia and during unplanned hospitalization. Last follow-up data were acquired in August 2008.

Since periodical follow-up is performed every 3-6 months, patients with more than six months of missing data were considered lost to follow-up.

Statistical analysis

Continuous data are expressed as mean ± standard deviation; categorical data are presented as numbers and percentages. Baseline characteristics for patients who received appropriate therapy versus those who did not were compared with the independent-sample t-test for continuous variables and Chi-square test for categorical variables. For all tests a p-value <0.05 was

considered significant. VT or VF, triggering appropriate ICD therapy was considered the primary endpoint. Cumulative incidences were analyzed by method of Kaplan-Meier. Mortality was considered a censoring event.

Results

Baseline characteristics

A total of 2437 patients were treated with an ICD during the study period. Of these, 184 (8%) were diagnosed with a congenital structural or monogenetic cardiac disease and therefore excluded from the study. Of the remaining 2253 patients, 1367 (61%) patients had a primary indication for ICD implantation of whom 154 (11%) had a replacement because of battery depletion. Of these patients, 114 (74%) did not receive appropriate therapy before device replacement and were therefore considered the study population. Mean follow-up was 71 ± 24 months after the initial implantation and 25 ± 21 months after device replacement. At baseline, the majority of patients (mean age 61 ± 11 years, 80% male) had a depressed LVEF (26 ± 9%, range 7-39%), wide QRS complex (136 ± 36 ms) and poor renal function (renal clearance 76 ± 31 ml/min). Sixty-seven (59%) patients had ischemic heart disease, 28 (25%) patients had a history of atrial fibrillation and the majority of patients were in New York Heart Association functional class 3 (n=60, 53%). Medication included beta blockers in 54%, ACE inhibitors in 80% and diuretics for heart failure in 71%. Baseline characteristics are summarized in Table 1.

Table 1. Baseline characteristics.

	All patients (n=114)
Clinical parameters	
Male gender	91 (80%)
Age (yrs)	61 ± 11
Ischemic heart disease	67 (59%)
NYHA functional class	
I	24 (21%)
II	27 (24%)
III	60 (52%)
IV	3 (3%)
QRS-duration (ms)	136 ± 36
Renal clearance (ml/min)*	76 ± 31
LVEF (%)	26 ± 9
Range (%)	7-39
History of atrial fibrillation	28 (25%)
Medication	
Diuretics	81 (71%)
ACE inhibitors	91 (80%)
Beta blocker	62 (54%)

** Renal clearance was determined with the formula of Cockcroft-Gault. ACE = angiotensin-converting enzyme; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.*

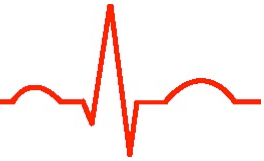
Device replacement

By definition, all patients in the study population had a device replacement because of battery depletion. Over-all device longevity was 47 ± 12 months and differences were observed between different types of ICDs. The longevity was 54 ± 10 months for single-chamber devices, 55 ± 15 months for dual-chamber devices and 42 ± 8 months for CRT-D devices (Table 2).

Table 2. Device longevity per type of ICD.

	All (n=115)	Single-chamber ICD (n=17)	Dual-chamber ICD (n=30)	CRT-D (n=67)
Longevity (months)	47 ± 12	54 ± 10	55 ± 15	42 ± 8

ICD = implantable cardioverter defibrillator; CRT-D = cardiac resynchronization therapy – defibrillator



Occurrence of ventricular arrhythmia

In the study population, 14 (12%) patients received appropriate therapy in response to VT or VF, on average 65 ± 21 months after the first implantation and 20 ± 15 months after device replacement. The cumulative event rate for appropriate therapy *after replacement* was 7% (95% CI 2-13%) at one year, 9% (95% CI 5-15%) at 2 years and 14% (95% CI 5-22%) at 3 years (Figure 1). In Table 3, baseline clinical characteristics between patients who received appropriate therapy versus patients who did not receive appropriate therapy are demonstrated. As can be seen, the only significant difference was observed in the number of patients who used beta blockers: 29% of patients who received appropriate therapy used beta blockers versus 58% of patients who did not receive appropriate therapy ($p<0.05$) (Table 3).

Table 3. Baseline characteristics for patients who received ICD therapy after replacement versus patients who did not receive ICD therapy after replacement.

	Patients who received therapy (n=14)	Patients who did not receive therapy (n=100)	p-value
Clinical parameters			
Male gender	11 (79%)	80 (80%)	0.569
Age (yrs)	60 ± 11	62 ± 11	0.798
Ischemic heart disease	11 (79%)	56 (56%)	0.108
NYHA functional class			0.467
I	4 (29%)	20 (20%)	
II	4 (29%)	23 (23%)	
III	5 (36%)	55 (55%)	
IV	1 (6%)	2 (2%)	
QRS-duration (ms)	125 ± 29	139 ± 35	0.263
Renal clearance (ml/min)*	83 ± 31	77 ± 30	0.678
LVEF (%)	23 ± 10	27 ± 9	0.211
Range (%)	7-39	10-39	
History of atrial fibrillation	5 (36%)	23 (23%)	0.301
Medication			
Diuretics	10 (71%)	71 (71%)	0.974
ACE inhibitors	10 (71%)	81 (81%)	0.403
Beta blocker	4 (29%)	58 (58%)	0.038

** Renal clearance was determined with the formula of Cockcroft-Gault. ACE = angiotensin-converting enzyme; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.*

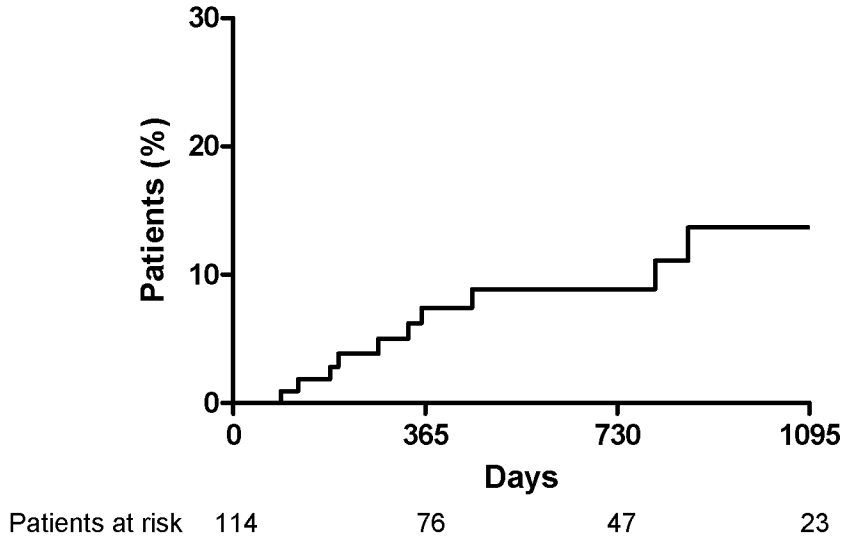


Figure 1: Appropriate therapy after a long event-free period. Kaplan-Meier curve for cumulative incidence of appropriate ICD therapy after device replacement.

Discussion

The main findings of the current study on the occurrence of ventricular arrhythmia after an event-free first ICD service-life can be summarized as follows: 1) 74% of patients did not receive appropriate therapy, prior to the first battery depletion; 2) Following device replacement after a therapy-free first ICD service-life, 14% of the patients received appropriate ICD therapy after 3 years of follow-up.

The current study is of additive value to current literature since it is the first to assess the need for ICD back-up after an event-free first battery service-life. These data could give clinicians better insight in the dilemma whether or not to replace an ICD.

The inclusion of primary prevention ICD treatment in the current guidelines increased the number of implantations dramatically. Because of reported device longevities of 4 - 4.7 years and an increased number of implantations,[13] a large number of ICD replacements because of battery

depletion can be expected.[16] Since primary prevention ICD recipients show a relatively low occurrence of appropriate therapy, battery depletion will occur prior to the need for ICD back-up in a large number of patients.[14, 17] This hypothesis is supported by the findings in the current study that in 74% of cases of battery depletion, the ICD has not been required to give its potentially life-saving therapy. Since the patients have not needed ICD back-up during this first battery life, clinicians involved in the follow-up of ICD patients will be posed with questions about the usefulness of device replacement.

The present study is the first to assess the occurrence of VA, requiring ICD back-up after an event-free first battery-life, making direct comparison to previous studies difficult. However, other studies have assessed the occurrence of first appropriate device therapy after long term follow-up and demonstrate a substantial rate of first VA, long after implantation. Alsheikh-Ali and co-workers have evaluated the occurrence and time-dependence of first appropriate therapy, standardized by patient-years in primary prevention ICD patients. The results demonstrated an increased rate of first appropriate therapy in the first two years following implantation. Annual rates of first appropriate therapy were similar in year three, four, five, six and seven after implantation. These results support the current findings that first VA can occur long after the initial implantation and thereby after ICD replacement because of battery depletion.[18] In the Leiden out-of-hospital cardiac arrest study, 456 secondary prevention ICD patients with ischemic heart disease were followed for a mean of 54 months. During this follow-up, Borleffs et al. described a 9% increase in first appropriate ICD therapy from the fifth to the eighth year following implantation. Additionally, the authors state that during this long period of follow-up, 12% of patients experiencing a life threatening VA had their first occurrence more than five years after implantation.[19] Finally, in a study by Tandri and co-workers, incidences of appropriate therapy after 5 event-free years were assessed in primary and secondary prevention ICD

recipients. In the total study population, probability of appropriate therapy was 8% over the following year, 20% over the next five years, and 24% over the next 10 years.[20]

Although the higher incidence of appropriate therapy in secondary prevention ICD patients might make comparison to findings in the currently studied (primary prevention) population difficult,[17] results from previous studies are consistent in the finding of a steady rate of first VA, even after a long event-free period. These findings, combined with the results of the present study indicate that, although the majority of patients do not receive appropriate therapy during first battery service-life, a substantial number of these patients will still receive potentially life-saving appropriate therapy after replacement, warranting device replacement.

Study limitations

Since patients were collected over a period of time, expanding guidelines for the implantation of defibrillators, treatment of acute myocardial infarction, and pharmacological antiarrhythmic therapy could have created a heterogeneous population. Furthermore, a significant group of patients who received an ICD for primary prevention at the Leiden University Medical Center could not be included in the current study, since their ICDs had not reach end of service life at the time of the study.

Conclusion

The current study demonstrates that the majority of primary prevention ICD patients do not experience VA during first battery service-life. However, a substantial number of these patients do experience appropriate ICD therapy after replacement justifying device replacement even if no VA occurred during the first ICD service life.

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Part II

Improvements in risk stratification

Chapter 4

Mortality Risk Score in Primary Prevention Implantable Cardioverter Defibrillator Recipients with Non Ischemic or Ischemic Heart Disease.

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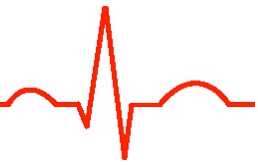
Abstract

Aims: To assess survival and to construct a baseline mortality risk score in primary prevention implantable cardioverter defibrillator (ICD) patients with non-ischemic or ischemic heart disease.

Methods and results: Since 1996, data of all consecutive patients who received an ICD system in the Leiden University Medical Center were collected and assessed at implantation. For the current study, all 1036 patients (age 63 (SD 11) years, 81% male) with a primary indication for defibrillator implantation were evaluated and followed for 873 (SD 677) days. During follow-up, 138 patients (13%) died. Non-ischemic and ischemic patients demonstrated similar survival but exhibited different factors that influence risk for mortality. A risk score, consisting of simple baseline variables could stratify patients in low, intermediate and high risk for mortality. In non-ischemic patients, annual mortality was 0.4% (95% CI 0.0-2.2%) in low risk and 9.4% (95% CI 6.6-13.1%) in high risk patients. In ischemic patients, mortality was 1.0% (95% CI 0.2-3.0%) in low risk and 17.8% (95% CI 13.6-22.9%) in high risk patients.

Conclusion: Utilisation of an easily applicable baseline risk score can create an individual patient-tailored estimation on mortality risk to aid clinicians in daily practice.



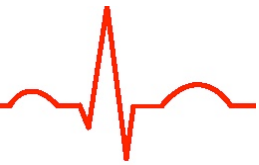
Introduction

Sudden cardiac death, mainly caused by ventricular arrhythmias degenerating into ventricular fibrillation, is responsible for 50% of all cardiac mortality worldwide.[1-3] Large randomised trials have shown a beneficial effect of an implantable cardioverter defibrillator (ICD), initially in survivors of life-threatening arrhythmias,[4-6] but more recently also as primary prevention of sudden arrhythmic death in selected non-ischemic and ischemic patients at high risk.[7-10] Since the implementation of primary prevention in the international guidelines, implantation rates have increased drastically to 160 000 yearly in the United States.[11-13] So far, data on the survival of primary prevention ICD patients are limited to post-hoc analyses of large randomised trials requiring specific patient characteristics for inclusion. This could cause the results to be less applicable to the more diverse, presently indicated population outside the setting of a clinical trial. Since 1996, all ICD recipients in the Leiden University Medical Center have been assessed and followed up. This cohort offers a unique opportunity to study mortality and to identify baseline parameters that influence risk. Furthermore, an easy-to-use and clinically applicable algorithm is created to aid clinicians in patient tailored survival estimations for patients with non-ischemic or ischemic heart disease.

Methods

Patients and study protocol

From 1996 to 2007, all consecutive patients who received an ICD system in the Leiden University Medical Center were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center). Characteristics at baseline, data of the implant procedure, and data of all follow-up visits were recorded. For the current study, patients with a primary indication for defibrillator implantation were evaluated.



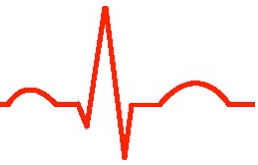
Eligibility for ICD implantation in this population was based on international guidelines for primary prevention which, due to evolving guidelines, might have changed over time. In the majority of patients, indication for an ICD was made in the presence of a depressed left ventricular ejection fraction [LVEF] with or without non sustained ventricular tachycardia (nsVT).[14, 15] Ischemic heart disease was defined as the presence of significant coronary artery disease (a diameter stenosis of at least 50% in at least one coronary artery).[16] Patients with congenital structural or monogenetic heart disease (associated with an increased risk of sudden arrhythmic death) were excluded from the analysis.

Definitions of variables

All tested variables were acquired at defibrillator implantation and were defined and categorised according to literature or common practice. Age was categorised in ≥ 70 years or < 70 years;[17] a history of nsVT was defined as a run of 3 to 30 ventricular ectopic beats at a rate > 120 beats per minute;[18] renal clearance was estimated with the formula of Cockroft-Gault and categorised in normal or stage 1 renal failure (> 90 ml/min), stage 2 renal failure (60-90 ml/min), or stage 3-5 renal failure (≤ 60 ml/min);[19] QRS duration was categorised as ≥ 130 ms or < 130 ms; LVEF was categorised as ≤ 25% or > 25%;[20] atrial fibrillation (AF) was defined as a history of AF, as documented on ECG; a history of smoking was defined if a patient had a positive answer when asked for past or present smoking;[21] and body mass index was defined as ≥ 30 kg/m^2 or < 30 kg/m^2.[22]

Device implantation

All defibrillator systems used were implanted transvenously and without thoracotomy. During the implant procedure testing of sensing and pacing thresholds and defibrillation threshold testing was performed. Used systems were manufactured by Biotronik (Berlin, Germany), Medtronic



(Minneapolis, MN, United States), Boston Scientific (Natick, MA, United States, formerly CPI, Guidant [St. Paul, MN, United States]) and St. Jude Medical/Ventritex (St. Paul, MN, United States).

Defibrillators were programmed as follows: a ventricular arrhythmia monitor zone was programmed in all patients (150-188 bpm) No therapy was programmed in this zone until during follow-up arrhythmias were detected. Ventricular arrhythmias faster than 188 bpm were initially attempted to be terminated with two bursts of ATP and, after continuation of the arrhythmia, with defibrillator shocks. In the case of a ventricular arrhythmia faster than 210 bpm, device shocks were the initial therapy. Furthermore, atrial arrhythmia detection was set to >170 bpm with SVT discriminators enabled. Settings were adapted, only when clinically indicated (i.e. hemodynamic well tolerated ventricular tachycardia at high rate; ventricular tachycardia in the monitor zone).

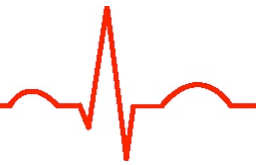
Long-term follow-up

Patient check-up was scheduled every three-six months. Device interrogation printouts were checked for appropriate and inappropriate ICD therapy (ATP or shocks). Therapies were classified as appropriate when they occurred in response to ventricular tachycardia or ventricular fibrillation and as inappropriate when triggered by sinus or supraventricular tachycardia, T-wave oversensing, or electrode dysfunction. Furthermore, follow-up included all-cause mortality.

In the Dutch health care system, all patients are followed by the implanting centre. Since periodical follow-up was performed every three to six months, patients without data on the past six months were considered as lost to follow-up.

Statistical analysis

Continuous data are expressed as mean with standard deviation (SD) or median with 25th and 75th percentile where appropriate; dichotomous data are presented as numbers and percentages.



Event rates for all-cause mortality were analyzed by method of Kaplan-Meier. Differences in event rates (non-ischemic vs. ischemic heart disease) were assessed using logistic regression. Missing values were imputed using the single imputation procedure.[23] Last follow-up data were acquired in November 2008.

To obtain a risk score, composed of robust, reproducible and non clinician driven variables, the use of medication at baseline was not used in its construction. All other baseline variables were entered as categorical variables. Firstly, the variables were studied in univariate logistic regression models, with all-cause mortality as outcome. Variables with a p-value <0.10 were further evaluated in a multivariate logistic model, using backward stepwise selection. At each step, the least significant variable was discarded from the model, until all variables in the model reached a p-value <0.25. With the variables' regression coefficient in this multivariate model, a simple risk stratification score was designed by giving a base regression coefficient the value of one point on the risk score and giving all variables the associating score, according to their multiplication of this base regression coefficient and rounding it of to the nearest whole or half number. Subsequently, the patient specific values for the predictors in the score were summed to obtain a score for each patient. The ability of the score to discriminate between patients who did and patients who did not reach the end-point was estimated by the area under the curve of the receiver operator curve. After the determination of the individual risk score per patients, cut offs were determined for a population at low, intermediate and high risk of mortality. These cut-offs were chosen to optimize the discriminative effect of the model without making groups too small. Bootstrap with 1000 resamples was used for internal validation and to assess the stability of variable selection.[24] In the calculation of the 95% confidence interval (95% CI) for event rates, a Poisson distribution of the observed number of events was presumed. All analyses (except bootstrapping analysis) were performed with SPSS for Windows, version 14.0 (SPSS, Chicago, IL). For the bootstrapping analysis, R (version 2.9.1) was used.

Results

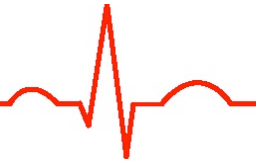
Baseline characteristics

Since 1996, data of 1086 consecutive patients receiving an ICD for primary prevention and without diagnosed congenital heart disease or monogenetic heart disease (associated with an increased risk of sudden arrhythmic death) were prospectively collected. Fifty patients (4.6%) were lost to follow-up. The remaining 1036 ICD recipients were included in the analysis. Median follow-up time was 721 days (interquartile range, 308 to 1271 days). The majority of patients (81% men, mean age 63 (SD 11) years) had a depressed LVEF (29 (SD 12) %), wide QRS (131 (SD 35) ms) and poor renal function (renal clearance 78 (SD 35) ml/min). Medication included beta blockers in 73%, ACE inhibitors or AT antagonists in 85% and diuretics for congestive heart failure in 75%. Baseline characteristics are summarised in Table 1. Seven-hundred-and-four (68%) out of all 1036 patients had ischemic heart disease. The remaining 332 (32%) patients were considered non-ischemic. Ischemic ICD recipients were more often male (87% vs. 66%, $p<0.001$), had a higher age (64 (SD 11) vs. 61 (SD 12) years, $p<0.001$) and shorter QRS duration (126 (SD 34) vs. 140 (SD 36) ms, $p<0.001$), as is shown in Table 1.

Follow-up

During a median follow-up time was 721 days (interquartile range, 308 to 1271 days), 138 patients (13%) died. Total follow-up was 2475 patient-years. Survival analysis showed a cumulative mortality of 6% (95% CI 4-7%) at one year, 17% (95% CI 13-20%) at three years and 27% (95% CI 22-32%) at six years follow-up. Stratification by type of underlying disease did not demonstrate differences in survival (Figure 1) (odds ratio, adjusted for age: 1.0, 95% CI 0.7-1.5).

A total of 6575 episodes of ventricular arrhythmia, causing appropriate device therapy, was noted in 220 (21%) patients. These consisted of 6220 arrhythmia episodes being terminated



by ATP in 148 (14%) patients and 355 episodes being terminated by ICD shocks in 113 (11%) patients.

Table 1. Baseline characteristics

	All (n=1036)	Non-ischemic (n=332)	Ischemic (n=704)	p-value	Patients with missing data
Clinical parameters					
Male gender (%)	835 (81)	220 (66)	615 (87)	<0.001	0
Age, mean (SD), years median (interquartile range), years	63 (11) 64 (56; 71)	61 (12) 64 (55; 70)	64 (11) 65 (57; 72)	<0.001	0
History of nsVT (%)	287 (28)	96 (29)	191 (27)	0.5	0
Renal clearance, mean (SD), ml/min*	78 (35)	80 (37)	77 (34)	0.3	41 (4)
QRS-duration, mean (SD), ms	131 (35)	140 (36)	126 (34)	<0.001	8 (1)
LVEF, mean (SD), %	29 (12)	29 (14)	29 (11)	0.7	59 (6)
History of atrial fibrillation (%)	283 (27)	107 (32)	176 (25)	0.015	2 (0)
Diabetes (%)	226 (22)	54 (16)	172 (24)	0.003	35 (3)
History of smoking (%)	491 (47)	146 (44)	345 (49)	0.130	63 (6)
Body mass index, mean (SD), kg/m^2	26 (4)	26 (4)	26 (4)	0.3	51 (5)
Implantable cardioverter defibrillator					
Single chamber	50 (5%)	17 (5%)	33 (5%)	0.8	0
Dual chamber	409 (40%)	83 (25%)	326 (46%)	<0.001	0
Cardiac resynchronization therapy	577 (56%)	232 (70%)	345 (49%)	<0.001	0
Medication					
Beta-blocker (%)	647 (63)	212 (64)	435 (62)	0.5	0
Sotalol (%)	112 (11)	27 (8)	85 (12)	0.057	0
ACE inhibitors / AT antagonist (%)	879 (85)	284 (86)	595 (85)	0.7	0
Statins (%)	681 (66)	106 (32)	575 (82)	<0.001	0
Diuretics for CHF (%)	781 (75)	271 (82)	510 (72)	<0.001	0
Amiodarone (%)	149 (14)	44 (13)	105 (15)	0.5	0

** Renal clearance was determined with the formula of Cockroft-Gault.*
ACE = angiotensin-converting enzyme; AT = angiotensin; CHF = congestive heart failure; LVEF = left ventricular ejection fraction; nsVT = non sustained ventricular tachycardia

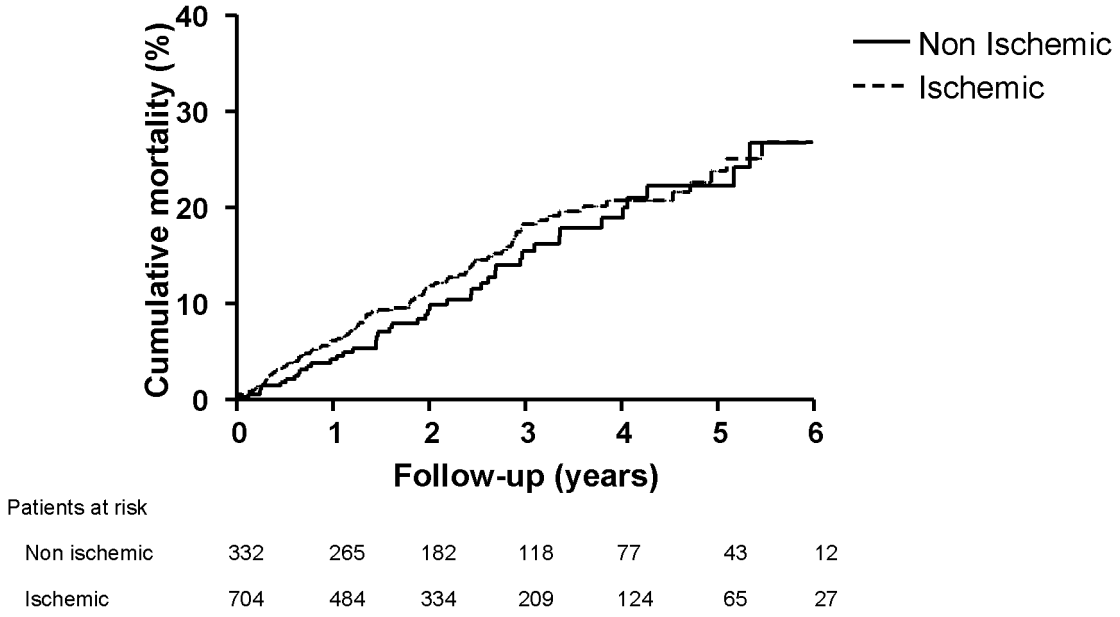


Figure 1: All-cause mortality. Kaplan-Meier curve for cumulative all-cause mortality in patients with non-ischemic heart disease vs. ischemic heart disease.

