Improvements in implantable cardioverter defibrillator patient stratification

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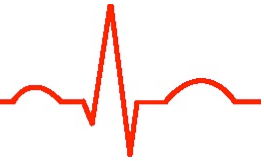
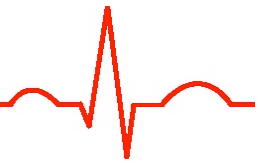


Chapter 1

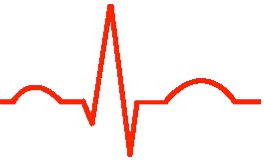
General introduction, aim and outline of the thesis



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.

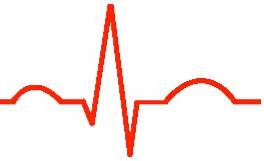
Since the survival rate of an episode of cardiac arrest is at best only 8%, the impact of secondary prevention ICD therapy on population mortality will be low.[10] Therefore focus shifted from secondary prevention to the identification of patients at risk of life-threatening VAs without a prior arrhythmic 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.

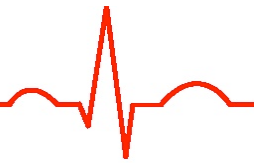
Table 3. Guidelines for implementation of implantable cardioverter defibrillators.

	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).

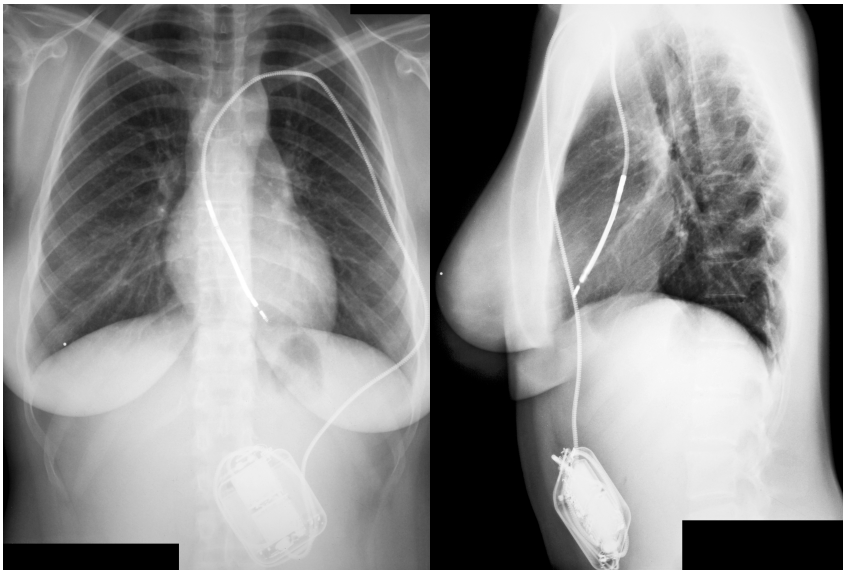


Figure 1: Example of abdominal implanted ICD system in 15-year old female

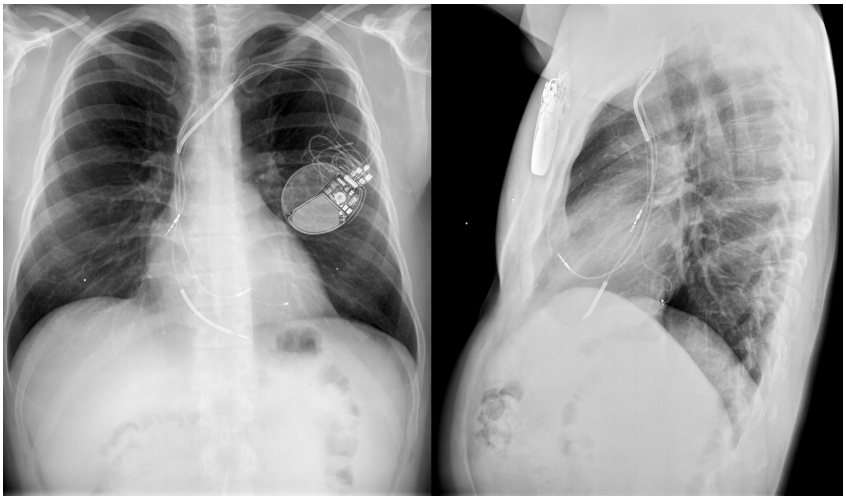


Figure 2: Example of pectoral implanted CRT-D system in 42-year old male

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]

