Implantable-cardioverter-defibrillator : clinical advancements in individualized and targeted treatment

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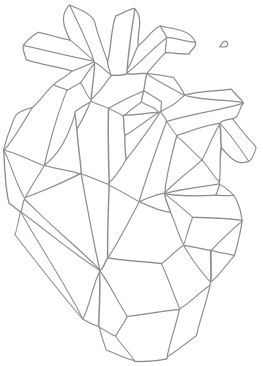
CHAPTER 1



General Introduction, Aim and Outline of the Thesis

Sudden Cardiac Death

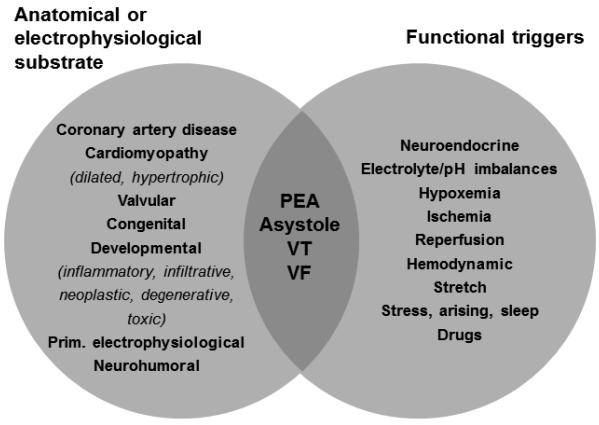
Sudden Cardiac Death (SCD) is defined as death from an unexpected circulatory arrest, occurring within an hour from the onset of symptoms in witnessed circumstances, or within 24 hours from last observed alive and without symptoms, in unwitnessed circumstances.[1] SCD remains a leading cause of death worldwide and accounts for ≥50% of all cardiovascular deaths.[2] Although accurate assessment of SCD is difficult, since the deaths occur in an unpredictable manner, the estimated global burden of SCD is 4 to 5 million deaths per year.[3]

Pathophysiology of sudden cardiac death

Sudden Cardiac Death is the result of cardiac arrhythmias, arising from an anatomical or electrophysiological substrate, which interacts with a functional trigger (Figure 1).[4] The arrhythmia induces a hemodynamic collapse with cessation of sufficient mechanical cardiac activity.[4] The predominant cardiac arrhythmias leading to SCD include ventricular tachycardia or fibrillation (VT/VF) in 75–80% of the deaths; the remaining 15–20% is attributed to bradycardia or pulseless electrical activity.[2 4]

The substrate for SCD depends on the underlying heart disease, ranging from no obvious cardiac abnormalities to advanced cardiomyopathies.[4] A prime condition contributing to SCD is coronary artery disease, which is present in 75–80% of the sudden cardiac deaths. In addition, 10–15% of the deaths suffered from non-ischemic cardiomyopathies or structural heart diseases (including hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia, sarcoidosis and myocarditis). In the remaining 5–10%, structural abnormalities are absent and these deaths are attributed to manifest or latent primary electrical disorders. Triggers that can imbalance cardiac substrates, resulting in the genesis of a ventricular arrhythmias, include: ischemia; hypoxia; drugs; physical or emotional stress; autonomic changes, and electrolyte imbalances.[2 4 5]

Figure 1. Interaction of anatomical or electrophysiological substrates and functional triggers potentially resulting in ventricular arrhythmias and causing sudden cardiac death.



The left circle includes anatomical and electrophysiological substrates, which in interaction with functional triggers in the right circle may result in PEA, asystole, VT or VF, potentially leading to sudden cardiac death. PEA = pulseless electrical activity; VT = ventricular tachycardia, VF = ventricular fibrillation.