Mortality risk score in non-ischemic heart disease

Univariate and subsequent multivariate logistic regression identified the following variables as suitable for the construction of a predictive model: (1) poor renal function, (2) poor LVEF, (3) history of AF and (4) high age. The strongest predictor of mortality was a renal clearance ≤60 ml/min (odds ratio 5.4, 95% CI 1.7-17.5), when compared to renal clearance > 90 ml/min (Table 2). Bootstrap analysis showed that renal clearance, LVEF, a history of AF and high age were selected in 97%, 95%, 60%, and 49% respectively. As base regression coefficient, 0.4 was used. For each variable, the appropriate risk score was determined by calculating the multiplications of this base regression coefficient (Table 3). The area under the receiver operator curve of the acquired risk score was reasonably good: 0.76 (95% CI 0.69 – 0.82). Application of this risk score on the study population with non-ischemic heart disease facilitates the stratification in three risk categories: (1) low risk (0-2 points); (2) intermediate risk (2.5-4 points); and (3) high risk (4.5-8 points).

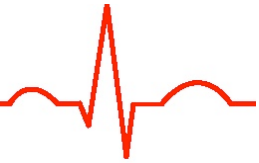


Table 2. Multivariate logistic regression model and corresponding risk score for patients with non-ischemic heart disease.

	Regression coefficient	Odds ratio (95% CI)	P-value	Score
Renal clearance*			.007	
≤60 ml/min	1.694	5.444 (1.696 – 17.472)		4
61-90 ml/min	0.837	2.309 (0.722 – 7.381)		2
LVEF ≤ 25%	0.991	2.694 (1.321 – 5.493)	.006	2.5
History of atrial fibrillation	0.481	1.693 (0.853 – 3.360)	.132	1
Age ≥ 70 yrs	0.401	1.493 (0.715 – 3.117)	.286	1

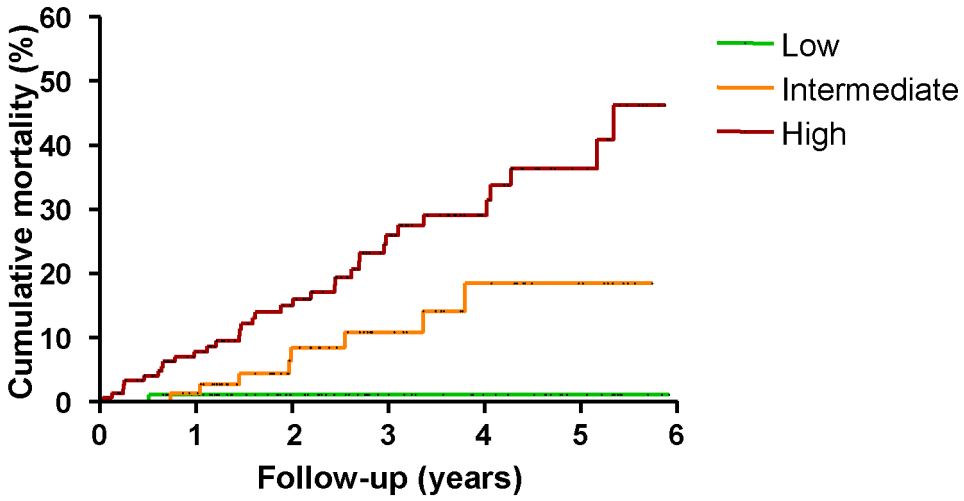
** Renal clearance was determined with the formula of Cockroft-Gault.*
CI = Confidence interval; LVEF = left ventricular ejection fraction

Table 3. Risk stratification and corresponding event rates for mortality in patients with non-ischemic heart disease.

	Risk score	Patients	Patient-years	Events	Event rate per 100 patient-years (95% CI)
Low risk	0-2	91	256	1	0.4 (0.0-2.2)
Intermediate risk	2.5-4	91	226	8	3.5 (1.5-7.0)
High risk	4.5-8	150	372	35	9.4 (6.6-13.1)
Total		332	854	44	5.2 (3.7-6.9)

In patients with low risk for all-cause mortality (91/332, 27%), one patient (1%) died during 256 patient-years, corresponding to an event-rate of 0.4 (95% CI 0.0-2.2) per 100 patient-years (Table 4). Survival analysis showed a cumulative mortality of 1% (95% CI 0-3%) at one year, three years and at six years follow-up (Figure 2). In the population with intermediate risk (91/332, 27%), eight patients (9%) died during 226 patient-years. Therefore, the calculated event rate is 3.5 (95% CI 1.5-7.0) per 100 patient-years. Survival analysis showed a survival of 1% (95% CI 0-4%) at one year, 11% (95% CI 2-19%) at three years and 18% (95% CI 6-31%) at six

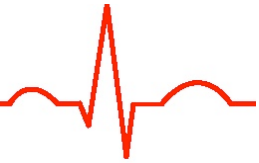
years follow-up. Finally, in the population with a risk score ≥ 4.5 points (150/332, 45%), 35 patients died during 372 patients-years, which corresponds to an event rate of 9.4 (95% CI 6.6-13.1) per 100 patients-years. For this group, survival was 8% (95% CI 3-12%) at one year, 26% (95% CI 17-35%) at three years and 46% (95% CI 30-62%) at six years follow-up.



Patients at risk

Low	91	77	54	35	27	17	6
Intermediate	91	73	46	31	20	12	4
High	150	117	84	54	32	16	4

Figure 2: Risk stratification for all-cause mortality in non-ischemic cardiomyopathy. Kaplan-Meier curve for cumulative all-cause mortality in patients with non-ischemic heart disease with low, intermediate, or high risk.



Mortality risk score in ischemic heart disease

In ICD patients with ischemic heart disease, the multivariate logistic model contained the following variables: (1) poor renal function, (2) history of smoking, (3) diabetes, (4) poor LVEF, (5) high age and (6) long QRS duration. Similar to the non-ischemic population, the strongest predictor of mortality was a renal clearance ≤60 ml/min (odds ratio 4.5, 95% CI 2.1-9.7), when compared to renal clearance > 90 ml/min (Table 4). Bootstrapping analysis showed that renal clearance, history of smoking, diabetes, LVEF, high age, and long QRS duration were selected in 100%, 100%, 98%, 99%, 97%, and 84% respectively. The area under the receiver operator curve of the acquired risk score was reasonably good: 0.81 (95% CI 0.76 – 0.87). Using 0.4 as the base regression coefficient, the risk score for each variable was determined. Stratification resulted in three risk categories: (1) low risk (0-2 points); (2) intermediate risk (3-7 points); and (3) high risk (8-13 points).

Table 4. Multivariate logistic regression model and corresponding risk score for patients with ischemic heart disease.

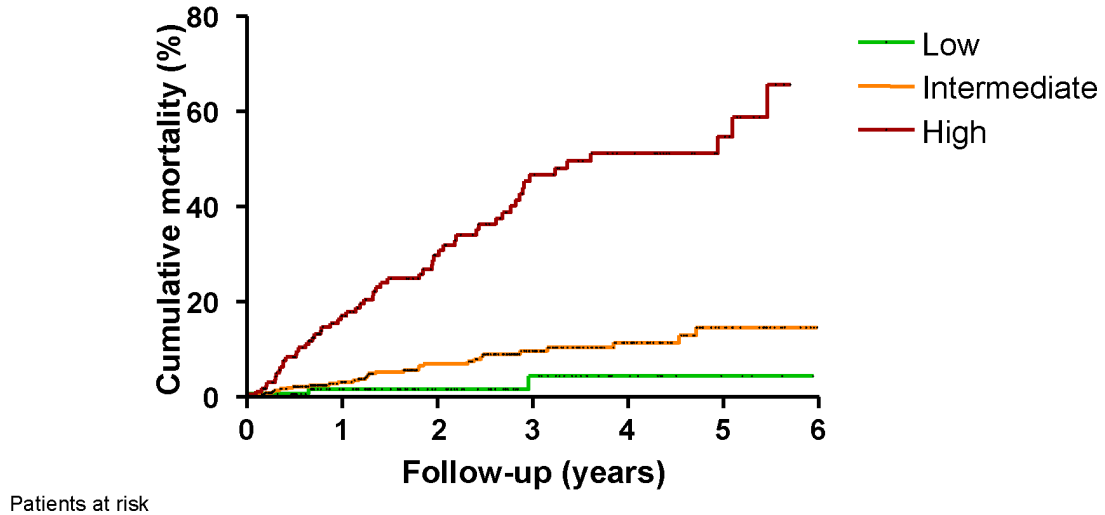
	Regression coefficient	Odds ratio (95% CI)	P-value	Score
Renal clearance*			.000	
≤60 ml/min	1.509	4.523 (2.119 – 9.657)		4
61-90 ml/min	0.388	1.474 (0.667 – 3.256)		1
History of smoking	1.146	3.145 (1.884 – 5.252)	.000	3
Diabetes	0.889	2.434 (1.466 – 4.041)	.001	2
LVEF ≤ 25%	0.870	2.388 (1.465 – 3.892)	.000	2
Age ≥ 70 yrs	0.788	2.200 (1.283 – 3.773)	.004	2
QRS duration ≥ 130 ms	0.498	1.694 (1.035 – 2.772)	.036	1

** Renal clearance was determined with the formula of Cockroft-Gault.*
CI = Confidence interval; LVEF = left ventricular ejection fraction

As can be seen in Table 5, event rates varied from 1.0 (95% CI 0.2-3.0) per 100 patient-years in the low-risk group, to 17.8 (95% CI 13.6-22.9) per 100 patient-years in the high risk group. Six-year mortality was 4% (95% CI 0-10%) in ischemic low risk patients, and 66% (95% CI 49-82%) in the high risk population.

Table 5. Risk stratification and corresponding event rates for mortality in patients with ischemic heart disease.

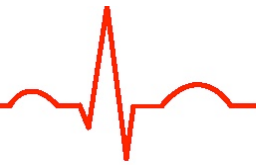
	Risk score	Patients	Patient-years	Events	Event rate per 100 patient-years (95% CI)
Low risk	0-2	127	291	3	1.0 (0.2-3.0)
Intermediate risk	3-7	416	993	31	3.1 (2.1-4.4)
High risk	8-13	161	337	60	17.8 (13.6-22.9)
Total		704	1621	94	5.8 (4.7-7.1)



Patients at risk

Low	127	91	58	35	19	11	7
Intermediate	416	292	209	135	80	42	19
High	161	104	68	41	27	14	3

Figure 3: Risk stratification for all-cause mortality in ischemic cardiomyopathy. Kaplan-Meier curve for cumulative all-cause mortality in patients with ischemic heart disease with low, intermediate, or high risk.



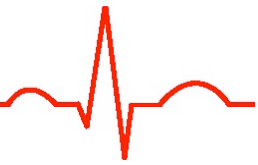
Discussion

In the current study on the long-term follow-up and the construction of an easy-to-use mortality risk score in non-ischemic and ischemic primary prevention ICD patients, the findings can be summarised as follows: 1) Cumulative mortality was approximately 5% per year; 2) Non-ischemic and ischemic patients demonstrated an equal survival; 3) Non-ischemic and ischemic ICD recipients exhibited a different risk profile in the prediction of mortality; 4) A baseline risk score can easily estimate an individual patient's risk for mortality.

Using the presented risk score, a patient, considered for primary prevention ICD treatment, could be stratified as follows: 1) determine if the patient has ischemic or non-ischemic heart disease to determine the risk factors, influencing mortality risk (Table 2 or Table 4); 2) add the risk score points, associated with patient's risk factors; 3) allocate patient as low, intermediate or high risk for mortality en estimate event-rate (Table 3 or Table 5).

Mortality

In the current analysis, 138 patients (13%) died during a mean follow-up of median follow-up time was 721 days (interquartile range, 308 to 1271 days). Cumulative mortality after one, three and six year was 6%, 17% and 27% respectively and was not different in non-ischemic or ischemic ICD recipients. Previously, few trials have been conducted on a population containing non-ischemic, as well as ischemic patients. Bardy and co-workers show a beneficial effect of defibrillator implantation in ICD recipients with non-ischemic or ischemic heart disease and congestive heart failure.[25] In their population, crude annual death rates reach up to 5.7% which are comparable to our annual crude death rate of 5.6%. Other large trials assessing the effect of an ICD in patients with ischemic heart disease only, demonstrate an annual death rate of 7.0% to 8.5%.[26, 27] These higher rates can be explained by the poor patient characteristics, required to be



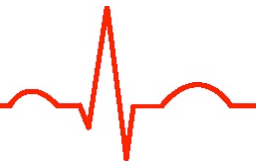
eligible for inclusion. The study population might therefore not prove to be completely representative for the "real life" population considered for defibrillator implantation.

Risk factors

The current study reveals different factors influencing risk for mortality for either type of heart disease. For all-cause mortality in non-ischemic patients, a history of AF, depressed LVEF, poor renal function and high age are predictors of mortality during follow-up. A depressed LV function has proven to be one of the most powerful markers of cardiac death in patients without an ICD, causing it to be the current main criterion for primary prevention defibrillator eligibility.[28, 29] Furthermore, AF, renal failure and high age have been described in the prediction of death in a population with, as well as without an ICD.[30-34] Furthermore, renal failure has previously been noted as one of the strongest predictors of mortality in a population with cardiac disease.[35, 36] Characteristics increasing risk for mortality in ischemic patients were more diverse: renal failure, a history of smoking, diabetes, poor LV function, high age and prolonged QRS duration. Risk stratification in the ischemic ICD recipients of MADIT II revealed similar risk factors, as described by Goldenberg et al.[37] Additionally, a sub-analysis of the MUSTT exposed these factors as predictors of mortality in the non-ICD treated arm.[38]

Risk score

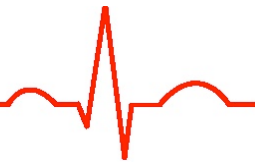
Previous studies constructing a risk score were mainly limited to patients in the setting of large clinical trials, requiring specific characteristics to be eligible for inclusion, and followed patients for a relatively short time. This might cause the findings to be less applicable to the more diverse population, currently receiving an ICD for primary prevention in a "real life" population. In a sub-study of the MUSTT, Buxton and co-workers constructed a model containing eight factors in patients with ischemic heart disease.[39] Since the MUSTT study was designed to test the ability of



electrophyiologically (EP) guided therapy to reduce risk of arrhythmic events, all included patients underwent EP testing. Inducibility of VT at EP testing was one of the factors, found to increase risk for all-cause mortality. In the current study, as in the present population receiving ICD treatment, not all patients underwent EP testing, therefore making it hard to assess its prognostic value. The power of the presented model to correctly identify patients in the MUSTT was 0.78, which is comparable to the 0.81 in the current study. Goldenberg and co-workers constructed a model with five factors in the post-myocardial infarction population of the MADIT II.[40] This model, containing New York Heart Association functional class, AF, a wide QRS, high age and renal failure, shows substantial resemblance with the model constructed in the current study.

Clinical implications

The results of this study imply that the large population, currently indicated for ICD treatment, can be easily stratified for mortality risk. The proposed risk score can prove an easily applicable mean to aid clinicians in making individual patient-tailored statements on risk for mortality, prior to defibrillator implantation in daily practice. Its utilisation could greatly increase survival estimation for the clinician, as well as the patient. Of note that the proposed risk score does require validation. Furthermore, clinicians have shown concern that the population, eligible for primary prevention ICD treatment, is of such magnitude that provision of ICD therapy will strain financial resources and the pool of trained personnel.[41, 42] In current daily practice, the choice on the most efficient allocation of ICD treatment is mostly based on the life expectancy of the patient. With the current study, a group of patients, currently indicated for ICD treatment, can be identified who have a very short life expectancy, regardless of ICD implantation. These findings could aid clinicians in current daily practice in their choices for the optimal allocation of ICD treatment.

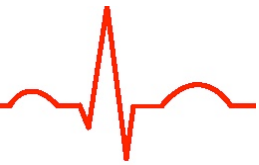


Limitations

This was a non-randomised prospective observational study, performed to assess the long-term follow-up in non-ischemic or ischemic primary prevention ICD patients outside the setting of a clinical trial. Since patients were collected over a period of eleven years, expanding guidelines for the implantation of defibrillators, treatment of acute myocardial infarction, and pharmacological antiarrhythmic therapy could have created a heterogeneous population.[43, 44] The currently constructed risk score does not take pharmacological treatment in consideration since inclusion of these clinician driven variables would lead to a less robust and reproducible score. Furthermore, since no control group was assessed, no statements can be made on the effect of ICD treatment. Finally, the constructed risk score requires external validation.

Conclusion

Non-ischemic and ischemic primary prevention ICD recipients demonstrate similar survival during long-term follow-up but exhibit different factors that influence risk for mortality. Utilisation of an easily applicable baseline risk score can create an individual patient-tailored estimation on mortality risk to aid clinicians in daily practice.



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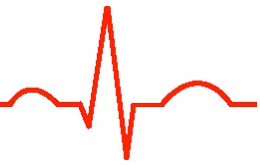

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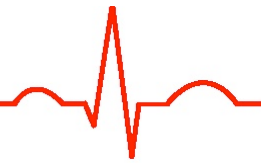

Chapter 5

Prognostic Importance of Atrial Fibrillation in Implantable Cardioverter Defibrillator Patients.

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J am Coll Cardiol 2009; 55:879-885

Abstract

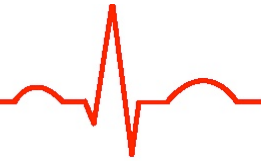
Objective: To assess the prevalence of different types of atrial fibrillation (AF) and their prognostic importance in implantable cardioverter defibrillator (ICD) patients.

Background: The prevalence of AF has taken epidemic proportions in the population with cardiovascular disease. The prognostic importance of different types of AF in ICD patients remains unclear.

Methods: Data on 913 (79% men, mean age 62±13 years) consecutive patients receiving an ICD at the Leiden University Medical Center were prospectively collected. Among other characteristics, the existence and type of AF (paroxysmal, persistent or permanent) was assessed at implantation. During follow-up, the occurrence of appropriate or inappropriate device therapy, as well as mortality was noted.

Results: At implantation, 73% of patients had no history of AF, 9% had a history of paroxysmal AF, 7% had a history of persistent AF and 11% had permanent AF. During 833±394 days follow-up, 117 patients (13%) died, 228 patients (25%) experienced appropriate device discharge and 139 patients (15%) received inappropriate shocks. Patients with permanent AF exhibited more than double the risk for mortality, ventricular arrhythmias triggering device discharge, and inappropriate device therapy. Patients with paroxysmal or persistent AF did not show a significant increased risk for mortality or appropriate device therapy but demonstrated almost three times risk for inappropriate device therapy.

Conclusions: In the population currently receiving ICD treatment outside the setting of clinical trials a large portion has either a history of AF or permanent AF. Both types of AF have prognostic implications for mortality and appropriate, as well as inappropriate device discharge.



Introduction

Large randomized trials have shown a beneficial effect of implantable cardioverter defibrillator (ICD) therapy, initially in survivors of life-threatening arrhythmias,(1-3) but more recently also in the primary prevention of sudden arrhythmic death in selected ischemic and non ischemic patients at high risk, based solely on a poor left ventricular ejection fraction (LVEF).(4-7) The implementations of these results in the international guidelines have, besides a considerable increase in the number of implants, caused a significant change in the population considered for ICD therapy as the majority of implantations now occurs in patients with a low LVEF and symptoms of heart failure (primary prevention patients) (8)

Atrial fibrillation (AF) is common in patients with low LVEF and symptoms of heart failure with a reported prevalence of AF in congestive heart failure patients of up to 50% in patients with New York Heart Failure (NYHA) functional class IV.(9-12). Furthermore, AF is associated with significant morbidity and mortality both in the general population and more specific in patients with heart failure.(13, 14)

As the number of ICD implants in patients with low LVEF and heart failure is increasing, it can be expected that more patients with paroxysmal, persistent or permanent AF will receive an ICD. So far, most studies focused on a single type of AF (e.g. paroxysmal/persistent or permanent AF) and were often conducted in the setting of a clinical trial.(15-19) The prevalence and prognostic implications of a history of AF at ICD implant remain unclear. The present study aims at providing insight in the effects of AF on mortality, occurrence of ventricular arrhythmias and inappropriate device therapy during long-term follow-up in a large cohort of ICD patients.

Methods

Patients and study protocol

Since 1996, all patients receiving an ICD at the Leiden University Medical Center were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center). Characteristics at baseline, data of the implant procedure, and data of all follow-up visits were recorded.

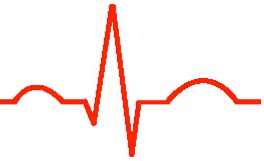
Eligibility for ICD implantation in this population was based on international guidelines which, due to evolving guidelines, might have changed over time. Patients were implanted after surviving life-threatening ventricular arrhythmias or in the presence of a depressed LVEF with or without non sustained ventricular tachycardia.(8, 20)

Atrial fibrillation

At baseline, patients were grouped according to the type of AF. This resulted in the following four groups: (1) patients without a history of (documented) AF, the "no AF" group; (2) patients with a history of paroxysmal AF as documented on ECG; (3) patients with a history of persistent AF as documented on ECG; and (4) patients with permanent, accepted AF. If the arrhythmia terminates spontaneously and within 7 days, AF is designated paroxysmal; when sustained beyond 7 days or being terminated by pharmacological or electrical cardioversion, AF is termed persistent. The category of persistent AF also includes cases of long-standing AF, usually leading to permanent AF, in which cardioversion has failed or has been foregone.(10, 21)

Device implantation

All defibrillator systems used were implanted transvenously and without thoracotomy. During the implant procedure testing of sensing and pacing thresholds and defibrillation threshold testing



was performed. Used systems were manufactured by Biotronik (Berlin, Germany), Medtronic (Minneapolis, MN, United States), Boston Scientific (Natick, MA, United States, formerly CPI, Guidant [St. Paul, MN, United States]) and St. Jude Medical/Ventritex (St. Paul, MN, United States).