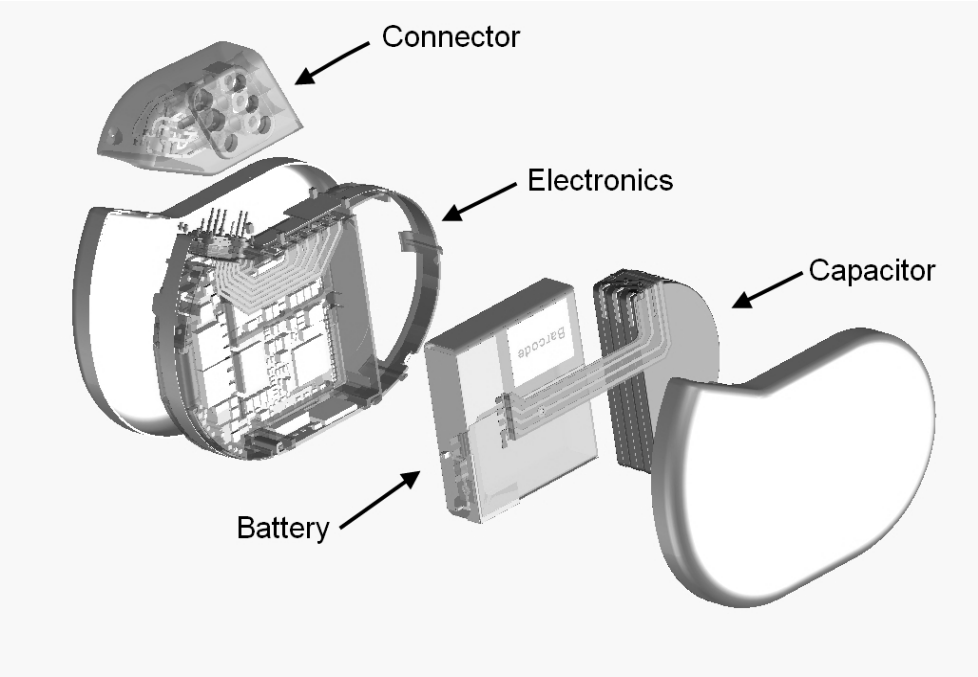
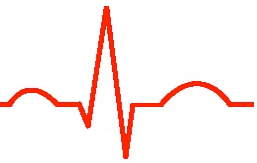


Figure 3: Exploded view of an ICD.

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]

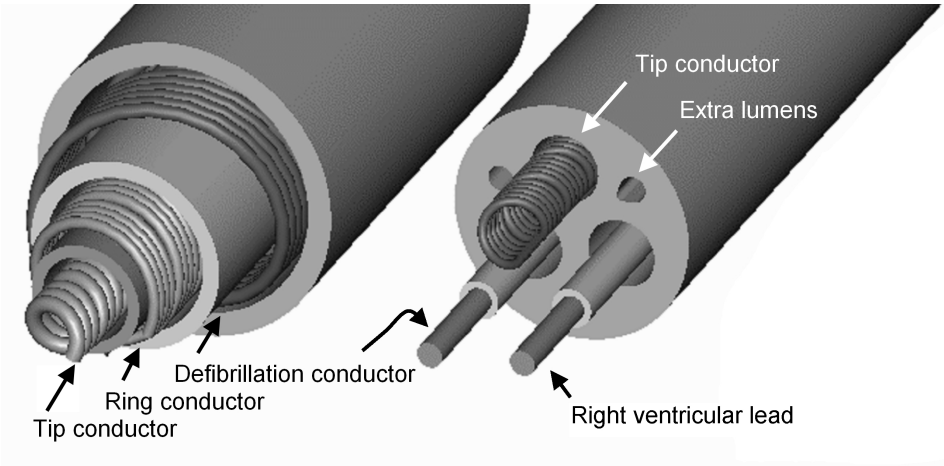


Figure 4: Cross section of coaxial lead construction of a single coil defibrillation lead with true bipolar sensing and pacing (left) and cross section of multilumen lead construction (right).

Longevity

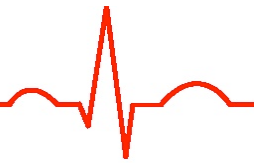
Since the first implantation in 1980, worldwide implantation rates have increased and, therefore, the number of ICD replacements is expected to increase dramatically. Most of the replacements are due to end of service life (battery depletion) and every implantation or replacement brings a substantial 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.



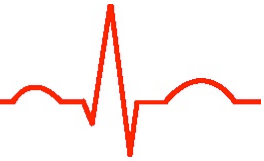
All currently available algorithms have some known limitations like false positive and false negative therapy delivery decisions but by combining some of these algorithms, the amount of inappropriate inhibition or therapy delivery can be further reduced. The complexity and combination of algorithms which 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

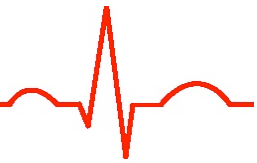
In January 2005, the subcutaneous implantable defibrillator system was tested. A device that can be implanted entirely subcutaneously and positioned based on anatomical markings. The absence of leads in the heart might decrease implantation procedural time and risk for complications.[29] Besides these 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

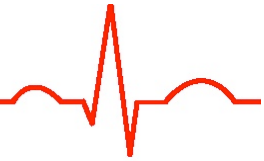


years (QALY) and the cost-effectiveness ranged from $34.000 to $70.200 per gained QALY. The upper limit of the cost-effectiveness was relatively high because of the inclusion of two negative trials (DINAMIT the CABG patch trial).[31] Cowie et al. also analyzed the cost-effectiveness of ICD therapy in 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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