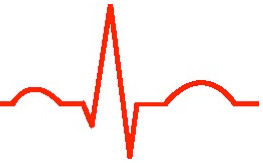
Long-term follow-up

Patient check-up was scheduled every three to six months. Device interrogation printouts were checked for appropriate and inappropriate ICD therapy (anti tachycardia pacing [ATP] or shocks). Therapies were classified as appropriate when they occurred in response to ventricular tachycardia or ventricular fibrillation and as inappropriate when triggered by sinus or supraventricular tachycardia, T-wave oversensing, or electrode dysfunction. Furthermore, follow-up included all-cause mortality.

In the Dutch health care system, all patients are followed by the implanting center. Since periodical follow-up was performed every three to six months, patients without data on the past six months were considered as lost to follow-up.

Statistical analysis

Continuous data are expressed as mean ± standard deviation; dichotomous data are presented as numbers and percentages. Comparison of continuous or dichotomous data was performed with the Student's *t* test for paired and unpaired data and Chi-square tests with Yates correction when appropriate. Non-parametric data (NYHA functional class) was compared using the Mann-Whitney U-test. Cumulative event rates (all-cause mortality, appropriate device therapy, appropriate device shocks and inappropriate device shocks) were analyzed by the method of Kaplan-Meier. The relation between different types of AF at baseline and the occurrence of end-points was assessed using a Cox proportional hazard model, calculating a hazard ratio with a



95%-confidence interval (95% CI) and adjusting for age, sex, renal clearance, LVEF, QRS-duration, NYHA functional class, and usage of beta-blockers. For all tests, a p-value <0.05 was considered significant.

Results

Baseline characteristics

Data of 955 consecutive patients receiving an ICD in the Leiden University Medical Center were prospectively collected. Forty-two patients (4.4%) were lost to follow-up. The remaining 913 ICD recipients were included in the analysis. Mean follow-up time was 833±394 days. The majority of patients (79% men, mean age 62±13 years) had a depressed LVEF (32±14%), wide QRS complex (127±35 ms) and poor renal function (renal clearance 83±38 ml/min). Medication included beta blockers in 76%, ACE inhibitors or AT antagonists in 82% and diuretics for heart failure in 70%. Baseline characteristics are summarized in Table 1.

Six-hundred-and-sixty-three (73%) out of all 913 patients had no history of AF (no AF), 84 (9%) patients had a history of paroxysmal AF, 64 (7%) patients had a history of persistent AF, and the remaining 102 (11%) patients had permanent AF. All patients with a history of paroxysmal or persistent AF were in sinus rhythm at discharge after device implantation. As is shown in Table 1, when compared to patients without a history of AF, patients with AF were older, had higher NYHA functional class and were more often treated with diuretics, amiodarone and oral anticoagulants.

Table 1. Baseline characteristics.

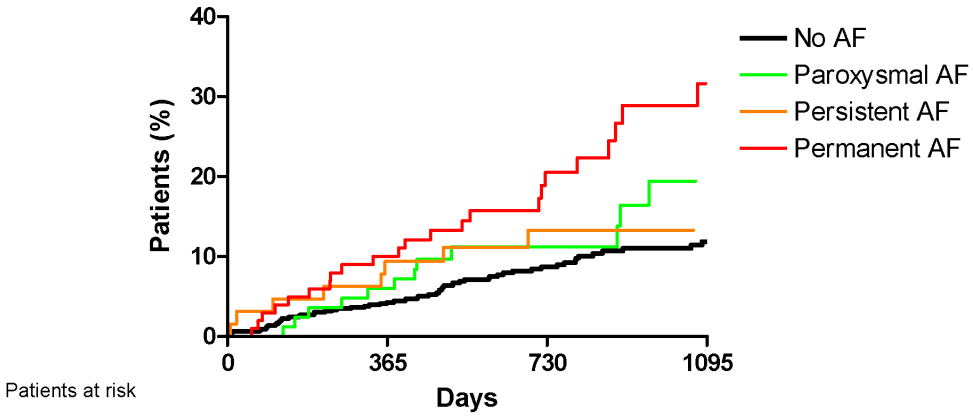
	All (n=913)	No AF (n=663)	Paroxysmal AF (n=84)	Persistent AF (n=64)	Permanent AF (n=102)
Clinical parameters					
Male gender	722 (79%)	515 (78%)	64 (76%)	53 (83%)	90 (88%)†
Age (yrs)	62±13	61±13	64±11*	66±10†	67±10‡
Secondary prevention	140 (15%)	94 (14%)	22 (26%)†	9 (14%)	15 (15%)
History of VT	93 (66%)	62 (66%)	15 (68%)	7 (78%)	9 (60%)
History of VF	47 (34%)	32 (34%)	7 (32%)	2 (22%)§	6 (40%)
Primary prevention	773 (85%)	569 (86%)	62 (74%)†	55 (86%)	87 (85%)
History of nsVT	201 (26%)	150 (26%)	17 (27%)	15 (27%)	19 (22%)
Ischemic heart disease	561 (61%)	423 (64%)	49 (58%)	39 (61%)	50 (49%)†
NYHA functional class					
I	228 (25%)	188 (28%)	17 (20%)	10 (16%)*	13 (13%)‡
II	346 (38%)	253 (38%)	37 (44%)	24 (38%)	32 (31%)
III	320 (35%)	208 (31%)	28 (33%)	30 (47%)*	54 (53%)‡
IV	19 (2%)	14 (2%)	2 (2%)§	0 (0%)§	3 (3%)§
Renal clearance (ml/min)	83±38	86±38	75±39†	77±43	72±29‡
QRS-duration (ms)	127±35	125±34	123±33	129±35	140±34‡
LVEF (%)	32±14	33±14	32±15	32±14	30±12
Diabetes	177 (19%)	127 (19%)	16 (19%)	14 (22%)	20 (20%)
History of smoking	380 (42%)	287 (43%)	36 (43%)	24 (38%)	33 (32%)*
Body mass index (kg/m^2)	26±4	26±4	26±4	6±4	26±4
Device type					
Single chamber	43 (5%)	20 (3%)	4 (5%)§	2 (3%)§	17 (17%)‡§
Dual chamber	409 (45%)	234 (49%)	39 (46%)	26 (41%)	20 (20%)‡
CRT-D	461 (51%)	319 (48%)	41 (49%)	36 (56%)	65 (64%)†
Medication					
Beta-blockers	691 (76%)	510 (77%)	63 (75%)	46 (72%)	72 (71%)
ACE inhibitors / AT antagonist	750 (82%)	548 (83%)	66 (79%)	49 (77%)	87 (85%)
Ca-antagonists	64 (7%)	52 (8%)	3 (4%)	3 (5%)§	6 (6%)
Diuretics	641 (70%)	440 (66%)	65 (77%)*	47 (73%)	89 (87%)‡
Statins	594 (65%)	445 (67%)	53 (63%)	44 (69%)	52 (51%)‡
Amiodarone	125 (14%)	68 (10%)	19 (23%)‡	15 (23%)†	23 (23%)‡
Aspirin	364 (40%)	300 (45%)	32 (38%)	22 (34%)	10 (10%)‡
Oral anticoagulants	504 (55%)	316 (48%)	51 (61%)*	42 (66%)†	95 (93%)‡

**p < 0.05; †p < 0.01; ‡p < 0.001. All compared with no AF group.*
§Comparison was performed with Yates correction.
ACE = angiotensin-converting enzyme; AT = angiotensin; CRT-D = cardiac resynchronization therapy-defibrillator; LVEF = left ventricular ejection fraction; nsVT = non sustained ventricular tachycardia; NYHA = New York Heart Association

Mortality

During a mean follow-up of 833±394 days, 117 patients (13%) died. Study population mortality was 5% (95% CI 4-7%) at one year, 11% (95% CI 8-13) at two years and 15% (95% CI 12-17) at three years of follow-up. In the comparison of the four groups, survival analysis showed a three year cumulative event rate for mortality of 12% (95% CI 9-15%) for no AF, 15% (95% CI 8-24%) for paroxysmal AF, 17% (95% CI 7-27%) for persistent AF, and 32% (95% CI 20-43%) for permanent AF (Figure 1).

Of interest, patients with paroxysmal AF or persistent AF did not demonstrate a significant higher risk for mortality. However, patients with permanent AF exhibited a 70% increased risk for mortality (adjusted hazard ratio 1.7, 95% CI 1.0-2.7, p=0.033).



Patients at risk				
No AF	663	618	358	198
Paroxysmal AF	84	78	44	22
Persistent AF	64	59	42	24
Permanent AF	102	89	49	23

Figure 1: All-cause mortality. Kaplan-Meier curve for all-cause mortality in patients without a history of AF (no AF), paroxysmal AF, persistent AF, or permanent AF.

Appropriate device therapy

During follow-up, ventricular arrhythmias, causing appropriate device therapy (ATP or shocks), were observed in 228 (25%) patients. A total of 5116 episodes was noted, consisting of 4793 (range 1-2194) episodes terminated with ATP in 166 patients and 304 (range 1-33) episodes terminated by ICD shock in 112 patients.

Cumulative event rate for appropriate device therapy (ATP or shock) was 15% (95% CI 13-18%) at one year, 24% (95% CI 21-27) at two years and 30% (95% CI 24-34) at three years of follow-up. As is shown in Figure 2, three years cumulative event rate for appropriate device therapy was 29% (95% CI 24-33%) for no AF, 26% (95% CI 14-39%) for paroxysmal AF, 26% (95% CI 13-38%) for persistent AF, and 49% (95% CI 36-61%) for permanent AF. Patients with permanent AF exhibited twice the risk for appropriate therapy, when compared to patients without a history of AF (adjusted hazard ratio 2.2, 95% CI 1.6-3.2, p<0.001). The group with no history of AF demonstrated similar event rates as patients with a history of paroxysmal or persistent AF.

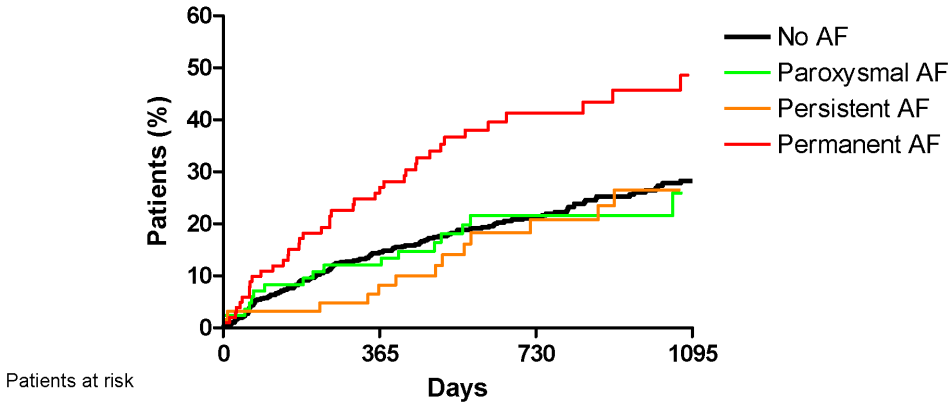
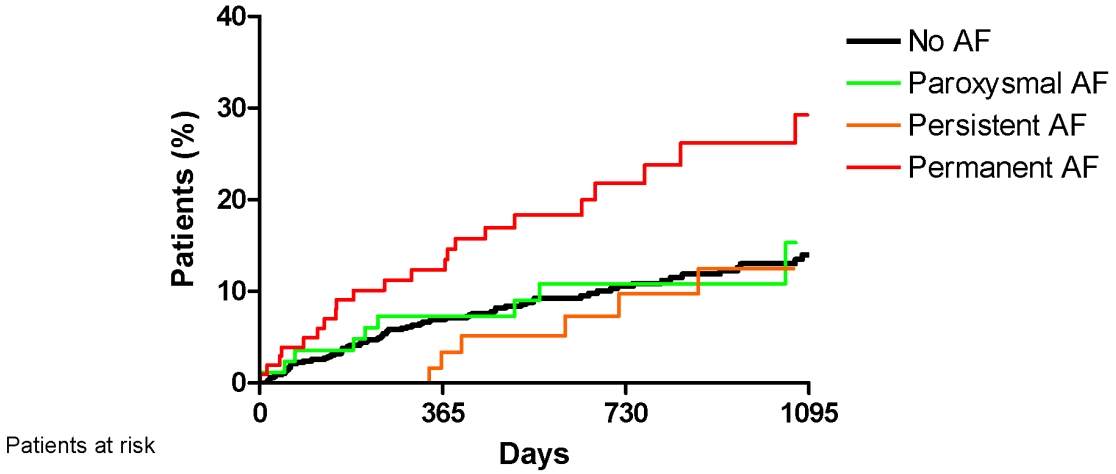


Figure 2: Appropriate device therapy. Kaplan-Meier curve for the occurrence of first appropriate device therapy in patients without a history of AF (no AF), paroxysmal AF, persistent AF, or permanent AF.



Patients at risk				
No AF	663	576	316	172
Paroxysmal AF	84	72	40	18
Persistent AF	64	57	38	20
Permanent AF	102	79	41	20

Figure 3: Appropriate device shock. Kaplan-Meier curve for the occurrence of first appropriate shock in patients without a history of AF (no AF), paroxysmal AF, persistent AF, or permanent AF.

As is shown in Figure 3 and Table 2, the occurrence of appropriate shocks alone showed a similar distribution as the occurrence of all appropriate therapy among the four groups. No differences were observed between patients without a history of AF and those with a history of paroxysmal or persistent AF. Moreover, a doubled risk of appropriate shocks was observed in the permanent AF group when compared to patients with no history of AF (adjusted hazard ratio 2.4, 95% CI 1.5-4.0, $p<0.001$).

Inappropriate device shocks

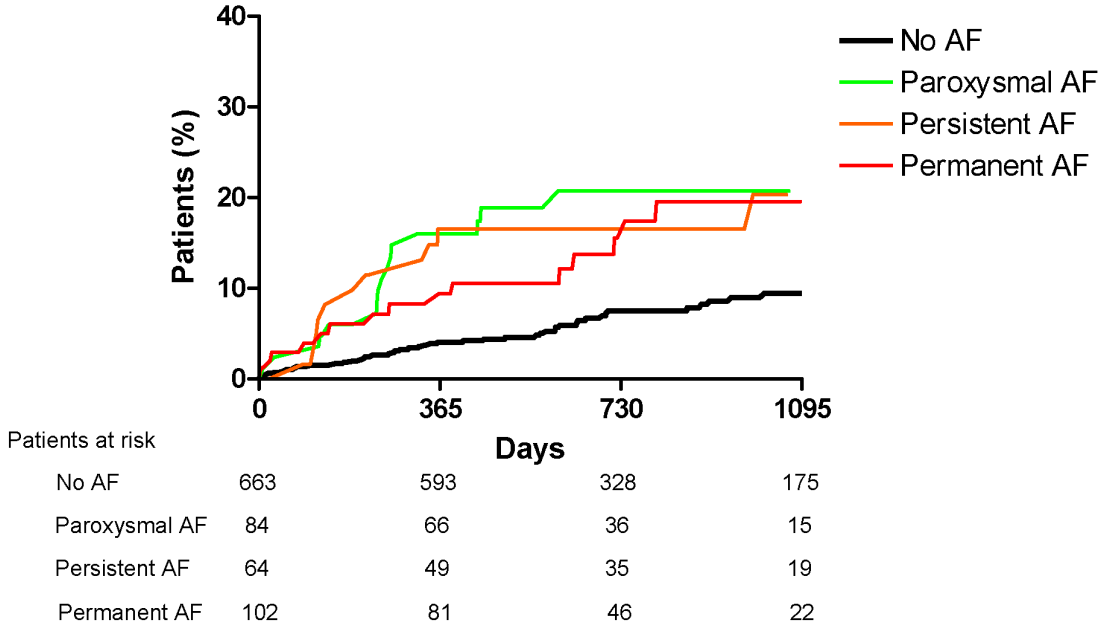
One-hundred-thirty-nine (15%) patients experienced at least one inappropriate device discharge. When comparing the four groups, major differences in event rates were observed. Three years event rate for inappropriate shocks was 13% (95% CI 10-17%) for no AF, 28% (95% CI 15-40%) for paroxysmal AF, 18% (95% CI 15-41%) for persistent AF, and 32% (95% CI 19-45%) for

Table 2. Event rates, hazard ratios, and p-values for end-points

	No AF	Paroxysmal AF	HR (95% CI)	Adjusted HR (95% CI)*	Persistent AF	HR (95% CI)	Adjusted HR (95% CI)*	Permanent AF	HR (95% CI)	Adjusted HR (95% CI)*
	663	84			64			102		
All-cause mortality	69 (10%)	11 (13%)	1.3 (0.7-2.5)	1.2 (0.6-2.3)	12 (19%)	1.6 (0.9-4.1)	1.2 (0.6-2.2)	25 (25%)	2.6 (1.6-4.1)	1.7 (1.0-2.7)
Appropriate therapy	154 (23%)	18 (21%)	1.0 (0.6-1.6)	1.0 (0.6-1.6)	14 (22%)	0.9 (0.5-1.5)	0.9 (0.5-1.6)	42 (41%)	2.1 (1.5-2.9)	2.2 (1.6-3.2)
Appropriate shock	72 (11%)	10 (12%)	1.2 (0.6-2.2)	1.2 (0.6-2.4)	8 (13%)	1.0 (0.5-2.2)	1.1 (0.5-2.4)	22 (22%)	2.2 (1.4-3.6)	2.4 (1.5-4.0)
Inappropriate shock	78 (12%)	21 (25%)	2.5 (1.6-4.1)	2.9 (1.7-4.8)	15 (23%)	1.9 (1.1-3.4)	2.5 (1.4-4.4)	25 (25%)	2.2 (1.4-3.5)	2.7 (1.7-4.4)

*Hazard ratio adjusted for age, sex, renal clearance, left ventricular ejection fraction, QRS duration, New York Heart Association functional class, usage of beta-blocker; CI = confidence interval; HR = hazard ratio

permanent AF (Figure 4). When compared to the group without a history of AF, the permanent AF group showed a more than doubled risk for the inappropriate shocks (adjusted hazard ratio 2.7, 95% CI 1.7-4.4, p<0.001). Patients with a history of paroxysmal AF had the highest risk for inappropriate device shocks (adjusted hazard ratio 2.9, 95% CI 1.7-4.8, p<0.001) during follow-up. It is of note that in the group without a history of AF, (new-onset) AF during follow-up was the cause of inappropriate device shocks in 27 patients (4%)

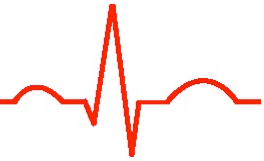


Patients at risk				
No AF	663	593	328	175
Paroxysmal AF	84	66	36	15
Persistent AF	64	49	35	19
Permanent AF	102	81	46	22

Figure 4: Inappropriate device shock. Kaplan-Meier curve for the occurrence of first inappropriate device shock in patients without a history of AF (no AF), paroxysmal AF, persistent AF, or permanent AF.

Discussion

The main findings of the current study on the prognostic importance of AF in ICD patients can be summarized as follows: (1) in the population, currently receiving ICD treatment, 9% have a history of paroxysmal AF, 7% have a history of persistent AF and 11% have permanent AF; (2) patients with permanent AF exhibited a more than doubled risk for mortality, ventricular



arrhythmias triggering device discharge, and inappropriate device shocks than patients without AF; (3) patients with a history of paroxysmal or persistent AF did not show a significantly increased risk for mortality or appropriate device therapy but demonstrated a almost tripled risk for inappropriate device shocks.

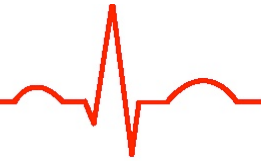
The present analysis adds to prior literature in that it discriminates between different types of AF and that it assesses the population, presently considered for ICD treatment outside the setting of clinical trial.

Mortality

Previous trials have demonstrated the importance of AF in the general population, as well as in a population with symptomatic or asymptomatic heart failure.(13, 14) Benjamin and co-workers showed that the occurrence of AF was associated with a 1.5- to 1.9-fold risk for all-cause mortality, even after adjustment for further cardiovascular conditions related to AF.(13) These findings seem comparable to the 1.7 times increased risk for mortality in patients with permanent AF, as observed in the current analysis. However, when specifically assessing a population with symptoms of heart failure, findings in current literature are inconsistent in the potential relation between AF and the risk for mortality.(14, 22-25) In a post-hoc analyses of the second Multicenter Automatic Defibrillator Implantation Trial, Zareba and co-workers made a comparison between patients with sinus rhythm and AF. Since AF was defined by its presence on the ECG at enrollment, one might assume that all the patients identified with AF have permanent AF and those with paroxysmal or persistent AF, if not coincidentally present at enrollment, will have been classified as having sinus rhythm.(7, 19) Furthermore, the trial only included primary prevention ICD recipients with a prior myocardial infarction. In contrast to the current study, Zareba at al. did not find a relationship between AF and mortality after adjustment for other variables.(19)

Appropriate ICD therapy

One might hypothesize that the occurrence of any type of AF is a marker of worse general cardiac status and therefore that AF will be positively correlated with the occurrence of ventricular arrhythmias. On the other hand, AF could initiate episodes of ventricular arrhythmias and might therefore directly influence the occurrence of ventricular arrhythmias and consequent appropriate device therapy. The facilitation of AF in the initiation of ventricular tachyarrhythmias has been observed by Roy and co-workers during an electrophysiological study.(26) Afterwards, Stein et al. observed 8.9% of the episodes of ventricular arrhythmia to be accompanied by AF.(27) Earlier studies suggested that ventricular arrhythmias are evoked by rapid and uncontrolled AV conduction.(28-30) More recently, Grönefeld et al. suggested that the AV nodal conduction pattern preceding ventricular tachyarrhythmia were short-long-short sequences, rather than solely a rapid conduction.(16) The irregular ventricular excitation leads to heterogeneous depolarization, which subsequently renders the myocardium more susceptible to ventricular arrhythmias.(31, 32) In line with the current findings, prior studies confirm AF to have a positive correlation with the occurrence of ventricular arrhythmias.(16-18) Interestingly, a post-hoc analysis of the Multicenter Automatic Defibrillator Implantation Trial II did not demonstrate a difference in the occurrence of appropriate therapy when comparing (mostly permanent) AF with patients in sinus rhythm.(19) A possible explanation for this difference could be that the permanent AF group in the current study is sicker in a manner not completely accounted for by post hoc statistical adjustment. The present study did not show an increase in appropriate device therapy in the groups with a history of paroxysmal or persistent AF, which could imply that these patients do not have a deterioration of general cardiac status of such magnitude to consequently cause higher occurrence of ventricular arrhythmia. Thus far, no analysis had been reported on the prognostic implications of different types of AF.



Inappropriate ICD shocks

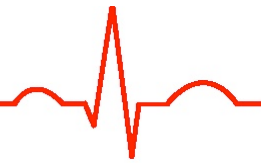
Previous studies have demonstrated the relationship between the existence of AF and inappropriate device discharge and the consequent negative effect of inappropriate device discharge on patient quality of life.(33-35) Furthermore, recent research has demonstrated the impact of inappropriate shock delivery on mortality.(33, 36) These findings stress the importance of clear identification of patients at high risk for inappropriate shocks in order to better inform patients and to optimize individual patient treatment. The current study maps the importance of different types of AF on the occurrence of inappropriate shocks and highlights the high event rate in patients with persistent, permanent and, most outspoken, paroxysmal AF. A potential explanation of the higher event rate in the paroxysmal AF group, even when compared to the group with permanent AF, can be explained by the fact that clinicians will more often adjust their treatment (such as AV-node ablation) if AF is ongoing. Additionally, the higher occurrence of ventricular arrhythmias in the group with permanent AF might cause a more aggressive pharmacological antiarrhythmic treatment.

Limitations

This was a non-randomized prospective observational cohort study, performed to assess the long-term follow-up in ICD patients outside the setting of a clinical trial. Since patients were collected over a period of four years, expanding guidelines for the implantation of defibrillators, treatment of acute myocardial infarction, and pharmacological antiarrhythmic therapy could have created an heterogeneous population. Furthermore, standard ICD settings at discharge could have been altered during follow-up. Finally, applying a different classification of AF might have altered the results.

Conclusion

In the population, currently receiving ICD treatment outside the setting of a clinical trial, 11% has permanent AF and 16% has a history of paroxysmal or persistent AF. The existence of permanent AF doubles the risk for mortality and appropriate, as well as inappropriate device therapy. Paroxysmal and persistent AF did not prove to have an effect on mortality or the occurrence of appropriate device discharge. However, the rate of inappropriate shocks is importantly increased in this group.



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Chapter 6

Clinical Prediction Model for Death prior to Appropriate Therapy in Primary Prevention Implantable Cardioverter Defibrillator Patients with Ischemic Heart Disease: the FADES Risk Score.

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Submitted

Abstract

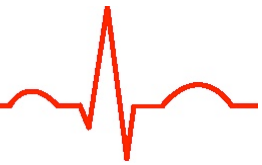
Objectives: The aim of the study was to assess the risk for non-benefit from implantable cardioverter defibrillator (ICD) treatment in primary prevention ICD patients with ischemic heart disease.

Background: Although the beneficial effect of ICD therapy has been well established as primary prevention in a selected population at high risk for sudden arrhythmic death, a substantial part does not benefit from ICD treatment during long-term follow-up.

Methods: Since 1996, all ICD recipients in the Leiden University Medical Center have been clinically assessed at implantation. For the current study, patients with ischemic heart disease and a primary indication for implantation have been included. During follow-up, all-cause mortality and device therapy (anti-tachycardia pacing or shock) were noted. Non-benefit was defined as death, prior to first appropriate ICD therapy. Out of baseline variables, a baseline risk score was constructed to estimate risk for non-benefit.

Results: Nine-hundred patients (87% men, mean age 64 ± 10 years) were included in the analysis. During a median follow-up of 669 days (interquartile range, 363 to 1322 days), 150 patients (17%) died and 191 (21%) patients received appropriate device therapy. A total of 114 (13%) patients were considered the non-benefit group. Stratification for non-benefit resulted in risk categorization of patients as low, intermediate or high-risk. Advanced age was the strongest predictor of non-benefit. Five-year cumulative incidence for non-benefit ranged from 12% (95% confidence interval (CI) 5–18%) in low-risk patients to 49% (95%CI 38–60%) in high-risk patients.

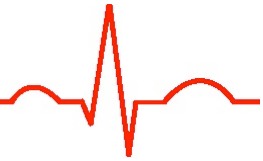
Conclusions: The risk of non-benefit can be predicted in primary prevention ICD patients with ischemic heart disease. The use of a baseline risk score facilitates patient-tailored risk estimation.



Introduction

Large randomized trials have demonstrated that implantable cardioverter defibrillator (ICD) treatment is the treatment of choice for patients with prior life-threatening arrhythmias (secondary prevention) (1-3) and for selected patients at high risk for sudden cardiac death, regardless of prior arrhythmia (primary prevention) (4-7). Since implementation of primary prevention in the international guidelines, implantation rates have increased dramatically to an estimated 275000 devices in 2008 (8, 9). However, with the inclusion of primary prevention in the currently ICD indicated population, rates of appropriate therapy for ventricular arrhythmias have decreased to 35% during long-term follow-up in the second Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) compared to 64% in secondary prevention patients (1, 10). Furthermore, clinicians have expressed concern that the number of patients needed to treat with a primary prevention ICD might be too high and that the population, eligible for primary prevention ICD treatment, is of such magnitude that provision of ICD therapy will strain financial resources and the pool of trained personnel (11). In addition, ICD therapy is associated with adverse events such as pocket related infections and inappropriate shocks (12). The relatively low actual need for defibrillator therapy during follow-up, combined with the associated adverse events and the incapability to implant all indicated patients, urges for refinement of the current selection criteria for ICD treatment. Therefore, it would be of interest to identify a population, currently receiving ICD treatment, not benefiting from ICD therapy (i.e. death prior to appropriate ICD therapy).

Since 1996, all patients receiving an ICD at the Leiden University Medical Center have been assessed and followed up. This thoroughly screened cohort provided an opportunity to identify ICD recipients who do not benefit from ICD treatment and to assess whether baseline parameters influence the risk of non-benefit. Finally, a clinically applicable risk model is constructed to aid clinicians in individual risk estimations for primary prevention ICD patients with ischemic heart disease.



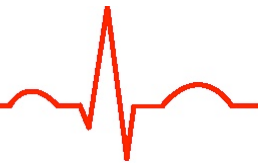
Methods

Since 1996, all patients who received an ICD at the Leiden University Medical Center were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, the Netherlands). Characteristics at baseline, data of the implant procedure and of all follow-up visits were recorded. For the current analysis, patients with a primary indication for defibrillator implantation and ischemic heart disease were selected.

It should be noted that, due to evolving guidelines, eligibility for ICD implantation in this population might have changed over time (13, 14). Nonetheless, in the majority of patients, indication for an ICD was made in the presence of a depressed left ventricular ejection fraction (LVEF) with or without non sustained ventricular tachycardia (8, 13). Ischemic heart disease was defined as the presence of significant coronary artery disease (a diameter stenosis of at least 50% in at least one coronary artery) (15, 16). Exclusion criteria for the current analysis consisted of congenital structural or monogenetic heart disease (associated with an increased risk of sudden arrhythmic death).

Clinical variables

All tested variables were collected at device implantation and defined and categorized according to literature or common practice. Age was categorized as <65 years, 65–74 years and ≥75 years; a history of non sustained ventricular tachycardia was defined as a run of 3 to 30 ventricular ectopic beats at a rate >120 beats per minute (6); renal clearance was estimated with the formula of Cockroft-Gault and categorized in normal or stage 1 renal failure (>90 ml/min), stage 2 renal failure (60-90 ml/min), or stage 3-5 renal failure (<60 ml/min) (17); QRS duration was categorized as <100 ms, 100-130 ms, or >130 ms; LVEF was categorized as ≤25% or >25%;(18) Heart failure symptoms were categorized as mild (New York Heart Association (NYHA) functional class I-II) or as severe (NYHA functional class III-IV) (19); atrial fibrillation was



defined as a history of atrial fibrillation as documented on ECG; a history of smoking was defined if a patient had a positive answer when asked for past or present smoking (20); and body mass index was categorized as <30 kg/m^2 or ≥30 kg/m (21).

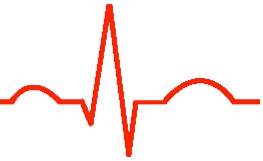
Device implantation

All ICD systems used were implanted in the pectoral region. Used systems were manufactured by Biotronik (Berlin, Germany), Medtronic (Minneapolis, MN, United States), Boston Scientific (Natick, MA, United States, formerly CPI, Guidant [St. Paul, MN, United States]) and St. Jude Medical/Ventritex (St. Paul, MN, United States).

Defibrillators were programmed as follows: a ventricular arrhythmia monitor zone was programmed in all patients (150-188 bpm). Ventricular arrhythmias faster than 188 bpm were initially attempted to be terminated with two bursts of anti-tachycardia pacing (ATP) and, after continuation of the arrhythmia, with defibrillator shocks. In the case of a ventricular arrhythmia faster than 210 bpm, device shocks were the initial therapy. Settings were adapted, only when clinically indicated.

Follow-up

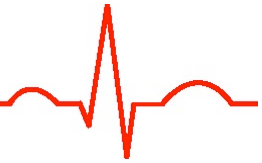
All patients were seen at the implanting center. Follow-up started at the time of implantation and lasted until death or last date of data acquisition (February 2009). Devices were interrogated every three to six months or more frequently when clinically indicated. Printouts of device interrogations were checked for delivered therapy, which was classified as appropriate when occurring in response to ventricular tachycardia or ventricular fibrillation. Furthermore, all-cause mortality was noted. Patients without data on the past six months were considered lost to follow-up. As previously reported, non-benefit from ICD treatment was defined as death from any cause, prior to appropriate ICD therapy (ATP or shock) (22, 23).



Statistical analysis

Continuous data are expressed as mean with standard deviation (SD) or median with 25th and 75th percentile where appropriate. Dichotomous data are presented as numbers and percentages. Baseline characteristics in the non-benefit group and the remaining study population were compared with the chi-square test and unpaired Student's *t*-test as appropriate. All-cause mortality, appropriate therapy, non-benefit and mortality after delivered appropriate therapy were analyzed by method of Kaplan-Meier, evaluated using the log rank test and presented with a 95% confidence interval (CI) (24). In the calculation of the cumulative incidence of non-benefit, appropriate therapy was considered a censoring event.

Baseline medication was excluded from risk score construction, since this clinician driven variable could bias the results and impede reproducibility. All other baseline variables were entered as categorical variables. Initially, the variables were entered in univariate logistic regression models, with non-benefit from ICD treatment as only outcome. Variables with a p-value <0.10 were further analyzed in a multivariate logistic regression model, using backward stepwise selection until all variables in the model reached a p-value <0.25. Based on the variables' regression coefficient in this multivariate model, a risk stratification score was constructed by giving a base regression coefficient the value of one point on the risk score and giving all variables the associating score, according to their multiplication of this base regression coefficient and rounding it off to the nearest whole or half number. Subsequently, the patient specific values for the predictors in the score were summed to obtain a score for each patient. The ability of the score to discriminate between patients who did and patients who did not reach the endpoint was estimated by the area under the curve of the receiver operating curve. After the determination of the individual patient risk score, cut-offs were determined for a population at low, intermediate and high risk of non-benefit from ICD treatment. These cut-offs were chosen to optimize the discriminative effect of the model without reducing the sizes of the groups. For



internal validation and to assess the stability of variable selection, bootstrap with 1000 resamples was used (25). All analyses were performed with SPSS for Windows, version 14.0 (SPSS, Chicago, IL).

Results

Patient characteristics

From 1996 to 2008, 935 patients with ischemic heart disease underwent ICD implantation for primary prevention. Thirty-five (3.7%) patients were lost to follow-up. Median follow-up of the remaining 900 patients was 669 days (interquartile range, 363-1322 days).

Baseline characteristics are provided in Table 1. The majority of patients (mean age 64±10 years) were male (87%), had a depressed LVEF (29±11%) and wide QRS (125±33 ms). Beta blockers were used by 63% of the patients, sotalol by 12% and ACE inhibitors or AT antagonists by 85%.

Incidence of all-cause mortality and first appropriate ICD therapy

During follow-up, 150 patients (17%) died. Cumulative incidence of all-cause mortality in the study population was 27% (95%CI 22-31%) after five years. A total of 3638 episodes of ventricular arrhythmia, causing appropriate device therapy, were noted in 191 (21%) patients. These consisted of 3333 arrhythmia episodes being terminated by ATP in 128 (14%) patients and 298 episodes being terminated by ICD shocks in 100 (11%) patients. Cumulative incidence of first appropriate therapy in the study population was 39% (95%CI 34-44%) after five years follow-up. For first appropriate shock, the cumulative incidence was 21% (95%CI 16-26%) after five years.

Table 1. Baseline characteristics

	Ischemic (n=900)	Patients with missing data
Clinical parameters		
Male gender (%)	779 (87)	0
Age, mean (SD), years	64 (10)	0
median (interquartile range), years	66 (57-72)	
NYHA functional class		17 (2)
I	193 (21)	
II	352 (39)	
III	325 (36)	
IV	30 (3)	
History of nsVT (%)	221 (25)	0
Renal clearance, mean (SD), ml/min	78 (37)	53 (6)
QRS-duration, mean (SD), ms	125 (33)	10 (1)
LVEF, mean (SD), %	29 (11)	52 (6)
History of atrial fibrillation (%)	228 (25)	3 (0)
Diabetes (%)	227 (25)	36 (4)
History of smoking (%)	429 (48)	50 (6)
Body mass index, mean (SD), kg/m^2	27 (4)	54 (6)
Implantable cardioverter defibrillator		0
Single chamber (%)	40 (4)	
Dual chamber (%)	423 (47)	
Cardiac resynchronization therapy (%)	437 (49)	
Medication		0
Beta-blocker (%)	570 (63)	
Sotalol (%)	106 (12)	
ACE inhibitors / AT antagonist (%)	767 (85)	
Statins (%)	742 (82)	
Diuretics for CHF (%)	651 (72)	
Amiodarone (%)	126 (14)	

Abbreviations: ACE, angiotensin-converting enzyme; AT, angiotensin; LVEF, left ventricular ejection fraction; nsVT, non sustained ventricular tachycardia; NYHA, New York Heart Association.

Non-benefit from ICD treatment

During follow-up, 114 (13%) patients died without prior appropriate ICD treatment and were considered the non-benefit group. Cumulative incidence of death without prior ICD treatment was 7% (95%CI 6-8%) after one year, 18% (95%CI 15-22%) after three years and 24% (95%CI 21-27%) after 5 years.

Comparison of the non-benefit group with the remaining study population demonstrated that the non-benefit group was older, had higher NYHA functional class, worse renal function, longer QRS duration, lower LVEF, and more often a history of diabetes and smoking (Table 2). Subsequently, multivariate logistic modeling for the prediction of non-benefit from ICD treatment contained the following variables: (1) age (65-74 and ≥75 years), (2) diabetes, (3) LVEF ≤25%, (4) NYHA functional class III-IV and (5) a history of smoking. The strongest predictor of non-benefit from ICD treatment was age ≥75 years (odds ratio 2.95, 95%CI 1.7-5.1%) (Table 3). Bootstrap analysis demonstrated that age, diabetes, LVEF, NYHA and smoking were selected in 99, 99, 98 96, 97%, respectively. The area under the receiver operator curve of the acquired risk score was reasonably good: 0.73 (95%CI 0.68 – 0.78).

For construction of the non-benefit prediction model, the following risk point cut-offs were used: (1) low risk (0-1.5 points); (2) intermediate risk (2-2.5 points); and (3) high risk (3-5.5 points). When extrapolated to the total study population, 371(41%) patients exhibited low risk of non-benefit, 323 (36%) patients intermediate risk and 206 (23%) patients high risk. Cumulative incidence of non-benefit after 5 years was 12% (95%CI 5-18%) in low risk patients, 22% (95%CI 12-32%) in intermediate risk patients and 49% (95%CI 38-60%) in high risk patients (Figure 1).

Table 2. Baseline characteristics of patients who do not benefit from ICD treatment versus the remaining study population.

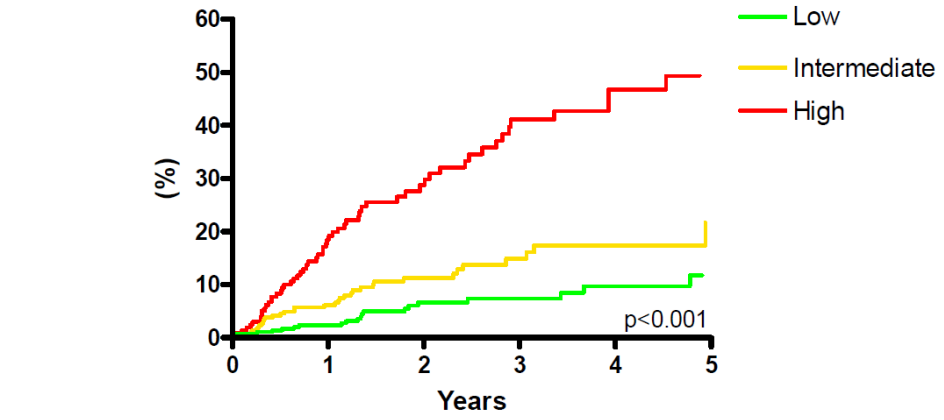
	Non-benefit group (n=114)	Remaining group (n=786)	p-value
Clinical parameters			
Male gender (%)	102 (90)	677 (86)	0.33
Age			< 0.001
< 65 years (%)	41 (36)	386 (49)	
65 - 74 years (%)	40 (35)	286 (36)	
≥ 75 years (%)	33 (29)	114 (15)	
NYHA functional class			< 0.001
I or II (%)	45 (39)	500 (64)	
III or IV (%)	69 (61)	286 (36)	
History of nsVT (%)	25 (22)	196 (25)	0.49
Renal failure			< 0.001
Stage 1 (> 90ml/min) (%)	15 (13)	262 (33)	
Stage 2 (60 – 90 ml/min) (%)	23 (20)	311 (40)	
Stage 3 (< 60 ml/min) (%)	76 (67)	213 (27)	
QRS-duration			0.01
< 100 ms (%)	15 (13)	163 (21)	
100-130 ms (%)	42 (37)	344 (44)	
>130 ms (%)	57 (50)	279 (35)	
LVEF ≤ 25% (%)	66 (58)	280 (36)	< 0.001
History of atrial fibrillation (%)	35 (31)	193 (25)	0.10
Diabetes (%)	46 (40)	181 (23)	< 0.001
History of smoking (%)	65 (57)	364 (46)	0.03
Body mass index ≥ 30 kg/m² (%)	18 (16)	144 (18)	0.31
Implantable cardioverter defibrillator			0.003
Single chamber (%)	2 (5)	38 (2)	
Dual chamber (%)	40 (49)	383 (35)	
Cardiac resynchronization therapy (%)	72 (46)	365 (63)	

Abbreviations: LVEF, left ventricular ejection fraction; nsVT, non sustained ventricular tachycardia; NYHA, New York Heart Association.

Table 3. Multivariate logistic regression model and corresponding risk score for non-benefit from ICD treatment

	Regression coefficient	Odds ratio (95% CI)	p-value	Score
Age			< 0.001	
65 – 74 years	0.26	1.30 (0.81 – 2.10)	0.28	.5
≥ 75 years	1.08	2.95 (1.69 – 5.14)	< 0.001	2
LVEF ≤ 25%	0.76	2.13 (1.40 – 3.24)	< 0.001	1.5
Diabetes	0.72	2.05 (1.33 – 3.15)	0.001	1
NYHA functional class III-IV	0.64	1.89 (1.23 – 2.90)	0.003	1
History of smoking	0.65	1.91 (1.25 – 2.94)	0.004	1

Abbreviations: CI, confidence interval; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.



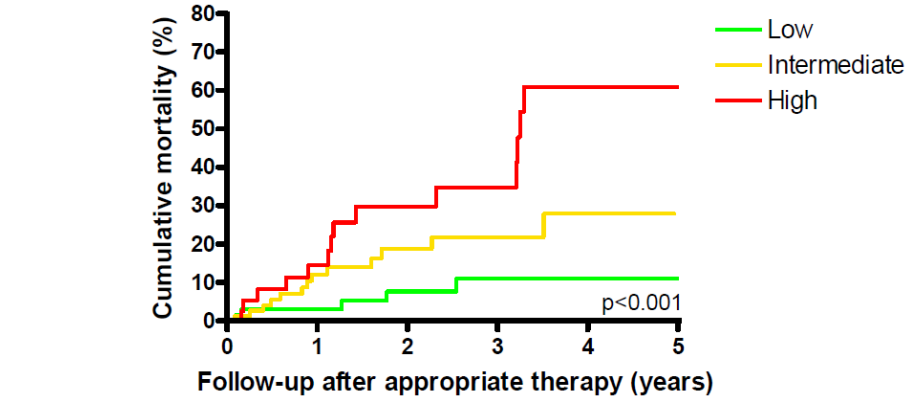
Patients at risk

Low	371	260	157	102	63	36
Intermediate	323	209	127	72	40	19
High	206	118	65	45	28	15

Figure 1. Risk stratification for non-benefit. Kaplan-Meier curve for non-benefit in patients with low, intermediate or high risk.

Follow-up after appropriate therapy

Cumulative incidences of appropriate therapy did not differ between the different non-benefit risk groups: 32% (95%CI 24-40%) in low risk patients, 46% (95%CI 35-37%) in intermediate risk patients and 44% (95%CI 31-58%) in high risk patients (p=NS). However, mortality after delivery of appropriate therapy did differ significantly between the non-benefit risk groups. After 5 years of follow-up, cumulative incidences of mortality after appropriate therapy were 11% (95%CI 1-21%) in low risk patients, 28% (95%CI 12-43%) in intermediate risk patients and 61% (95%CI 38-83%) in high risk patients (p<0.001; Figure 2).



Patients at risk						
Low	73	49	35	25	11	9
Intermediate	78	50	31	19	11	7
High	40	27	15	11	6	4

Figure 2. Mortality after appropriate therapy. Kaplan-Meier curve for mortality after appropriate therapy for patients with low, intermediate or high risk of non-benefit of ICD treatment.

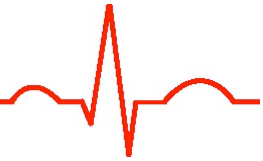
Discussion

In the current study on the identification of primary prevention ICD patients with ischemic heart disease who do not benefit from ICD treatment, the findings can be summarized as follows: 1) Five-year cumulative incidence was 27% for all-cause mortality and 39% for first appropriate ICD therapy; 2) Five-year cumulative incidence of non-benefit was 24%; 3) Strongest predictor of non-benefit was advanced age; 4) Almost 50% of high risk patients did not benefit from ICD treatment after five years follow-up.

The current study adds to current literature in that it is the first to propose a risk model for the estimation of non-benefit in primary prevention ICD patients with ischemic heart disease.

In recent literature, several subgroup analyses of the MADIT-II focused on the identification of patients who were most likely to receive appropriate device therapy. These analyses mentioned interim hospitalization for heart failure or a coronary artery event, no beta-blocker usage, current smoking, NYHA class >II, renal dysfunction, high body mass index and digitalis use as factors increasing the risk of ventricular arrhythmia during follow-up (20, 26, 27). Interestingly, these baseline predictors for ICD therapy were similar to baseline variables associated with an increased risk for mortality (26, 28). Consequently, the patients with the highest risk of receiving potentially life-saving appropriate device therapy have the worst prognosis, regardless of the implanted device. This paradox makes the findings in literature difficult to interpret. Therefore, a different approach to assess ICD efficacy was necessary. Koller and co-workers combined appropriate ICD therapy with all-cause mortality and defined non-benefit from ICD treatment as death prior to appropriate therapy, instead of focusing on patients with the lowest occurrence of ICD therapy. They demonstrated that usage of diuretics for heart failure – which was considered a surrogate of advanced heart failure – compared with nonuse was found to be the only significant predictor of non-benefit from ICD treatment. The current analysis demonstrated that besides advanced heart failure, a history of smoking, diabetes and higher age were also associated with non-benefit from ICD treatment. Differences between the study by Koller et al and the current analysis might be explained by the limited set of variables, smaller population size and heterogeneity (e.g. primary and secondary prevention ICD patients) of the study population assessed in the analysis of Koller and co-workers (23).

Goldenberg et al demonstrated in a risk analysis of MADIT-II that benefit from ICD treatment is following a U-shaped pattern with evident benefit for patients with intermediate risk of all-cause mortality and little benefit in low and high-risk patients (29). This principle implies two non-benefiting groups at both ends of this efficacy curve. One group comprises patients with major comorbidities, in whom the risk of non-arrhythmic mortality exceeds the risk of arrhythmic



(sudden) death. The other group consists of relatively healthy ICD patients who exhibit very low risk for life-threatening ventricular arrhythmia. It should be noted that, according to the observed risk factors, the current risk stratification identified the first mentioned group of non-benefit ICD patients with high risk of non-arrhythmic mortality. To identify the other group (i.e. with low-risk for ventricular arrhythmia) a different approach is desirable. Hallstrom and co-authors focused on predictors of recurrent arrhythmia in a subgroup analysis of the Antiarrhythmics versus Implantable Cardioverter Defibrillator Trial as secondary prevention of sudden cardiac death and identified, based on sextiles of the hazard distribution, a subgroup for which ICDs did not render survival advantage over amiodarone (22). Indeed, they reported on a 'healthy' subgroup, presenting with an isolated episode of ventricular fibrillation, few comorbidities and moderate preserved LVEF, which was not likely to benefit from ICD treatment over amiodarone.

Refinement of the current selection criteria for primary prevention patients with ischemic heart disease is essential. The current study provides a model to predict the individual risk for non-benefit, which may assist physicians in the decision-making process whether or not to prophylactically implant an ICD. It is however important to realize that patients at high-risk for non-benefit do not per se receive no appropriate ICD therapy at all. Some of the parameters that are associated with high risk of non-benefit are also identified as predictors of all-cause mortality, sudden cardiac death or appropriate therapy, like advanced age, depressed ejection fraction and smoking (26, 29, 30). This paradox could be explained with the short life-expectancy of this very sick group of patients. Consequently, even after potentially life-saving appropriate ICD therapy, life expectancy is still very short in high-risk patients (Figure 2). Thus, despite the fact that ICD therapy is not uncommon is this subset of patients, the survival advantage of prophylactic ICD implantation is limited.

Limitations of the findings are due to the non-randomized prospective study design. Since patients were collected over a long period of time, evolving guidelines could have created a

heterogeneous population. Additionally, the proposed risk score does not take clinician driven variables (medication) or follow-up acquired variables (hospitalizations, adverse events) in account since this could lead to a decrease in baseline applicability and reproducibility. Finally, the constructed risk score requires validation.

A significant number of primary prevention ICD patients with ischemic heart disease does not benefit from ICD treatment during long-term follow-up. The use of a baseline risk score can facilitate patient-tailored risk estimation of the non-benefit (death, prior to first appropriate ICD therapy).

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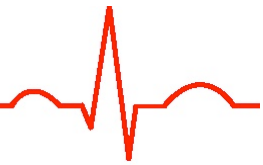

Chapter 7

Predicting Ventricular Arrhythmias in Patients with Ischemic Heart Disease: Clinical Application of the ECG derived QRS-T Angle

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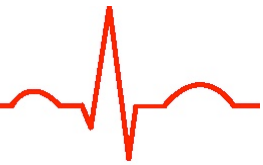
Abstract

Background: In primary prevention implantable cardioverter defibrillator (ICD) patients, the incidence of life-threatening ventricular arrhythmias resulting in ICD therapy is relatively low, prompting for better risk stratification. The aim of this study was to assess the value of the QRS-T angle for prediction of ICD therapy and mortality in primary prevention patients with ischemic heart disease (IHD).

Methods and results: ICD patients (n=412, 361 male, age 63±11 years) with IHD and a left ventricular ejection fraction ≤ 40% were included. After device implantation, the occurrence of appropriate ICD therapy and mortality was noted. A survival analysis was performed comparing patients with a planar QRS-T angle ≤ 90º (n=124, 30%) to patients with a planar QRS-T angle > 90º before device implantation. Furthermore, patients with a spatial QRS-T angle ≤ 100º (n=56, 14%) were compared to patients with a spatial QRS-T angle > 100º, prior to implant.

For patients with a planar QRS-T angle >90º as compared to ≤ 90º, the adjusted hazard ratio for the occurrence of appropriate device therapy was 2.4 (95% CI 1.1-5.2); a spatial QRS-T angle > 100º was associated with an adjusted hazard ratio of 7.3 (95% CI 1.0-53.8). Furthermore, a spatial QRS-T angle ≤ 100º exhibited a positive predictive value of 98% (95% CI 95-100%) for the prediction of an appropriate therapy-free follow-up.

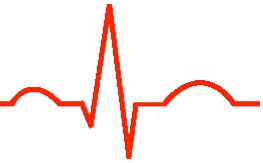
Conclusions: A wide QRS-T angle is a strong predictor of appropriate device therapy in primary prevention ICD recipients with IHD. Furthermore, a spatial QRS-T angle ≤ 100º might be of value in the identification of patients in whom, although currently indicated, ICD treatment should be reconsidered.



Introduction

Sudden cardiac death (SCD), mainly caused by ventricular arrhythmias, accounts for approximately 50% of all cardiac mortality worldwide.[1-3] It is recognised that patients with ischemic heart disease and depressed left ventricular ejection fraction (LVEF) are at high risk of SCD,[4, 5] and large randomised trials have demonstrated that implantable cardioverter defibrillator (ICD) therapy reduces all-cause mortality, as well as SCD. [6-10] Implementation of these results in the international guidelines resulted in a significant increase of the number of ICD implantations.[11, 12] However, long-term follow-up studies in currently indicated patients show a relatively low incidence of ventricular arrhythmias that trigger ICD therapy.[13] Additionally, approximately 6% of ICD patients experience severe device-related adverse events (i.e. pocket infections, sepsis), causing the need for surgical re-intervention, additional hospitalization, or even death.[14, 15] This led to critical appraisal of the wide-spread application of ICD therapy and stressed the need for more precise risk stratification criteria.[16] In an attempt to identify those criteria, post-hoc analyses of the second Multicenter Automatic Defibrillator Implantation Trial (MADIT II) revealed several clinical criteria associated with an increased risk for ventricular arrhythmias resulting in appropriate device therapy.[17-19] So far, however, in low LVEF patients no criteria have been recognised which may identify patients at low risk of ventricular arrhythmias during follow-up. If possible to identify a low risk population, ICD therapy in this group may be reconsidered.

Recently, a wide angle between the QRS and T axes, the QRS-T angle, on the standard 12-lead ECG was recognised as a novel and easy applicable marker of increased risk for cardiovascular mortality.[20, 21] Subsequently, a wide QRS-T angle was found to be



associated with the increased incidence of appropriate device therapy and mortality in primary prevention ICD recipients with non-ischemic cardiomyopathy.[22] However, no data are available on the value of the QRS-T angle in ICD patients with IHD.

The aim of the current study was, to assess the value of the QRS-T angle in predicting life threatening ventricular arrhythmias in primary prevention ICD patients with IHD. Furthermore the value of the QRS-T angle was evaluated as a parameter to identify patients at low risk for ventricular arrhythmias.

Methods

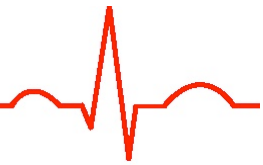
Patients

Patients with IHD who underwent implantation of an ICD, based on the international treatment guidelines, in the Leiden University Medical Center were selected for the current study.[11] Criterion for inclusion were a depressed LVEF (<40%) with or without a history of non sustained ventricular tachycardia. Since 1996, these patients were prospectively registered in the departmental Cardiology Information System (EPD-Vision®).[23] Prior to implantation, a comprehensive assessment of patient characteristics was performed as described previously.[24]

During follow-up, the occurrence of appropriate ICD therapy and patient mortality was noted. In addition, for the purpose of this study, the ECG made before implantation was analyzed.

Implantable cardioverter defibrillator implantation and follow-up

All defibrillator systems were implanted transvenously without thoracotomy. Device follow-up was scheduled every three to six months. All printouts were carefully checked for appropriate and inappropriate ICD therapy. In case of any ICD therapy, an electrophysiologist, blinded to QRS-T measurements, determined whether or not the ICD therapy was appropriate. All therapies, either

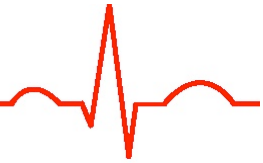


anti-tachycardia pacing (ATP) or shock, were classified as appropriate when they occurred in response to life threatening arrhythmias; ventricular tachycardia (VT) or ventricular fibrillation (VF) and as inappropriate when triggered by sinus or supraventricular tachycardia (SVT), T-wave oversensing, or electrode dysfunction.

Defibrillators were programmed as follows: ventricular arrhythmia faster than 150 bpm was monitored by the device without consequent defibrillator therapy. Ventricular arrhythmias faster than 188 bpm were initially attempted to be terminated with two bursts of ATP and, after continuation of the arrhythmia, with defibrillator shocks. In the case of a ventricular arrhythmia faster than 210 bpm, device shocks were the initial therapy. Furthermore, atrial arrhythmia detection was set to >170 bpm with SVT discriminators enabled. Settings were adapted, only when clinically indicated (i.e. hemodynamic well tolerated ventricular tachycardia at high rate; ventricular tachycardia in the monitor zone).

Electrocardiographical analysis

First, the quality of ECGs was evaluated. If electrode displacement, missing leads or signal noise was present, the ECGs were excluded from the analysis. Since right ventricular pacing alters normal cardiac conduction and results, by definition, in an abnormal QRS-T angle, patients with a pacemaker were excluded from the analysis.[25] Subsequently, the ECGs were analyzed with a dedicated computer program (LEADS, Leiden ECG Analysis and Decomposition Software).[26] Full details on the computation method and LEADS based values of vector characteristics in healthy subjects, have been extensively described earlier.[27] In short, the software converts the standard ECG into a vectorcardiogram and computes the three dimensional orientation of the QRS- and T-axes. Thereafter, the QRS-T angle is calculated in the plane formed by the QRS- and T-axes, the *spatial* QRS-T angle. In addition, the more commonly used but less precise projection of the spatial QRS-T angle in the frontal plane, the *planar* QRS-T angle, was computed. Previous



studies demonstrated that a spatial QRS-T angle wider than 100º is associated with the presence of cardiac disease and increased cardiovascular mortality.[20, 21] Pavri et al. recently demonstrated that a planar QRS-T angle wider than 90º is associated with an increased incidence of appropriate device shocks and mortality[22]. In the present study, these cut-offs (100º for the spatial and 90º for the planar QRS-T angle) were applied.

Statistical analysis

A survival analysis, comprising of the following end-points, was performed: (1) first appropriate ICD therapy (ATP and/or shock); (2) all-cause mortality; and (3) a composite end-point of all-cause mortality and first appropriate device therapy, whichever occurs first. ICD recipients with a narrow QRS-T angle were compared to those with a wide QRS-T angle. The points of cut-off were pre-defined as described above, 100º for the spatial and 90º for the planar QRS-T angle. Cumulative event rates of end-points were analyzed by the method of Kaplan-Meier. Relationships between baseline parameters and end-points were assessed with Cox's proportional hazard regression analysis. For the composite end-point, survival time was defined as time to all-cause death or appropriate device therapy, whichever occurred first. For each variable a hazard ratio with a 95%-confidence interval (95% CI) was calculated. Therapy-free follow-up was defined as a study follow-up without the occurrence of appropriate ICD therapy.

Continuous data are expressed as mean ± standard deviation or median and quartiles where appropriate; dichotomous data are presented as numbers and percentages. Comparison of data at baseline was performed with the Student's *t* test for unpaired data and Chi-square tests with Yates correction when appropriate.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Patients and follow-up

A total of 460 patients with ischemic heart disease and a LVEF ≤ 40% underwent ICD implantation for primary prevention of sudden cardiac death in the Leiden University Medical Center. Thirty-two (7%) patients were excluded due to the presence of a pacemaker and 16 (3%) patients were excluded since their ECG prior to device implantation could not be analyzed because of technical reasons such as electrode displacement, missing leads, or signal noise. The remaining 412 (90%) ICD recipients (63±11 yrs, 88% male) were included in the analysis and were followed for 22±17 months (range 0 to 77 months). Baseline characteristics are summarised in Table 1.

During follow-up, 46 (11%) patients died, and a total of 482 episodes of appropriate device therapy for ventricular arrhythmias occurred in 56 (14%) patients; 386 episodes of ventricular arrhythmia, terminated by ATP in 35 (8%) patients, and 96 episodes triggering device shocks in 28 (7%) patients. During follow-up, the first end-point (first appropriate device therapy) was reached in 56 patients (24 shock, 32 ATP), the second end-point (all-cause death) was reached in 46 patients and the composite end-point (death or first appropriate device therapy) was reached in 96 patients (40 patients all cause deaths, 56 appropriate therapy).

Table 1. Patient characteristics

	All patients	Planar QRS-T angle ≤ 90º		Spatial QRS-T angle ≤ 100º	
		Yes	No	Yes	No
Patients	412	124 (30%)	288 (70%)	56 (14%)	356 (86%)
Clinical parameters					
Age (yrs)	63±11	61±11	64±10*	62±11	63±10
Male (%)	361 (88%)	110 (89%)	251 (87%)	51 (91%)	310 (87%)
Biventricular ICD (%)	194 (47%)	43 (35%)	151 (52%)†	22 (39%)	172 (48%)
LVEF (%)	26±7	28±7	25±7†	30±6	26±7†
NYHA functional class					
I-II	261 (63%)	92 (74%)	169 (59%)*	41 (73%)	220 (62%)
III-IV	151 (37%)	32 (26%)	119 (41%)*	15 (27%)	136 (38%)
History of diabetes mellitus (%)	110 (27%)	24 (19%)	86 (30%)*	6 (11%)	104 (29%)†
History of nicotine abuse (%)	190 (46%)	55 (44%)	135 (47%)	29 (52%)	161 (45%)
Current nicotine abuse (%)	86 (21%)	25 (20%)	60 (21%)	12 (21%)	74 (21%)
History of atrial fibrillation / lutter (%)	98 (24%)	24 (19%)	74 (26%)	10 (18%)	88 (25%)
Atrial fibrillation / flutter at implantation (%)	39 (9%)	8 (6%)	31 (11%)	2 (4%)	37 (10%)
History of nonsustained VT (%)	81 (20%)	24 (19%)	57 (20%)	10 (18%)	71 (20%)
Body mass index (kg/m²)	27±4	26±4	27±5	27±3	27±4
Medication					
Beta blocker (%)	317 (77%)	99 (80%)	218 (76%)	42 (75%)	275 (77%)
ACE inhibitor / AT antagonist (%)	358 (87%)	110 (89%)	248 (86%)	49 (88%)	309 (87%)
Diuretics for CHF (%)	317 (77%)	90 (73%)	227 (79%)	38 (68%)	279 (78%)
Statins (%)	349 (85%)	111 (90%)	238 (83%)	53 (95%)	296 (83%)*
Amiodarone (%)	57 (14%)	15 (12%)	42 (15%)	1 (2%)	56 (16%)†
ECG parameters					
Heart rate (bpm)	66±16	66±15	66±16	67±16	66±15
QRS duration (ms)	130±33	120±29	134±34†	115±28	132±33†
QTc Bazett (ms)	431±51	431±52	431±51	434±50	431±52
Frontal QRS-T angle (º)	116±52	47±24	146±26†	62±33	125±50†
Spatial QRS-T angle (º)	139±32	112±35	151±22†	75±18	149±20†

* $p<0.05$; † $p<0.01$ as compared to patients with a narrow planar/spatial QRS-T angle.
ACE = angiotensin converting enzyme; AT = angiotensin; CHF = congestive heart failure; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; VT = ventricular tachycardia.

QRS-T angle and all-cause mortality

In 124 (30%) patients, a planar QRS-T angle smaller or equal to 90º was measured on the baseline ECG. As summarised in Table 1, patients with a narrow planar QRS-T angle were more likely to be younger (61±11 yr vs. 64±10 yr, p<0.05), to have a better LVEF (28±7% vs. 25±7%, p<0.001), and shorter QRS duration (120±29 ms vs. 134±34 ms, p<0.001). The hazard ratio of a planar QRS-T angle > 90º for mortality was 3.1 (95% CI 1.3-7.3) as compared to patients with a narrow planar QRS-T angle. The cumulative event-free follow-up for all cause mortality in patients with a narrow planar QRS-T angle was 99% (95% CI 98-100%) at one year, 92% (95% CI 87-98%) at two years, and 92% (95% CI 87-98%) at four years of follow-up (Figure 1).

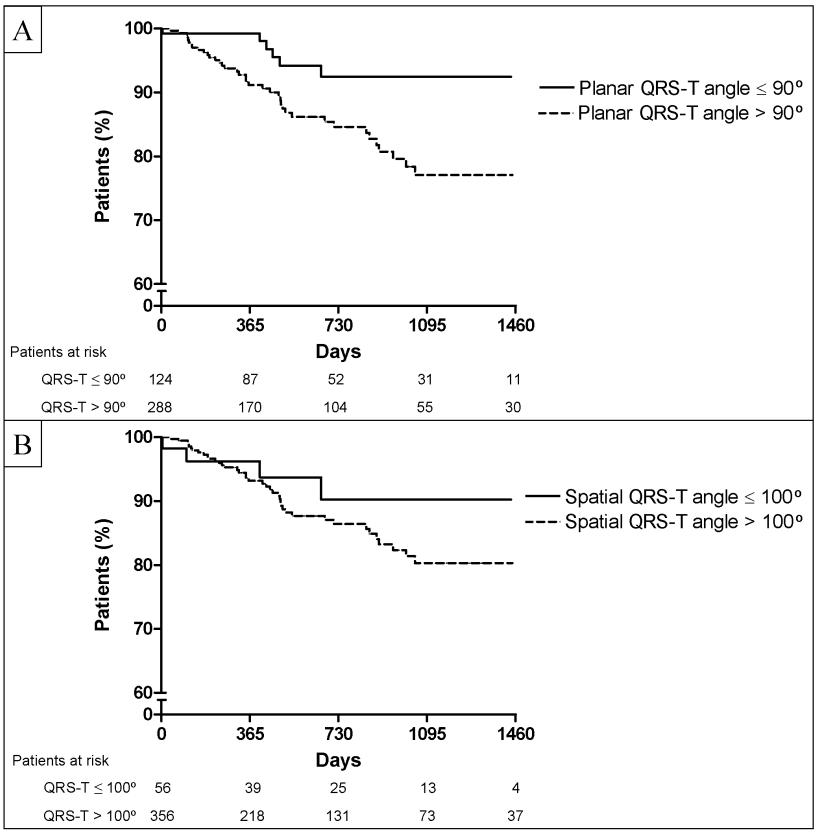
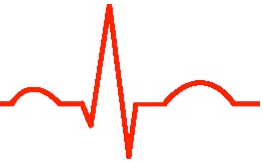


Figure 1. Kaplan-Meier curve for cumulative event rate for all cause mortality in patients with a planar QRS-T angle ≤ 90º vs. a planar QRS-T angle > 90º (panel A) and with a spatial QRS-T angle ≤ 100º vs. a spatial QRS-T angle > 100º (panel B).



Fifty-six (14%) patients had a baseline spatial QRS-T angle smaller than or equal to 100º. These patients were younger, had a more preserved LVEF (30±6% vs. 26±7%, p<0.01), a shorter QRS duration (115±28 ms vs. 132±33 ms, p<0.01), used statins more often (95% vs. 83%, p<0.05) and were using amiodarone less frequently (2% vs. 16%, p<0.01) (Table 1). As is shown in Table 2, patients with a wide spatial QRS-T angle exhibited a hazard ratio for all-cause mortality of 1.7 (95% CI 0.6-4.9).

Table 2. Event rates, hazard ratios, and p-values for end-points

	Planar QRS-T angle ≤ 90º		HR (95% CI)	**Adjusted** HR (95% CI)*	**Spatial QRS-T angle ≤ 100º**		HR (95% CI)	**Adjusted** HR (95% CI)*
	Yes	No			Yes	No		
Appropriate therapy	8/124 (6.5%)	48/288 (16.7%)	2.9 (1.4-6.1)	2.4 (1.1-5.2)	1/56 (1.8%)	55/356 (15.4%)	9.9 (1.4-1.7)	7.3 (1.0-53.8)
All-cause mortality	6/124 (4.8%)	40/288 (13.9%)	3.1 (1.3-7.3)	2.3 (1.0-5.6)	4/56 (7.1%)	42/356 (11.8%)	1.7 (0.6-4.9)	1.0 (0.4-3.2)
Appropriate therapy and all-cause mortality	14/124 (11.3%)	82/288 (28.5%)	2.9 (1.6-5.0)	2.3 (1.3-4.1)	5/56 (8.9%)	91/356 (25.6%)	3.4 (1.4-8.3)	2.3 (0.9-5.9)

*Hazard ratio was adjusted for age, sex, LVEF, and QRS duration.
CI = confidence interval; HR = hazard ratio

QRS-T angle and ventricular arrhythmia

The hazard ratio of a planar QRS-T angle wider than 90º for the occurrence of ventricular arrhythmia triggering appropriate device therapy was 2.9 (95% CI 1.4-6.1). When adjusted for age, sex, LVEF and QRS duration, the hazard ratio was 2.4 (95% CI 1.1-5.2). Furthermore, this group demonstrated an almost threefold risk increase (hazard ratio 2.9, 95% CI 1.6-5.0) for the composite end-point of appropriate therapy and mortality (Table 2). The cumulative event-free follow-up for appropriate therapy in patients with a narrow planar QRS-T angle was 95% (95% CI 90-99%) at one year, 93% (95% CI 87-98%) at two years, and 89% (95% CI 81-98%) at four

years of follow-up (Figure 2).

As is shown in Table 2, patients with a wide spatial QRS-T angle exhibited a near tenfold risk for the occurrence of ATP or shocks (hazard ratio 9.9, 95% CI 1.4-71.7) during follow-up. When adjusted for age, sex, LVEF, and QRS duration the hazard ratio was 7.3 (95% CI 1.0-53.8). Strikingly, the cumulative event-free follow-up for ventricular arrhythmia which triggered device therapy was 100% at two years and 96% (95% CI 87-100%) at four years of follow-up, as can be readily seen in Figure 2.

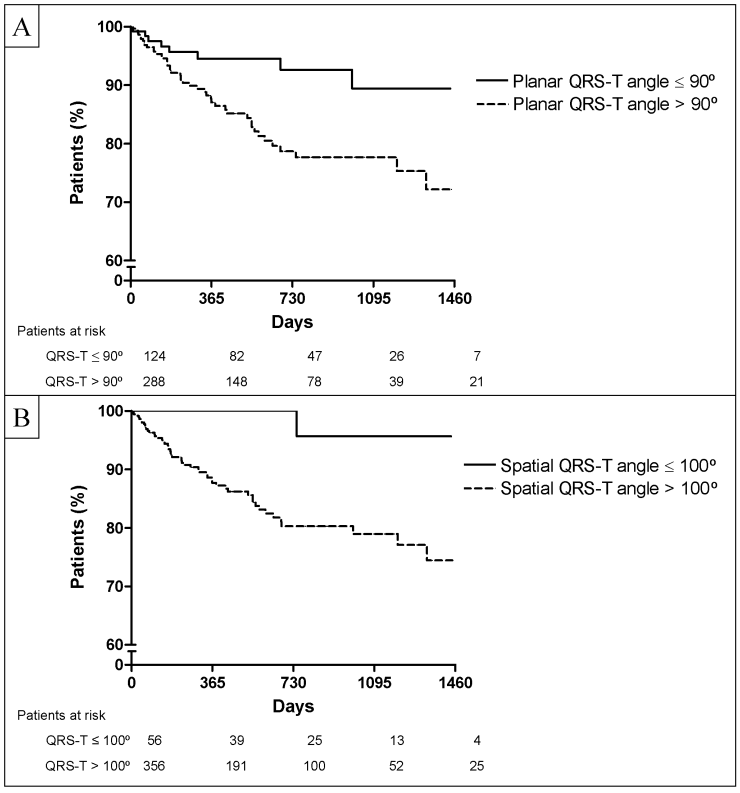


Figure 2. Kaplan-Meier curve for cumulative event rate for appropriate therapy in patients with a planar QRS-T angle ≤ 90º vs. a planar QRS-T angle > 90º (panel A) and with a spatial QRS-T angle ≤ 100º vs. a spatial QRS-T angle > 100º (panel B).

Identification of patients free of life-threatening arrhythmias

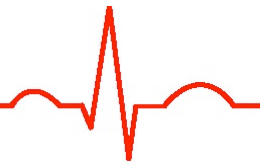
Evaluation of the usefulness of a planar QRS-T angle smaller than or equal to 90º at baseline in the prediction of an appropriate therapy-free follow-up revealed a positive predictive value of 94% (95% CI 89-98%) and a negative predictive value of 17% (95% CI 12-21%).

The spatial QRS-T angle had a positive predictive value of 98% (95% CI 95-100%) and a negative predictive value of 15% (95% CI 12-19%) for the prediction of an appropriate therapy-free follow-up. Most importantly, only 2% of the patients with a spatial QRS-T angle ≤ 100º had appropriate device discharges during follow-up, the only event occurring after 745 days (Figure 2).

Discussion

In the current study on the clinical application of the planar and spatial QRS-T angle in the prediction of ventricular arrhythmias in ischemic primary prevention ICD patients, the main findings can be summarised as follows: after adjustment for age, sex, LVEF, and QRS-duration, 1) patients with a wide planar QRS-T angle exhibited a nearly 2.5-fold risk for mortality, as well as for appropriate device therapy; 2) patients with a wide spatial QRS-T angle had a sevenfold risk for ventricular arrhythmias triggering appropriate device therapy; and 3) patients with a spatial QRS-T ≤ 100º prior to implantation, exhibited an absolute risk of 2% for appropriate therapy during follow-up.

With primary prevention ICD therapy as a class I indication in international guidelines in patients with a low LVEF, the indicated population, and therefore the worldwide defibrillator implantation rates, have increased significantly.[11, 12] This expansion is of such magnitude that health care systems might lack the logistic capacity and financial means to meet the demand of



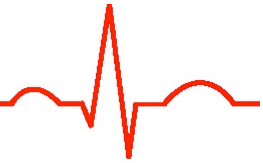
ICD implantations.[16, 28] Furthermore, MADIT II demonstrated a cumulative incidence of the need for defibrillator back-up of only 35% of patients after three years.[13] Moreover, 6% of ICD treated patients, experience severe device-related adverse events.[14] These issues underscore the need for better risk stratification within the indicated population.

Ideally, a parameter for the identification of a population at high or at low risk for the need for defibrillator back-up should be non-invasive and easily acquired. An ECG derived parameter such as the QRS-T angle, validated in the current analysis, would fit these demands.

Risk stratification with the QRS-T angle

The QRS-T angle is the angle between the electrical axes of depolarisation and repolarisation. In the present study, clinical application of both the planar as well as the spatial QRS-T angle has been investigated in primary prevention ICD recipients with ischemic heart disease. The planar QRS-T angle is the projection of the spatial QRS-T angle in the frontal plane. As with any projection, it is sensitive to variations of the anatomical position of the heart in thorax. Therefore, the spatial QRS-T angle, which is calculated in the plane that the QRS- and T-axes form, is a more robust clinical tool. This is an important issue as the results from this study demonstrate that a narrow spatial angle is associated with a lower risk of ventricular arrhythmias. And although the spatial QRS-T angle cannot be derived directly from the surface ECG, recent studies have provided easy methods to acquire the spatial QRS-T angle from the standard 12-lead ECG.[29]

In our population of ischemic primary prevention ICD recipients, patients with a wide planar QRS-T angle demonstrated a hazard ratio of 2.5 for the need of defibrillator back-up and 3.1 for all-cause mortality. In the recently published post hoc analysis of the DEFINITE trial, by Pavri and co-workers[22], the planar QRS-T angle was analyzed as a predictor of the composite end-point of appropriate device therapy, mortality, and resuscitated cardiac arrest in a population

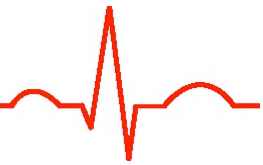


with *non*-ischemic cardiomyopathy. In this study, the hazard ratio of a planar QRS-T angle wider than 90º for the occurrence of appropriate device therapy was 1.95 (95% CI 1.24-3.08). The hazard ratio for all-cause mortality was 1.81 (95% CI 1.04-3.13).

After adjustment for other commonly used risk factors, the presence of a spatial QRS-T angle wider than 100º was associated with a hazard ratio of 7.3 for the occurrence of device therapy for ventricular arrhythmias as compared to patients with a spatial QRS-T angle ≤ 100º, in our population. More importantly, all patients with a spatial QRS-T angle ≤ 100º were free of device generated therapy during two years following implantation. This indicates that the spatial QRS-T angle may have an important potential for risk stratification in patients with ischemic heart disease.

Previous studies on the spatial QRS-T angle have already indicated its high value in the risk stratification for cardiac death in a population without ICDs.[20, 21] In a large cohort of patients, Yamazaki et al. observed a hazard ratio of 1.9 (95% CI 1.7-2.1) on cardiovascular death for a spatial QRS-T angle > 100º after correction for other ECG parameters.[21]

As a consequence of the balanced regulation of electrical activation and recovery of the ventricles, a narrow QRS-T angle is generally observed in healthy individuals.[27] Ventricular scar or residual ischemia, which is the arrhythmic substrate in ischemic cardiomyopathy, causes a disbalance of this process, sometimes referred to as electrical heterogeneity or discordance of de- and repolarisation.[30] Vectorcardiographically, these alterations in cardiac electrophysiology become, amongst others, apparent through directional changes of the QRS and T vectors and consequent widening of the QRS-T angle. When patients with ischemic cardiomyopathy have a narrow QRS-T angle, which is then associated with electrical homogeneity, it could be postulated that the amount of arrhythmic substrate is limited and may even be absent. The high incidence of ventricular arrhythmias in patients with a wide QRS-T angle and the low incidence in patients with a narrow QRS-T angle, as observed in the current study, underscores this principle.

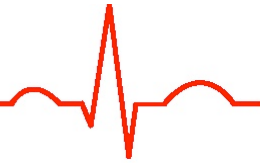


Clinical implications

Several non-invasive parameters that could improve patient selection for ICD therapy have been proposed. These include LVEF, QRS duration, QT interval, heart rate variability, ventricular ectopy on ambulatory monitoring, exercise capacity, and T-wave alternans.[31] In addition, total cosine R to T, which is also a measure of QRS-T concordance like the QRS-T angle, has been proven a promising parameter in the mortality risk stratification in patients following myocardial infarction.[32, 33] However, this variable has not been assessed in an ICD treated population, to our knowledge. Although the majority of these parameters appear promising, only LVEF has proven its usefulness in patient selection for ICD implantation and is currently the most important factor in the clinician's choice whether or not an ICD is indicated.[11] Still, in the implanted ischemic population, identified as being at high risk for ventricular arrhythmia based on depressed LVEF, 35% of patients actually experiences appropriate device therapy during follow-up, prompting for the identification of a sub-population at low risk.[13] In our population of ischemic primary prevention ICD recipients, patients with a spatial QRS-T angle ≤100º demonstrated no ventricular arrhythmias during the first two years following implantation and only 2% during further follow-up. These results imply that this parameter could be used in the discrimination of patients in whom the beneficial effects of an ICD might not exceed the costs and potential morbidity accompanying ICD therapy.

Limitations

This was a non-randomised prospective observational study, performed to assess the long-term follow-up in ischemic primary prevention ICD recipients and to assess the value of the planar and spatial QRS-T angle in baseline risk stratification. Adjustment for additional variables in the multivariable Cox model was limited by the number of end-points reached. Furthermore, some



patients without therapy during study follow-up might have reached an end-point, had follow-up been longer. Additionally, since not all patients had post-mortem ICD interrogation, some cases of death might have been arrhythmic. Finally, since patients were included over a period of 11 years, expanding guidelines for the implantation of defibrillators, treatment of acute myocardial infarction, and pharmacological anti-arrhythmic therapy could have created an inhomogeneous population.

Conclusion

In patients with ischemic heart disease, currently indicated for primary prevention ICD therapy, a baseline spatial QRS-T angle > 100º is associated with a sevenfold risk for the occurrence of appropriate device therapy, even after adjustment for commonly used risk factors. More importantly, a spatial QRS-T angle ≤ 100º on the ECG prior to implantation can identify patients with very low risk of life-threatening ventricular arrhythmias in whom the beneficial effect of ICD treatment might not exceed the costs and potential complications.

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Chapter 8

Update on Medtronic Sprint Fidelis and St. Jude Medical Riata Implantable Cardioverter-Defibrillator Leads Performance

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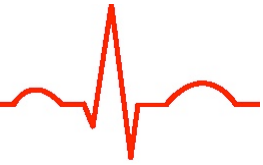
Submitted

Abstract

Background: The performance of small diameter implantable cardioverter defibrillator (ICD) leads has been questioned. The current study provides an update on the lead failure and cardiac perforation rate of Medtronic's Sprint Fidelis ICD lead and St. Jude Medical's Riata ICD lead in comparison to a large benchmark cohort.

Methods and Results: Since 1996, all ICD system implantations at the Leiden University Medical Center, the Netherlands, are registered. For the current study, data on 396 Sprint Fidelis leads (follow-up 3.4±1.5 years), 165 8-French (F) Riata leads (follow-up 4.6±2.6 years) and 30 7-F Riata leads (follow-up 2.9±1.3 years) were compared with a benchmark cohort of 1602 transvenously implanted ICD leads (follow-up 3.4±2.7 years) and assessed for the occurrence of lead failure and cardiac perforation. During follow-up, the yearly lead failure rate of the Sprint Fidelis lead, 7-F Riata lead, 8-F Riata lead and the benchmark cohort was 3.54%, 2.28% 0.78% and 1.14%, respectively. In comparison to the benchmark cohort, the adjusted hazard ratio of lead failure was 3.7 (95%CI 2.4-5.7, $p<0.001$) for the Sprint Fidelis lead and 4.2 (95%CI 1.0-18.0, $p<0.05$) for the 7-F Riata lead. Only one cardiac perforation was observed (0.05%) in the Riata group versus none in the Sprint Fidelis lead population.

Conclusion: The risk of lead failure was significantly increased for both the Sprint Fidelis and the 7-F Riata lead in comparison the benchmark cohort. The occurrence of cardiac perforations was rare.



Background

Manufacturers of implantable cardioverter defibrillator (ICD) leads constantly aim to improve design to allow easier implantation of additional leads, maintain venous blood flow and reduce subclavian crush syndrome.[1] However, recently became clear that these developments go together with some serious drawbacks. In particular, studies have reported on higher-than-expected lead failure rates for Medtronic's Sprint Fidelis lead (Medtronic Inc, MN, USA) as well as for St. Jude's 7-F Riata lead (St. Jude Medical Inc, MN, USA).[2-6] Moreover, studies have observed relatively high cardiac perforation rates associated with the Riata 1580/1581 lead (8-F) and the Riata 7000 series (7-F).[5, 7] As a consequence, Medtronic ceased production of the Sprint Fidelis lead and announced several safety advisories to improve early detection and reduce the number of inappropriate shocks due to lead failure. [4, 8, 9]

Given the high number of leads implanted worldwide (268 000 Sprint Fidelis leads and 227 000 Riata leads) it is important to monitor these patients carefully and provide up-to-date data on lead performance. Our center reported earlier on preliminary results of the performance of the Sprint Fidelis and 7-F Riata lead.[7, 10] This study provides an update on the performance of both leads with an extended follow-up duration and compares lead failure and cardiac perforation rates of the Sprint Fidelis lead, the Riata 7-F and the Riata 8-F lead with complication rates of a large benchmark cohort. Furthermore, the effects of Medtronic's safety advisories are evaluated.

Methods

Patient population

Since 1996, all patients who received an ICD system at the Leiden University Medical Center, Leiden, the Netherlands, are registered in the departmental Cardiology Information System (EPD-vision®, Leiden University Medical Center). Data of the implant procedure and all follow-up

visits were recorded. For the current analysis, only patients with a Sprint Fidelis lead (Medtronic Inc, MN, USA; model type 6949, 6948, 6931, 6930) and patients with a Riata lead (St. Jude Medical Inc, MN, USA; model type 1570, 1580, 1582, 7000, 7001, 7002, 7020) were included. For comparison of follow-up data, a large benchmark cohort of patients with transvenously implanted defibrillation leads, other than Sprint Fidelis leads or Riata leads was used. These leads were manufactured by Boston Scientific (MA, USA [formerly CPI Guidant, MN, USA]), Biotronik (Germany), Medtronic (MN, USA) and St. Jude Medical/Ventritex (MN, USA).

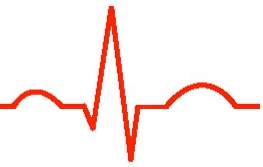
Eligibility for ICD implantation was based on international guidelines and included both secondary prevention and primary prevention of sudden cardiac death.[11, 12] Testing of sensing and pacing thresholds and defibrillation threshold testing were performed during the implant procedure.

Follow-up

The follow-up was from lead implantation to February 1, 2011. Periodic device interrogation was performed every 3–6 months or earlier if patient had symptomatic events. During these examinations, all leads were systematically evaluated for adequate function and integrity. As reported previously, all patients with a Sprint Fidelis lead and a Medtronic device were invited for implementation of Medtronic's safety advisories.[10] In brief, advisories consisted of adjustment of device settings, uploading of the Lead Integrity Algorithm and remote monitoring with CareLink®.[10] The benchmark cohort was followed and assessed for the occurrence of lead failure up to February 2008.[7]

Definition of lead failure and cardiac perforation

Defibrillation lead removal or capping was classified as lead failure if one of the following criteria was met: (1) undersensing or oversensing of normal electrical cardiac activity; (2)



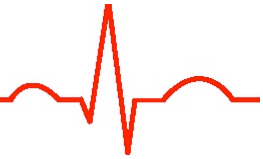
incapability of sensing, pacing, or defibrillation; (3) inappropriate shocks secondary to electrical noise artifacts; (4) abnormal lead impedance; (5) Lead Integrity Algorithm triggering an ICD alert.[3, 4] Cardiac perforation was diagnosed when a pericardial effusion was detected by transthoracic echocardiography in combination with abnormal lead impedance and/or pacing thresholds during follow-up.[5]

Statistical analysis

Continuous variables were analyzed as mean±SD. Categorical variables were analyzed as percentages as numbers and percentages. The cumulative incidence of lead failure was calculated using the Kaplan-Meier methodology. Chi-square tests were used to compare categorical variables and student t-tests were used for continuous variables. The occurrence of lead failure was compared with the benchmark cohort using three groups based on manufacturer and lead diameter: 1) Sprint Fidelis leads, 2) 7-F Riata leads (comprising lead model types 7000, 7001, 7002, 7020) and 3) 8-F Riata leads (comprising lead model types 1570, 1580, 1582). Cumulative incidences were analyzed by method of Kaplan-Meier and compared using the log-rank test. The 95% confidence intervals (CI) were calculated as 1.96 times the standard error in each direction. Multivariate Cox regression analysis, adjusted for known confounders (left ventricular ejection fraction, age, gender, and cardiomyopathy), was used to assess the risk of lead failure, described as hazard ratios (HR) with 95% CI.[13, 14] The statistical tests were performed using SPSS 18.0 for Windows. For all tests, a p-value <0.05 was considered significant.

Results

Since 1996, a total of 396 Sprint Fidelis defibrillation leads were implanted in 390 patients and 195 Riata defibrillation leads were implanted in 188 patients. The benchmark cohort consisted of



1602 leads, implanted in 1553 patients. As can be seen in Table 1, the majority of patients was male and had ischemic cardiomyopathy. During an average follow-up of 3.5±2.5 years, 372 patients died. To our knowledge, no patient died as a direct or indirect result of lead failure or cardiac perforation.

Table 1. Baseline clinical characteristics.

	Patients with Sprint Fidelis lead (n=390)	Patients with 7-F Riata lead (n=28)	Patients with 8-F Riata lead (n=160)	Benchmark cohort (n=1553)
Baseline characteristics				
Age, year	63±12	63±13	63±12	61±14
Male sex, %	81	89	82	80
Ejection fraction, %	32±14	39±11	38±15	34±14
Ischemic etiology, %	67	74	72	64
Primary indication, %	73	67	58	58

ICD = Implantable cardioverter defibrillator; F = French

Sprint Fidelis lead performance

The average follow-up of all 396 Sprint Fidelis lead was 3.4±1.5 years. As demonstrated in Table 2, the majority of patients received a Sprint Fidelis lead of Model Type 6931 (62%). During follow-up, 47 leads (12%) failed. These were implanted in 47 patients, of whom, 17 (36%) received 117 inappropriate shocks in total. Average time from implant to lead failure was 2.6±1.0 years. As can be seen in Figure 1, cumulative incidence of lead failure increased exponentially after 1 year of follow-up. After 2 years of follow-up, cumulative incidence was 4.1% (95%CI 1.9-6.3%), after 4 years 15.0% (95%CI 10.7-19.3%) and after 6 years 17.8% (95%CI 12.9-22.7%). In addition, yearly lead failure rates in first, second, third and fourth year of follow-up were 0.4%, 3.8%, 5.2% and 7.3%, respectively.

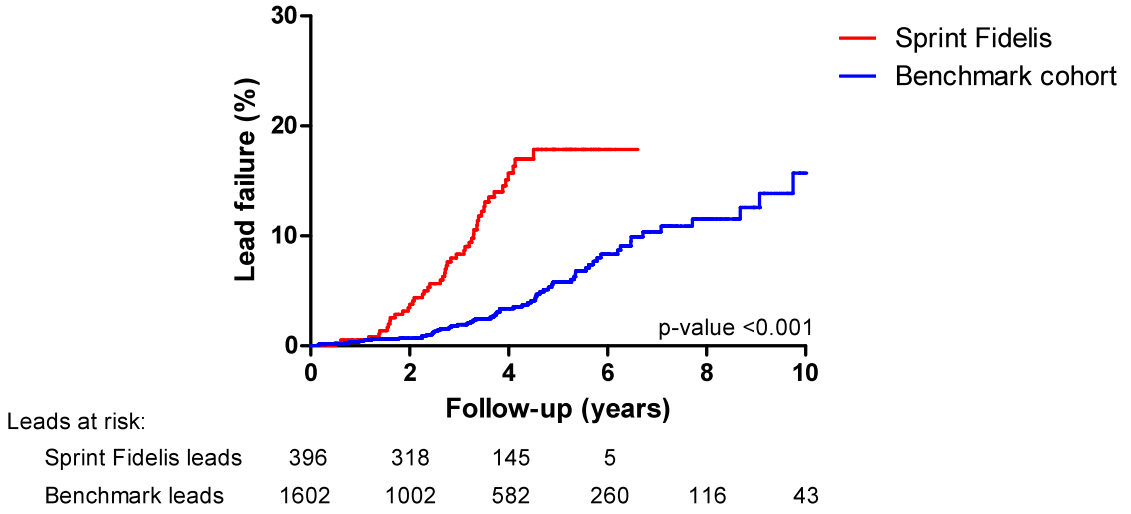


Figure 1. Failure of Sprint Fidelis leads. Kaplan Meier curve for cumulative incidences of lead failure.

Of the 47 failed leads, 8 failures (17%) were observed during routine evaluation, 21 patients (45%) were warned by a device alert without experiencing inappropriate shocks, 18 patients (38%) received inappropriate shocks of whom 2 patients were alerted by the device minutes before the shocks. Prior to implementation of the Lead Integrity Algorithm (only available for Medtronic ICDs), 10 out of 15 (67%) patients with a Medtronic ICD received an inappropriate shock related to lead failure. After implementation, 6 out of 24 (25%) patients received an inappropriate shocks related to lead failure ($p<0.05$). In addition, average number of repetitive inappropriate shocks decreased from 5.6±7.7 to 1.0±2.9 inappropriate shocks per case of lead failure ($p<0.05$) after implementation of the advisories. No cardiac perforations were observed in patients with a Sprint Fidelis lead.

Table 2. Model type of all implanted ICD leads.

Benchmark cohort (n=1602)	
Biotronik 8-F, n (%)	98 (6)
Boston Scientific 11-F, n (%)	163 (10)
Boston Scientific 9-F, n (%)	911 (57)
Medtronic 10.5-F, n (%)	76 (5)
Medtronic 9-F, n (%)	322 (20)
St Jude Medical 11-F, n (%)	32 (2)
Medtronic's 7-F Sprint Fidelis leads (n=396)	
6930, n (%)	1 (<1)
6931, n (%)	247 (62)
6948, n (%)	48 (12)
6949, n (%)	100 (25)
St Jude Medical's 7-F and 8-F Riata leads (n=195)	
1570, n (%)	114 (59)
1580, n (%)	44 (22)
1582, n (%)	7 (4)
7000, n (%)	5 (3)
7001, n (%)	1 (<1)
7002, n (%)	23 (12)
7020, n (%)	1 (<1)

ICD = Implantable cardioverter defibrillator; F = French

Removal of the leads was performed in 25 (53%) of the cases, sealing of the lead occurred in 22 patients (47%; Table 3). Two minor complications (4.2%) associated with Sprint Fidelis lead revision were observed: 1) right atrial lead dislodgement and 2) detachment of the distal part of the Sprint Fidelis lead (model type 6949) during manual traction, which required an extra intervention.

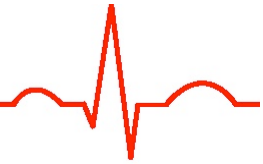


Table 3. Performance of the implanted ICD leads

	Sprint Fidelis (n=396)	Riata 8-F (n=165)	Riata 7-F (n=30)	Benchmark cohort (n=1602)
Active, n (%)	198 (50.0)	90 (54.5)	19 (63.3)	1063 (66.4)
Failed, n (%)	47 (11.9)	6 (3.6)	2 (6.7)	62 (3.9)
Non-active, n (%)	110 (27.8)	51 (30.9)	5 (16.7)	314 (19.6)
Died, n (%)	81 (20.4)	32 (19.4)	3 (10.0)	256 (16.0)
Prophylactically replaced or sealed, n (%)	12 (3.0)	0 (0.0)	0 (0.0)	0 (0.0
Replaced/sealed for other reasons, n (%)	7 (1.8)	2 (1.2)	1 (3.3)	15 (0.9)
Infection, n (%)	10 (2.5)	17 (10.3)	0 (0.0)	43 (2.7)
Followed up elsewhere, n (%)	41 (10.4)	18 (10.9)	4 (13.3)	163 (10.1)
Average follow-up, y	3.4±1.5	4.6±2.6	2.9±1.3	3.4±2.7
Total follow-up, y	1327.1	767.0	87.6	5449.3
Failure rate %/y	3.54	0.78	2.28	1.14

ICD = Implantable cardioverter defibrillator; F = French

Riata lead performance

Of the 195 implanted Riata leads, 165 leads had a diameter of 8-F and 30 leads a diameter of 7-F. During an average follow-up of 4.4±2.5 years, 8 (4.1%) leads implanted in 7 different patients failed. Due to the failure, 2 patients experienced a total of 11 inappropriate shocks. For 7-F leads, cumulative incidence of lead failure was 3.8% (95%CI 0-11.2) after 2 years and 8.0% (95%CI 0-18.8) after 4 years. For 8-F leads, cumulative incidence was 1.5% (95%CI 0-3.5%) after 2 years and 3.2% (95%CI 0.1-6.3%) after 4 years of follow-up (Figure 2). Average time from implant to lead failure was 1.9±0.5 years for 7-F leads and 3.8±2.3 years for 8-F leads.

Revision of the 8 failed leads resulted in removal of 3 leads and sealing of 5 leads. One complication occurred during these revisions, which consisted of right atrial lead dislodgement. One cardiac perforation (0.5%), caused by a 7-F Riata lead, model type 7002, was observed within 1 day following ICD implantation and confirmed by echocardiography.

Lead performance in benchmark cohort

In 1602 leads in the benchmark cohort, 62 cases (3.9%) of lead failure occurred during 3.4±2.7 years follow-up. Cumulative incidence of lead failure was 0.7% (95%CI 0.3-1.1%) after 2 years of follow-up, 3.4% (95%CI 2.2-4.6%) after 4 years, 8.3 % (95%CI 5.9-10.7%) after 6 years and 11.5% (95%CI 8.2-14.8%) after 8 years (Figure 1&2). Average time from implant to lead failure was 4.2±2.3 years.

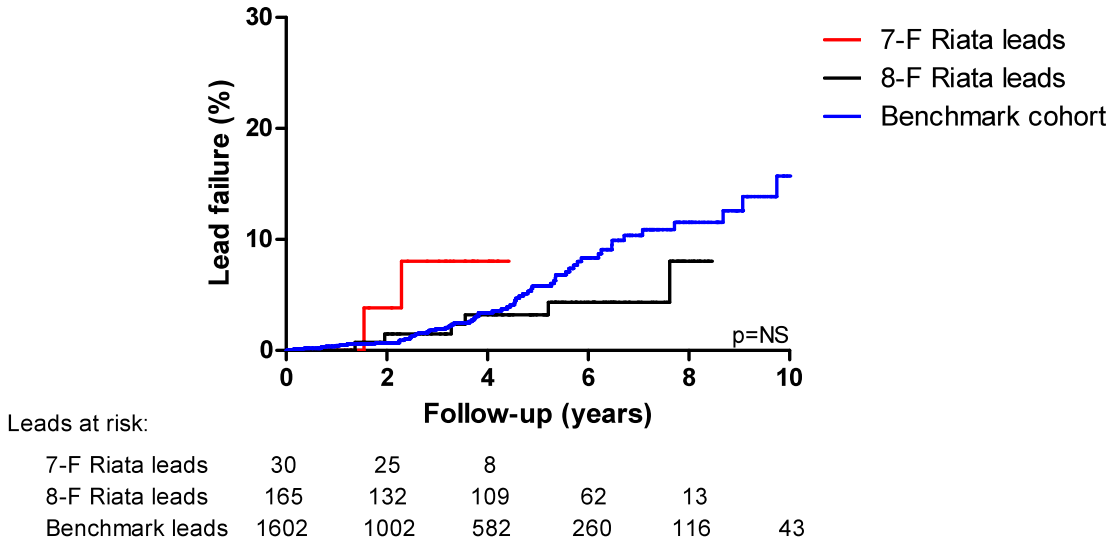


Figure 2. Failure of Riata leads. Kaplan Meier curve for cumulative incidences of lead failure, grouped by lead diameter (French).

Differences in failure rate

As can be seen in Table 2, major differences in failure rates were observed between the groups. Whereas the benchmark cohort and the 8-F Riata leads demonstrated yearly lead failure rates of 1.14% and 0.78%, respectively, the Sprint Fidelis showed a yearly lead of 3.54% and the 7-F Riata lead of 2.28%. The adjusted risk of failure was 3.7 times higher for Sprint Fidelis leads in comparison to the benchmark cohort (HR 3.7 95%CI 2.4-5.7, p<0.001) and 4.2 times higher for the Riata 7-F leads in comparison to benchmark cohort (HR 4.2 95%CI 1.0-18.0, p<0.05).

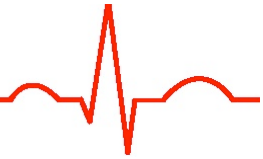
Discussion

The principal findings of this update study can be summarized as follows: 1) the risk for lead failure was significantly increased for both the Sprint Fidelis and the 7-F Riata lead as compared to a benchmark cohort, 2) implementation of Medtronic's safety advisories significantly reduced the number of inappropriate shocks, 3) cardiac perforations occurred rarely.

Sprint Fidelis lead performance

Three years after its introduction in 2004, Hauser et al. were first to report the higher-than-expected failure rate of Sprint Fidelis leads.[2] Within three months following this preliminary report, Medtronic suspended distribution and announced recommendations for impedance alert programming, followed one year later, by recommending the usage of remote monitoring and Lead Integrity Algorithm. Since then several studies have reported high yearly failure rates varying from 2.8% to 3.6%.[2, 14-16] The current study observed an overall yearly lead failure rate of 3.5% as compared to 1.1% in the benchmark cohort. Additionally, this failure rate accelerated over time: if a lead survived its first 3 years of follow-up, the failure rate for the following year increased up to 7.3%. This accelerating phenomenon was first described by Farwell et al. during a mean follow-up of 1.7 year and in the current study with an extended follow-up of 3.5 years, this was confirmed.[3] This sheds important light on the still ongoing discussion whether or not to replace the leads prophylactically, especially since an estimated 166000 Sprint Fidelis leads are still active worldwide.[17]

To come to a well-considered decision, one should realize that the risk of complications with lead revision is substantial. In literature, complication rates associated with revision/extraction of Sprint Fidelis leads vary. Whereas Maytin et al observed no major and only



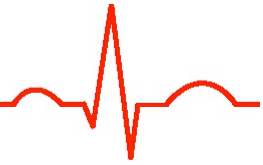
two minor complications in 348 patients who underwent Sprint Fidelis lead revision, Parkash et al reported on major complications in 7.0% and minor complications in 7.5% of 468 Sprint Fidelis lead revisions.[18, 19] Noteworthy, all revisions reported in the study by Maytin et al were performed by highly skilled operators with a large volume of experience.[18] In the current study, no major complications occurred and the minor complication rate was 4.2%. Overall, the complication rate is still too high to justify prophylactic lead replacement, although, taken in mind the accelerating risk of lead failure, over time the benefits of prophylactic lead replacement might outweigh the lead failure-related risks.

Riata lead and cardiac perforation

Around 2007, several studies and case reports observed higher-than-expected cardiac perforation rates in patients with a Riata lead. When taken these reports as a whole, the cardiac perforation rate was 2.5% which far exceeds registry data (<0.5%).[20] Hereafter, Danik et al demonstrated a comparable rate (2.8%) in a larger population with longer follow-up duration. However, they observed perforations only in patients with a specific Riata lead model type including 1580/1581 (8-F) and 7000 (7-F) and stated that similarities in design of the lead, rather than the size of the lead alone, might contributed to this relatively high complication rate.[5] In addition, Ellis and Rottman found comparable high risks of cardiac perforation for these specific lead types.[6]

In sharp contrast to the previous reports is an industry-sponsored study of the Riata lead, comprising more than 15 000 patients. They observed a perforation rate of 0.38% and owed the differences with the previous results to a statistical phenomenon.[21, 22] In the current study, only one perforation was observed in a patient with a Riata lead (0.5%) versus none in patients with a Sprint Fidelis lead, which is in accordance with the large registry studies.[21, 22]

Failure of the Riata lead



Interestingly, this study also demonstrated that the adjusted risk of failure for the 7-F Riata leads was more than four times higher than the benchmark cohort. This was earlier observed in a study by Ellis et al. who demonstrated in 62 patients with a 7-F Riata lead an even higher failure rate of 8.1% during a follow-up of less than 1 year.[6] And although this is preliminary data of a small cohort of 30 (this study) and 62 leads, the high lead failure rate is worrying. Again data of the multiple registry studies did not support this and reported a lead failure rate of <1%.[21, 22] However, it should be noted that data of industry driven studies are sometimes better than clinical practice studies – as was the case with data of Medtronic on the performance of the Sprint Fidelis lead.[14] For proper analysis, it is therefore essential to have a non-industry driven European or worldwide data registry.[23]

Limitations

The presented results are subjected to the usual limitations of a retrospective analysis. Furthermore, cases of lead failure and cardiac perforation might occur without symptoms or changes in electric parameters, causing them to go unnoticed.

Conclusion

From this study becomes clear that the risk of Sprint Fidelis lead failure continues to accelerate over time. Adverse events related to Sprint Fidelis lead failure were significantly reduced as a result of the safety advisories. A comparable failure rate was observed for the smallest 7-F Riata lead. In contrast, no higher-than-expected cardiac perforation rates were observed for the Sprint Fidelis and the Riata leads.

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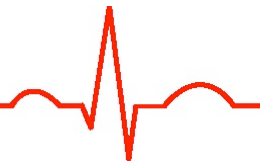
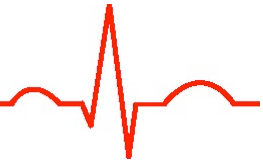


Summary, conclusions and future perspectives



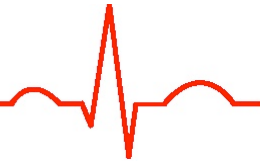
Summary

The general introduction (**Chapter 1**) of this thesis describes how implantable cardioverter defibrillator (ICD) therapy became the treatment of choice for patients at risk for life-threatening arrhythmias either as secondary or primary prevention. **Chapter 1** further specifies on specific technical developments, large randomized controlled trials leading to the construction of currently adopted international guidelines, future developments, cost-effectiveness and currently used methods for risk stratification.

The aim of this thesis was to give better insight in the treatment of patients at risk for life-threatening arrhythmias by studying a large population of patients treated with ICD therapy outside the setting of a clinical trial. Firstly, to assess long-term follow-up in patients with different indications for implantation and to give better insight in the need for device replacement (**Part I**). Secondly, to improve risk stratification by evaluating the currently used parameters and to evaluate the added value of new parameters (**Part II**).

Part I: The actual need for defibrillator backup during long-term follow-up

In **Chapter 2** we assessed differences in mortality and ICD therapy between patients who had a primary or secondary indication for ICD implantation. All patients treated with ICD therapy were included with the only exception of patients with congenital monogenetic cardiac disease. A total of 2134 patients were included of whom 1302 (61%) patients received an ICD for primary prevention and 832 (39%) patients for secondary prevention. During a mean follow-up of 3.4 ± 2.8 years, 423 (20%) patients died. The 5-year cumulative incidence of mortality was 25% (95% CI 21-29%) for primary prevention patients and 23% (95% CI 20-26%) for secondary prevention patients. During the first 3 years of follow-up, differences in mortality between both groups increased, whereas after 3 years the differences remained stable. For appropriate therapy,



secondary prevention patients exhibited a 74% increased risk for appropriate therapy as compared to primary prevention patients (HR 1.7, 95% CI 1.5-2.0, p<0.001).

This study demonstrates the difference in long-term follow-up between primary and secondary prevention ICD patients.

The purpose of **Chapter 3** was to give clinicians better insight in the dilemma whether or not to replace an ICD after an event-free first battery service-life. In patients treated for primary prevention, the relatively low incidence of ventricular arrhythmias (VA), combined with the limited battery service-life potentially results in a large group of patients who have had no benefit of the ICD during the first service-life. One-hundred-and-seventy-eight primary prevention ICD patients who had a replacement because of battery depletion and who did not received appropriate therapy before device replacement were included in the current analysis. During a mean follow-up of 22 ± 21 months after device replacement, 136 (76%) patients had not received appropriate ICD therapy. The 3-year cumulative incidence of appropriate therapy (following replacement) was 19% (95% CI 10-29%).

This study demonstrates that despite the majority of patients treated for primary prevention do not experience VA during first battery service-life, a substantial number of these patients do experience appropriate ICD therapy after replacement and therefore justifying device replacement.

Part II: Improvements in risk stratification

The aim of **Chapter 4** was to assess survival in primary prevention ICD recipients with non-ischemic or ischemic heart disease and to construct a baseline mortality risk score. In the study 1036 patients were included and were followed-up for 29 ± 22 months. During follow-up 138 (13%) patients died. Non-ischemic and ischemic patients demonstrated similar survival but

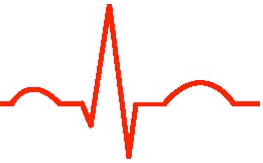


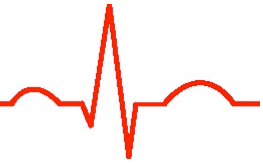
exhibit different factors that influence the risk for mortality. A risk score, consisting of simple baseline variables could stratify patients in low, intermediate and high-risk for mortality. In non-ischemic patients, annual mortality was 0.4% (95% CI 0.0-2.2%) in low-risk and 9.4% (95% CI 6.6-13.1%) in high-risk patients. In ischemic patients, annual mortality was 1.0% (95% CI 0.2-3.0%) in low-risk and 17.8% (95% CI 13.6-22.9%) in high-risk patients.

This chapter shows that utilization of an easy applicable baseline risk score can create an individual patient-tailored estimation on mortality risk to aid clinicians in daily practice.

In **Chapter 5** we assessed the prevalence of different types of atrial fibrillation (AF) and their prognostic importance in ICD patients. The presence of a history of AF (paroxysmal, persistent or permanent), the effect of AF on the occurrence of appropriate or inappropriate device therapy, as well as mortality was noted in 913 ICD patients. At implantation, 73% of patients had no history of AF, 9% had a history of paroxysmal AF, 7% had a history of persistent AF and 11% had permanent AF. During 27 ± 13 months follow-up, 117 (13%) patients died, 228 (25%) patients experienced appropriate device discharge and 139 (15%) patients received inappropriate shocks. Patients with permanent AF exhibit more than double the risk of mortality, ventricular arrhythmias triggering device discharge and inappropriate device therapy. Patients with paroxysmal or persistent AF did not show a significant increased risk of mortality or appropriate device therapy, but demonstrated an almost threefold increased risk of inappropriate therapy.

This study clearly demonstrates that different types of AF have prognostic implications for mortality, appropriate therapy as well as inappropriate device discharge.

In an attempt to identify patients who do not benefit from ICD treatment, **Chapter 6** defined non-benefit from ICD treatment as death, prior to appropriate ICD therapy. Out of a number of different routinely acquired baseline variables such as age, ejection fraction and diabetes mellitus,

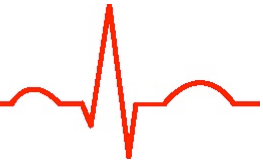


a baseline risk score was constructed to estimate the risk for non-benefit in 900 ischemic primary prevention ICD recipients. Stratification for non-benefit resulted in risk categorization of patients as low, intermediate or high-risk. Advanced age was the strongest predictor of non-benefit. Five-year cumulative incidence for non-benefit ranged from 12% (95% CI 5-18%) in low-risk patients to 49% (95% CI 38-60%) in high-risk patients.

This study shows that the risk of non-benefit can be predicted which might have important clinical consequences.

The aim of **Chapter 7** was to assess the value of the ECG derived QRS-T angle for prediction of ICD therapy and mortality in primary prevention patients with ischemic heart disease. For this, 412 ICD patients with ischemic heart disease and a left ventricular ejection fraction (LVEF) ≤ 40% were included. After device implantation, the occurrence of appropriate ICD therapy and mortality was noted. A survival analysis was performed comparing patients with a planar QRS-T angle ≤ 90° (n=124, 30%) to patients with a planar QRS-T angle > 90° before device implantation. Furthermore, patients with a spatial QRS-T angle ≤ 100° (n=56, 14%) were compared to patients with a spatial QRS-T angle > 100°, prior to implant. For patient with a planar QRS-T angle > 90° as compared to ≤ 90°, the adjusted hazard ratio for the occurrence of appropriate device therapy was 2.4 (95% CI 1.1-5.2); a spatial QRS-T angle > 100° was associated with an adjusted hazard ratio of 7.3 (95% CI 1.0-53.8). Furthermore, a spatial QRS-T angle ≤ 100° exhibit a positive predictive value of 98% (95% CI 95-100) for the prediction of an appropriate therapy-free follow-up.

This study shows that an easy acquirable ECG derived parameter can be a powerful predictor of appropriate device therapy in primary prevention ICD recipients with ischemic heart disease. Furthermore, a spatial QRS-T angle ≤ 100° might be of value in the identification of patients in whom, although currently indicated, ICD treatment should be reconsidered.

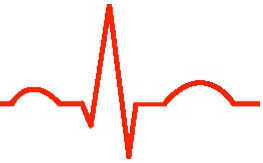


In **Chapter 8** we provided an update on the lead failure and cardiac perforation rate of Medtronic's Sprint Fidelis ICD lead and St. Jude Medical's Riata ICD lead in comparison to a large benchmark cohort. For this, data on 396 Sprint Fidelis leads (follow-up 3.4±1.5 years), 165 8-French (F) Riata leads (follow-up 4.6±2.6 years) and 30 7-F Riata leads (follow-up 2.9±1.3 years) were compared with a benchmark cohort of 1602 transvenously implanted ICD leads (follow-up 3.4±2.7 years) and assessed for the occurrence of lead failure and cardiac perforation. During follow-up, the yearly lead failure rate of the Sprint Fidelis lead, 7-F Riata lead, 8-F Riata lead and the benchmark cohort was 3.54%, 2.28% 0.78% and 1.14%, respectively. In comparison to the benchmark cohort, the adjusted hazard ratio of lead failure was 3.7 (95%CI 2.4-5.7, $p<0.001$) for the Sprint Fidelis lead and 4.2 (95%CI 1.0-18.0, $p<0.05$) for the 7-F Riata lead. Only one cardiac perforation was observed (0.05%) in the Riata group versus none in the Sprint Fidelis lead population.

This study demonstrates that the risk of lead failure was significantly increased for both the Sprint Fidelis and the 7-F Riata lead in comparison the benchmark cohort. The occurrence of cardiac perforations was rare.

Conclusions and future perspectives

Since the introduction of the ICD by Dr Michel Mirowski in 1980, large randomized trials undisputedly demonstrated the beneficial effect of ICD therapy in patients at risk for life-threatening arrhythmias. Despite the results of many large randomized trials, much remains unclear about ICD recipients in the daily practice, outside the setting of a clinical trial. The current thesis clarifies a few aspects in the rapidly increasing ICD treated population. Firstly, during long-term follow-up, differences in the incidence of all-cause mortality and the occurrence of appropriate and inappropriate device therapy were assessed between patients with different

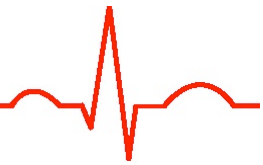


ICD implantation indications (primary vs. secondary). As expected, patients treated for secondary prevention are at increased risk for appropriate therapy. However, similar event-rates of all-cause mortality were observed between both groups. Furthermore, insight was given in the actual need for device replacement in patients with a long event-free period. Secondly, this thesis evaluated the currently used parameters for risk stratification and also evaluated the added value of new parameters. A baseline mortality risk score derived from simple baseline clinical variables was constructed and the prognostic importance of atrial fibrillation on the occurrence of device therapy and mortality was assessed. To improve baseline risk stratification, the value of new parameters derived from a simple ECG was assessed for the prediction of ventricular arrhythmia.

Future research should primarily focus on risk assessment strategies for the primary prevention of SCD. Improvement of the current risk assessment strategies can maximize overall ICD benefit. To achieve this, two different patient populations should be identified: 1) patients who are currently eligible for ICD implantation, but who have demonstrated no benefit from the device during follow-up; and 2) patients at high risk for SCD without an indication for ICD treatment.

Sudden cardiac death

Despite advances in preventing and treating cardiovascular disease, sudden cardiac death (SCD) remains a major public health issue in the Western world. In the United States alone, the annual incidence of SCD varies from 180.000 to 460.000 each year of which most fatal events occur outside the hospital.[1] Since the introduction of ICD therapy, many studies have proven the beneficial effect of ICD treatment for the primary prevention of SCD. The survival benefit is demonstrated in a patient population who are at high risk for SCD according to currently used risk parameters. Currently used parameters to estimate the risk for SCD are: age, sex, smoking, high cholesterol, physical activity, hypertension, QRS duration, renal function and LVEF.[2] It is



therefore reasonable that patients with many positive risk factors for arrhythmia, show significant survival benefit. Recent international guidelines, with LVEF as the single most important risk stratification tool, have recommended ICD treatment for a wide range of patients with cardiac disease. Therefore, a major part of the population who are at high risk for SCD are indicated for an ICD. However, the majority of cases of SCD still occurs in patients without known cardiac disease or risk factors, causing ICD treatment to have relatively low impact on the incidence of SCD in the general population. Therefore, without novel parameters for the timely identification of patients at high-risk for SCD, the majority of cases of SCD cannot be prevented. To significantly reduce the incidence of SCD, future efforts should focus on the identification of more specific parameters in combination with LVEF to identify this "unknown" subgroup in the general population.

Death, prior to first appropriate ICD therapy

The beneficial effect of ICD therapy is well established and since the implementation of primary prevention in the international guidelines, implantation rates increased to an estimated 275.000 devices in 2008.[3] However, potentially life-saving ICD treatment is accompanied by adverse events such as inappropriate shocks and pocket related infections.[4] As previously described, there is an "unknown" subgroup in the general population which could benefit for treatment and, therefore, should be identified. On the other hand, within the current indicated ICD population, the incidence of appropriate therapy is relatively low and a substantial part even dies, prior to a first appropriate therapy. Koller and co-workers analyzed the incidences of appropriate ICD therapy and all-cause mortality and defined non-benefit as death prior to appropriate therapy. The study demonstrated during a follow-up of 7 years, an incidence of all-cause mortality of 11% without prior ICD therapy.[5] The current thesis assessed the risk for "non-benefit" from ICD treatment in 900 primary prevention ICD patients with ischemic heart disease and showed that a

population can be identified that has a 5-year cumulative incidence of non-benefit (death, prior to appropriate therapy) of 50%. One could conclude that these patients, although currently indicated, have no benefit from ICD treatment. However, its negative effects are still present in these patients, stressing the importance of timely identification of this population. The exclusion of these patients from ICD treatment should improve optimal allocation of these costly devices and should increase over-all benefit in the population that will benefit from treatment. Future research will primarily have to focus on further evaluation of the individual patient who currently has an indication for ICD treatment but does not benefit from ICD treatment. Patients should possibly be reconsidered for ICD implantation if they can be identified prior to implantation. The developed risk-scores in the current thesis may contribute to identifying these patients.

When dr Mirowski introduced his idea to prevent sudden cardiac death, his vision immediately met criticism. Thirty years later criticism shifted to feasibility and effectiveness of ICD therapy. The patient population that is eligible for ICD treatment is growing each day, therefore future research should focus on the individual person to decrease the “non benefit” population. Secondly, new baseline parameters must be identified to improve risk stratification. And thirdly, technological improvements need to be developed to decrease the drawbacks of ICD therapy. The era of the ICD has begun, but thirty years later device development is still far from completed.

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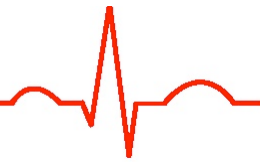
4. Van Erven EL, Schalij MJ. Troubleshooting implantable cardioverter-defibrillator related problems. *Heart* 2008; 94:649-60.
5. Koller MT, Schaer B, Wolbers M et al. Death without prior appropriate implantable cardioverter-defibrillator therapy: a competing risk study. *Circulation* 2008; 117:1918-26.



Samenvatting,

conclusies

en toekomstperspectieven

Samenvatting

De algemene introductie van dit proefschrift (**Hoofdstuk 1**) beschrijft hoe de behandeling met een Implanteerbare Cardioverter Defibrillator (ICD) de behandeling van eerste keus werd voor patiënten die een risico hebben op het ontwikkelen van levensbedreigende ventriculaire ritmestoornissen. In dit eerste hoofdstuk wordt dieper ingegaan op de technologische ontwikkelingen die de afgelopen jaren hebben plaatsgevonden. Daarnaast wordt er gekeken naar grote gerandomiseerde studies die een verschuiving teweeg hebben gebracht van secondaire naar primaire preventie en die hebben geleid tot de huidige internationale richtlijnen voor de implantatie van ICD's. worden eventuele toekomstperspectieven, de kosteneffectiviteit van ICD's en de op dit moment gebruikte methodes voor risico stratificatie behandeld.

Het doel van dit proefschrift is om meer inzicht te krijgen in patiënten die een risico hebben op het ontwikkelen van levensbedreigende ventriculaire ritmestoornissen en hiervoor met een ICD worden behandeld. Om deze doelstelling te bereiken is een grote patiëntenpopulatie, buiten de setting van gerandomiseerde studies, langdurig gevolgd. De resultaten van dit onderzoek zijn in twee onderdelen beschreven. Allereerst worden in **deel I** verschillen beschreven tussen patiënten die voor primaire of voor secondaire preventie een ICD hebben gekregen. Tevens wordt in dit deel van het proefschrift onderzocht of een ICD gewisseld moet worden als zich nog geen ritmestoornissen hebben voorgedaan. **Deel II** beschrijft de onderzoeksresultaten van de huidige gebruikte parameters voor risicostratificatie en de toegevoegde waarde van nieuwe parameters.

Deel I: De werkelijke noodzaak om tijdens lange-termijn follow-up een ICD als reserve therapie te hebben

In **Hoofdstuk 2** onderzochten we of er verschil is in de incidentie van sterfte tussen patiënten die een primaire of een secondaire indicatie hadden voor ICD implantatie. Tevens is er gekeken of er verschillen in incidentie van ICD therapie zijn tussen beide groepen. Met uitzondering van patiënten met een congenitale monogenetische hartziekte, werden alle patiënten met een ICD in het onderzoek geïncludeerd. In totaal werden 2134 patiënten met een ICD geïncludeerd. Hiervan hadden 1302 (61%) patiënten een primaire indicatie voor implantatie en 832 (39%) patiënten een secondaire indicatie. Tijdens een gemiddelde follow-up van 3.4 ± 2.8 jaar zijn 423 (20%) patiënten overleden. Voor de primaire preventie ICD patiënten was de 5-jarige cumulatieve incidentie van sterfte 25% (95% CI 21-29%), voor de secondaire preventie ICD patiënten was dit 23% (95% CI 20-26%). Gedurende de eerste 3 jaar van de follow-up werden er groter wordende verschillen gezien in sterfte tussen beide groepen, echter na deze 3 jaar bleven de verschillen gelijk. In vergelijking met primaire preventie ICD patiënten, hebben secondaire preventie ICD patiënten een verhoogd risico van 74% op het krijgen van terechte therapie (HR 1.7, 95% CI 1.5-2.0, $p<0.001$).

Deze studie laat tijdens langdurige follow-up de verschillen zien tussen primaire preventie en secundaire preventie ICD patiënten.

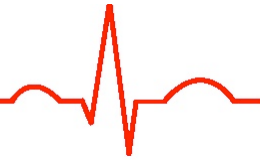
Het doel van **Hoofdstuk 3** is om clinici beter inzicht te geven indien zij voor het dilemma komen te staan om een ICD te vervangen, nadat patiënten tijdens de levensduur van de eerste ICD geen therapie hebben gekregen. In primaire preventie ICD patiënten kan een relatief lage incidentie van ventriculaire ritmestoornissen, in combinatie met een beperkte levensduur van de batterij van de ICD, resulteren in een grote groep patiënten die geen baat heeft gehad van de eerste ICD implantatie. In het onderzoek werden 187 primaire preventie ICD patiënten geïncludeerd die een

vervanging van hun ICD hebben gehad, omdat de batterij van de ICD leeg was geraakt en zij gedurende deze periode geen terechte ICD therapie hebben gekregen. Tijdens een gemiddelde follow-up van 22 ± 21 maanden na het vervangen van de ICD, hebben 136 (76%) patiënten geen terechte ICD therapie gekregen. Na vervanging was de 3-jarige cumulatieve incidentie van terechte ICD therapie 19% (95% CI 10-29%).

Deze studie laat zien dat het grootste deel van primaire preventie ICD patiënten gedurende de levensduur van de eerste ICD geen ventriculaire ritmestoornis ontwikkelt. Echter, een substantiële hoeveelheid van deze patiënten ontwikkelt toch nog een ventriculaire ritmestoornis nadat de ICD vervangen is. Vervanging van de ICD in patiënten die tijdens de levensduur van de eerste ICD geen terechte therapie hebben gekregen, wordt hierdoor gerechtvaardigd.

Deel II: Verbeteringen in risicostratificatie

In **Hoofdstuk 4** hebben we gekeken naar sterftecijfers in patiënten met een primaire indicatie voor een ICD met ischemische of niet-ischemische hartziekten. Tevens hebben we een risicoscore gemaakt om de sterfte in deze groep in te kunnen schatten. In het onderzoek werden 1036 patiënten geïncludeerd die een gemiddelde follow-up hadden van 29 ± 22 maanden. Tijdens de follow-up zijn 138 (13%) patiënten overleden. Ondanks het feit dat er geen verschillen in het risico op sterfte werden gevonden tussen patiënten met ischemische of niet-ischemische hartziekten, bleken de twee groepen van elkaar onderscheiden te kunnen worden door verschillende factoren die van invloed zijn op het risico op sterfte. Met behulp van een risicoscore, bestaande uit eenvoudige baseline variabelen, konden patiënten gestratificeerd worden in laag, middelhoog en hoog risico op overlijden. Bij de niet-ischemische patiënten was de jaarlijkse sterfte 0.4% (95% CI 0.0-2.2%) bij laag risico en 9.4% (95% CI 6.6-13.1%) bij hoog



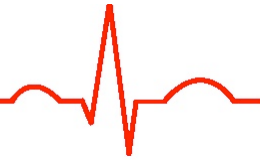
risico patiënten. Bij ischemische ziekten was de jaarlijkse sterfte 1.0% (95% CI 0.2-3.0%) bij een laag risico en 17.8% (95% CI 13.6-22.9%) bij een hoog risico.

Deze studie laat zien dat met behulp van een gemakkelijk toepasbare pre-implantatie risicoscore een sterfte risicoschatting gemaakt kan worden, toegespitst op een individuele patiënt. Gebruik van deze risicoscore kan clinici in de dagelijkse praktijk ondersteunen in hun beleid bij deze patiënten.

In **Hoofdstuk 5** onderzoeken we in 913 patiënten met een ICD de prevalentie van verschillende soorten atrium fibrilleren (AF) en de prognostische waarde hiervan op sterfte en het voorkomen van terechte of onterechte ICD therapie. Ten tijde van ICD implantatie had 73% van de patiënten geen voorgeschiedenis van AF, 9% had een voorgeschiedenis van paroxysmaal AF, 7% van persistent AF en 11% van permanent AF. Tijdens een gemiddelde follow-up van 27 ± 13 maanden zijn 117 (13%) patiënten overleden, kregen 228 (25%) patiënten terechte ICD therapie en 139 (15%) patiënten onterechte ICD therapie. Patiënten met permanent AF hadden een meer dan dubbel risico op overlijden, ventriculaire aritmieën en onterechte therapie. Patiënten met paroxysmaal of persistent AF toonden geen significant verhoogd risico op sterfte of terechte therapie, echter wel een bijna drievoudig verhoogd risico op onterechte ICD schokken.

Deze studie toont het prognostisch belang aan van deze veelvoorkomende ritmestoornissen bij patiënten die worden behandeld met een ICD.

Hoofdstuk 6 gaat over de identificatie van patiënten die geen baat hebben bij behandeling met een ICD, de zogenaamde “non-benefit” groep. Dit zijn patiënten die overlijden, nog voordat zij een terechte ICD therapie hadden gekregen. In 900 primaire preventie ICD patiënten met een ischemische hartziekte, werd een risicoscore geconstrueerd op grond van een aantal verschillende standaard vastgelegde baseline variabelen zoals leeftijd, ejectiefractie en comorbiditeit (diabetes



mellitus). De risicoscore werd gebruikt om vóór ICD implantatie de kans op non-benefit in te schatten. Met behulp van deze risicoscore konden patiënten worden verdeeld in categorieën met een laag, gemiddeld of hoog risico, waarbij een hoge leeftijd de sterkste voorspeller was van non-benefit. De 5 jarige cumulatieve incidentie voor non-benefit varieerde van 12% (95% CI 5-18%) in patiënten met een laag risico tot 49% (95% CI 38-60%) in hoog risico patiënten.

Deze studie toont aan dat het risico op non-benefit voor ICD implantatie kan worden voorspeld, hetgeen belangrijke klinische consequenties kan hebben voor de overweging om een ICD te implanteren.

Het doel van **Hoofdstuk 7** is het evalueren van de voorspellende waarde van de QRS-T hoek op een ECG voor ICD therapie en mortaliteit. Hiervoor werden 412 primaire preventie patiënten met ischemische hartziekte en een linker ventrikel ejectie fractie (LVEF) van ≤ 40% geïncludeerd. Tijdens follow-up werden terechte ICD therapie en mortaliteit geregistreerd. Een survival analyse werd uitgevoerd waarbij 124 (30%) patiënten met een kleine (≤ 90°) QRS-T hoek voor ICD implantatie, werden vergeleken met patiënten met een grote (> 90°) QRS-T hoek. Tevens werden 56 (14%) patiënten met een ruimtelijke QRS-T hoek ≤ 100° vergeleken met patiënten met een ruimtelijke QRS-T hoek van > 100°. Patiënten met een QRS-T hoek > 90° hadden een meer dan tweevoudig vergroot risico op het optreden van terechte therapie dan patiënten met een hoek ≤ 90° (relatieve risico 2.4, 95% CI 1.1-5.2). Een ruimtelijke QRS-T hoek van > 100° was geassocieerd met een gecorrigeerd relatief risico van 7.3 (95% CI 1.0-53.8%). Een ruimtelijke QRS-T hoek ≤ 100° had een positief voorspellende waarde van 98% (95% CI 95-100%) voor een klinisch beloop zonder terechte therapie.

Deze studie toont aan dat een eenvoudige, van ECG afgeleide parameter, een krachtige voorspeller kan zijn van terechte therapie bij primaire preventie ICD patiënten met een ischemische hartziekte. Bovendien kan een ruimtelijke QRS-T hoek ≤ 100° van waarde zijn bij de

identificatie van patiënten bij wie, hoewel volgens de richtlijn geïndiceerd, een ICD behandeling heroverwogen dient te worden.

In **Hoofdstuk 8** hebben we een update geleverd over de incidentie van lead falen en het voorkomen van perforaties bij de Medtronic's Sprint Fidelis ICD lead en de St. Jude Medical's Riata ICD leads in vergelijking met een groot benchmark cohort. Hiervoor hebben we data van 396 Sprint Fidelis leads (follow-up 3.4±1.5 jaar), 165 8-French (F) Riata leads (follow-up 4.6±2.6 jaar) en 30 7-F Riata leads (follow-up 2.9±1.3 jaar) vergeleken met een benchmark cohort van 1602 transveneus geïmplanteerde ICD leads (follow-up 3.4±2.7 jaar). We hebben gekeken of er verschil zat in de incidentie van perforaties en lead falen tussen de verschillende leads. Tijdens follow-up was de jaarlijkse incidentie van lead falen voor de Sprint Fidelis lead, 7-F Riata lead, 8-F Riata lead en de benchmark cohort respectievelijk 3.54%, 2.28%, 0.78% en 1.14%. In vergelijking met het benchmark cohort, was de aangepaste hazard ratio voor lead falen 3.7 (95%CI 2.4-5.7, $p<0.001$) voor de Sprint Fidelis lead en 4.2 (95%CI 1.0-18.0, $p<0.05$) voor de 7-F Riata lead. Er was maar 1 perforatie geobserveerd (0.05%) in de Riata groep en niet een in de Sprint Fidelis leads.

Deze studie laat zien dat in vergelijking met het benchmark cohort het risico op lead falen significant verhoogd was voor de Sprint Fidelis en de 7-F Riata leads. Perforaties kwamen zelden voor.

Conclusies en toekomstperspectieven

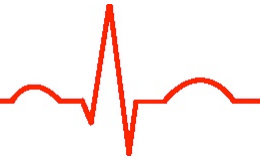
Sinds de introductie van de ICD door dr Mirowski in 1980, hebben verschillende gerandomiseerde studies onbetwist aangetoond dat ICD therapie een gunstig effect heeft op patiënten die risico lopen op het krijgen van een levensbedreigende ventriculaire aritmie. Ondanks de resultaten van grote gerandomiseerde studies is er nog steeds veel onduidelijkheid

over de behandeling van patiënten in de dagelijkse praktijk, buiten de setting van een klinische studie. In dit proefschrift is een aantal aspecten van ICD behandeling in een steeds groter wordende groep patiënten nader onderzocht. Ten eerste zijn tijdens een lange follow-up van verschillende subpopulaties van ICD patiënten (primair vs. secondair), verschillen geëvalueerd in de incidentie van sterfte en het optreden van terechte en onterechte therapie. Zoals verwacht hebben patiënten die ICD hebben ontvangen voor secondaire preventie, in vergelijking tot primaire preventie, een verhoogd risico op het krijgen van terechte therapie. Echter, er werden geen verschillen gevonden in de incidentie van sterfte tussen beide groepen. Verder werd aanvullende informatie gegeven over de noodzaak om een ICD te vervangen bij patiënten die een lange periode vanaf implantatie geen ICD therapie hebben gekregen. Ten tweede zijn in dit proefschrift de huidige parameters geëvalueerd die gebruikt worden voor risicostratificatie en daarbij werd ook gekeken naar de toegevoegde waarde van nieuwe parameters. Een baseline risicoscore voor sterfte werd gemaakt op basis van simpele klinische variabelen. Verder is er gekeken naar de invloed van atrium fibrilleren op het krijgen van ICD therapie en het optreden van sterfte. Om op baseline de risicostratificatie te verbeteren, is van een simpel ECG een nieuwe parameter afgeleid en de toegevoegde waarde hiervan op het voorspellen van ventriculaire aritmieën, geëvalueerd.

Toekomstig wetenschappelijk onderzoek zou zich primair moeten richten op manieren om het risico in te schatten op plotselinge hartdood in de primaire preventie groep. Door het verbeteren van de huidige risico stratificatie technieken kan de effectiviteit van ICD therapie gemaximaliseerd worden. Dit kan gedaan worden door de identificatie van 2 verschillende patiënten populaties: 1) patiënten die in aanmerking komen voor ICD implantatie, maar tijdens follow-up geen baat hebben van de behandeling; en 2) vroegtijdige identificatie van patiënten die overlijden aan plotselinge hartdood maar volgens de huidige richtlijnen niet in aanmerking komen voor ICD implantatie.

Plotselinge hartdood

Ondanks de vooruitgang in het voorkomen en behandelen van cardiovasculaire ziekte blijft plotselinge hartdood in de Westerse wereld een belangrijk maatschappelijk gezondheidsprobleem. In de Verenigde Staten alleen al sterven elk jaar tussen de 180.000 en 460.000 personen aan plotselinge hartdood, waarvan het overgrote deel buiten het ziekenhuis plaatsvindt.[1] Sinds de introductie van de ICD hebben vele studies het gunstige effect aangetoond voor de primaire preventie van plotselinge hartdood. Het overlevingsvoordeel is bestudeerd in een patiënten populatie die volgens de huidige risicoparameters een verhoogd risico hebben op plotselinge hartdood. De huidige parameters die gebruikt worden om het risico op plotselinge hartdood in te schatten zijn: leeftijd, geslacht, roken, hoog cholesterol, lichamelijke activiteit, hypertensie, QRS lengte, nierfunctie en (LVEF).[2] Het is daarom ook logisch dat patiënten met positieve risicofactoren voor het ontwikkelen van aritmieën een significant overlevingsvoordeel laten zien. De internationale richtlijnen, met LVEF als belangrijkste risico stratificatie methode, adviseren ICD therapie aan een breed scala van patiënten met hartziekte. Een groot deel van de populatie met een verhoogd risico op plotselinge hartdood heeft daarom een indicatie voor ICD behandeling. Echter, het grootste deel van de gevallen van plotselinge hartdood treedt op in patiënten die niet op de hoogte zijn van hun hartziekte. Omdat dit een heel groot deel is, zal ICD behandeling relatief weinig invloed hebben op de incidentie van plotselinge hartdood in de algehele bevolking. Zonder nieuwe parameters voor de tijdige identificatie van patiënten met een hoog risico op plotseling hartdood, kan het overlijden van deze patiënten niet worden voorkomen. Om de incidentie van plotselinge hartdood significant te verminderen, zijn dus meer specifieke parameters nodig om deze “onbekende” subgroep in de algehele bevolking tijdig te kunnen identificeren.



Overlijden voor het krijgen van een eerste terechte ICD therapie

Sinds de toevoeging van primaire preventie in de internationale richtlijnen is het gunstige effect aangetoond dat ICD therapie heeft op patiënten die risico lopen op het krijgen van een levensbedreigende ventriculaire aritmie. In 2008 is het aantal ICD's dat geïmplanteerd werd gestegen naar een geschatte hoeveelheid van 275.000.[3] Desondanks gaat het overlevingsvoordeel van de behandeling met een ICD gepaard met ongunstige gebeurtenissen zoals onterechte shocks en pocket gerelateerde infecties.[4] Zoals eerder al beschreven, bestaat er in de algehele bevolking een onbekende subgroep die voordeel zou kunnen hebben van behandeling met een ICD. Deze subgroep moet echter nog geïdentificeerd worden. Aan de andere kant is de incidentie van terechte therapie binnen de huidige populatie die een indicatie heeft voor ICD behandeling, relatief laag. Een deel overlijdt zelfs voor het krijgen van een eerste terechte therapie. Koller et al. analyseerden de incidentie van terechte ICD therapie en sterfte en definieerde "non-benefit" als overlijden voor het krijgen van een eerste terechte therapie. De studie liet tijdens een follow-up van 7 jaar zien dat 11% overleed vóór het krijgen van een eerste terechte therapie.[5] In dit proefschrift is in 900 primaire preventie ICD patiënten met ischemische hartziekte het risico op "non-benefit" in kaart gebracht, waaruit bleek dat een groep te identificeren is die een 5-jaars cumulatieve incidentie van non-benefit (overlijden voor een eerste terechte therapie) heeft van 50%. Hieruit zou geconcludeerd kunnen worden dat deze patiënten, ondanks dat zij een indicatie hebben voor ICD behandeling, geen baat hebben van de behandeling. Desalniettemin lopen deze patiënten nog wel het risico op het krijgen van onterechte shocks of pocket gerelateerde infecties, wat het belang benadrukt om deze onbekende subgroep tijdig te identificeren. Exclusie van deze patiënten voor ICD behandeling zou de indicatie stelling voor het implanteren van deze dure behandelingsmethode verbeteren en daarbij het algehele voordeel dat patiënten hebben, binnen de populatie die baat heeft van behandeling met een ICD, verhogen. Toekomstig wetenschappelijk onderzoek zal zich vooral moeten focussen op verdere evaluatie van de individuele patiënt die op

dit moment geen indicatie heeft voor ICD behandeling, maar wellicht wel baat hiervan zou kunnen hebben. Deze patiënten zouden heroverwogen moeten worden voor ICD implantatie als ze voor implantatie al geïdentificeerd zouden kunnen worden. De in dit proefschrift ontwikkelde risico scores zouden bij de identificatie van deze patiënten kunnen helpen.

Toen dr Mirowski zijn idee introduceerde over het voorkomen van plotselinge hartdood werd hier direct kritiek op geuit. Dertig jaar later is de kritiek verschoven naar de toepasbaarheid en effectiviteit van ICD therapie. Elke dag groeit de patiënten populatie die in aanmerking komt voor ICD behandeling. Daarom zou onderzoek wat in de toekomst nog gaat plaatsvinden zich moeten richten op de individuele persoon. Dit met als doel de patiënten populatie die geen baat heeft van ICD behandeling te verminderen. Daarnaast moeten nieuwe baseline parameters geïdentificeerd worden om risicostratificatie te verbeteren. Ten slotte moeten technologische ontwikkelingen plaatsvinden om de negatieve aspecten van ICD behandeling terug te dringen. De era van de ICD is begonnen, maar 30 jaar later is de ontwikkeling van de ICD nog steeds verre van afgerond.

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List of Publications

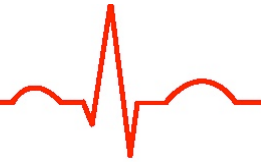
Borleffs CJW, **van Welsenes GH**, van Bommel RJ, van der Velde ET, Bax JJ, van Erven L, van der Bom JG, Rosendaal FR, Schalij MJ. Mortality Risk Score in Primary Prevention Implantable Cardioverter Defibrillator Recipients with Non Ischemic or Ischemic Heart Disease. *Eur Heart J* 2009; 31:712-718

Borleffs CJW, van Rees JB, **van Welsenes GH**, van der Velde ET, van Erven L, Bax JJ, Schalij MJ.Prognostic Importance of Atrial Fibrillation in Implantable Cardioverter Defibrillator Patients. *J am Coll Cardiol* 2009; 55:879-885

Borleffs CJW, Scherptong RWC, Man S-C, **van Welsenes GH**, Bax JJ, van Erven L, Swenne CA, Schalij MJ. Predicting Ventricular Arrhythmias in Patients with Ischemic Heart Disease: Clinical Application of the ECG derived QRS-T Angle. *Circ Arrhythm Electrophysiol* 2009; 2:548-554

Borleffs CJW, Thijssen J, de Bie MK, van Rees JB, **van Welsenes GH**, van Erven L, Bax JJ, Cannegieter SC, Schalij MJ. Recurrent Implantable Cardioverter Defibrillator Replacement Is Associated with an Increasing Risk of Pocket-Related Complications. *Pacing Clin Electrophysiol.* 2010; 33:1013-9

Van Welsenes GH, Borleffs CJW, van Rees JB, Atary JZ, Thijssen J, van der Wall EE, van Erven L, Schalij MJ. Improvements in 25 years of Implantable Cardioverter Defibrillator therapy. *Neth Heart J.* 2011; 19:24-30



Van Welsenes GH, van Rees JB, Borleffs CJW, Cannegieter S, Stijnen T, Bax JJ, van Erven L, Schalij MJ. Long-term follow-up of primary and secondary prevention implantable cardioverter defibrillator patients. *Europace* 2011; 13:389-394

Van Welsenes GH, Borleffs CJW, van Rees JB, Thijssen J, Trines SA, van Erven L, Schalij MJ. Primary prevention ICD recipients: the need for defibrillator back-up after an event-free first battery service-life. *J Cardiov Electrophysiol* 2011; in press.

Borleffs CJW, van Rees JB, **van Welsenes GH**, van der Velde ET, Bax JJ, van Erven L, Putter H, van der Bom JG, Schalij MJ.Clinical Prediction Model for Death prior to Appropriate Therapy in Primary Prevention Implantable Cardioverter Defibrillator Patients with Ischemic Heart Disease: the FADES Risk Score. *Submitted*

Van Welsenes GH, van Rees JB, Borleffs CJW, Thijssen J, van der Velde ET, van der Wall EE, van Erven L, Schalij MJ. Update on Medtronic Sprint Fidelis and St. Jude Medical Riata Implantable Cardioverter Defibrillator Leads Performance. *Submitted.*

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Curriculum Vitae

De auteur van dit proefschrift werd geboren op 4 september 1983 in Utrecht. In 2002 behaalde hij zijn VWO eindexamen aan het STEBO te Utrecht, na in 2000 geslaagd te zijn van zijn HAVO eindexamen aan Het Nieuwe Lyceum te Bilthoven. Na een jaar Domeingerichte Economie gedaan te hebben aan de Universiteit van Utrecht begon hij in 2003 met de studie Geneeskunde aan de Universiteit van Amsterdam. Tijdens zijn studie is hij gestart met onderzoek te doen naar implanteerbare cardioverter defibrillatoren in het Leids Universitair Medisch Centrum. Tijdens zijn co-schappen is hij hiermee door gegaan wat heeft geleid tot een promotieonderzoek onder leiding van Prof. Dr. M.J. Schalij en Dr. C.J.W. Borleffs. De resultaten hiervan staan beschreven in dit proefschrift.

Per 1 oktober 2011 is hij begonnen als AGNIO op de cardiologie afdeling van het Onze Lieve Vrouwe Gasthuis. Hij heeft een relatie met Esther Koele.