The role of anti-arrhythmic drugs in the prevention of sudden cardiac death

Because of the complex interaction between the different cardiac substrates and the triggers leading to SCD it has been challenging to develop targeted prevention strategies.[6] Preventive therapies currently available include anti-arrhythmic drugs and implantation of an implantable cardioverter-defibrillator (ICD).[7]

The efficacy of anti-arrhythmic drug (AAD) therapy in prevention of SCD has been extensively investigated. Class I AAD is a very diverse drug group that establishes suppression of premature ventricular beats by blockage of the fast Na+ channels. However, the Cardiac Arrhythmia Suppression Trial, demonstrated in 1727 post myocardial infarct patients that administration of encainide or flecainide resulted in increased arrhythmic and non-arrhythmic deaths.[8]

Class II AAD (beta-blockers) suppress the sympathetically mediated mechanisms in the heart, thereby decreasing the heart rate. Beta-blockers reduce mortality and arrhythmic deaths as was demonstrated in a meta-analysis, based of 6 large randomized clinical trials, by Teerlink et al.. Beta-blockers were associated with a 38% relative risk reduction of SCD.[9]

Finally, class III AAD comprise of the K+ channel blockers aiming to inhibit or terminate ventricular arrhythmias by increasing the action potential duration and refractory period. The class III AAD distinguishes Sotalol and amiodarone. The Survival with Oral d-Sotalol trial assessed the efficacy of sotalol for the reduction of SCD in 3121 post-myocardial infarction or heart failure patients.[10] The trial was prematurely terminated and demonstrated in increase in overall and arrhythmic mortality. Amiodarone has a complex mechanism of action since blockage of both the slow and the fast K+ channel is established.[11] There have been several studies evaluating the efficacy of amiodarone in the prevention of SCD both in post myocardial infarction patients and in patients with heart failure. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) is one of the pivotal trials that randomized 2521 patient with either ischaemic or non-ischaemic heart disease to ICD therapy, amiodarone or placebo.[12] The occurrence of all-cause mortality in the amiodarone arm was comparable with the placebo arm. A meta-analysis by Piccini et al., which included 15 randomized trials, demonstrated that although SCD was reduced by 26% in the amiodarone arm, all-cause mortality was comparable with the placebo arm.[11] Furthermore, amiodarone therapy was associated with a significant increased risk of thyroid and pulmonary toxicity.[11]

Thus far, the role of AAD therapy in prevention of SCD has been disappointing. Therefore, the current international guidelines state that 'the available antiarrhythmic drugs, other than beta-blockers, should not be used as primary therapy for the prevention of SCD'.[7]

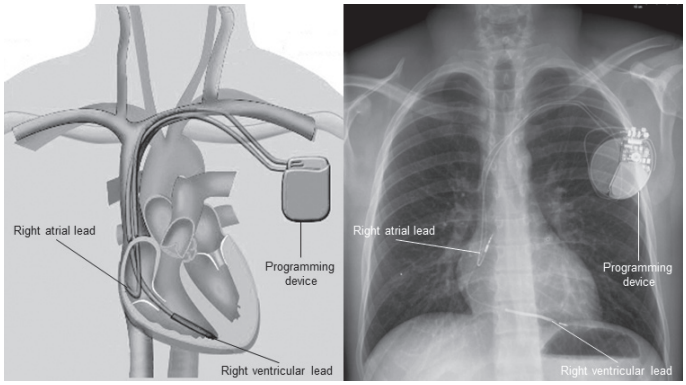
Implantable Cardioverter-Defibrillator

The lack of efficacy of AAD therapy led to extensive investigation and ultimately widespread implementation of implantable cardioverter-defibrillator (ICD) therapy.[6 7]

An implantable cardioverter-defibrillator is an implantable device comprising of a programming device and leads.[13] Via the leads, positioned intracardially, the programming device continuously monitors and registers the heart rhythm and heart rate (Figure 2). When potential life-threatening arrhythmias occur, the device will attempt to terminate these ventricular arrhythmias either with painless antitachycardia pacing (ATP) or, the delivery of 1 or more electrical shocks.

In 1967 Dr Michel Mirowski conceived the concept of ICD therapy driven by the sudden, cardiac death of his mentor prof. Heller.[13] Extensive investigation led to the development of the first ICD model which was first tested in animals in 1976, and successfully implanted in the first human

Figure 2. Position of the implantable cardioverter-defibrillator with programming device and leads in the thorax



The left figure illustrates the position of the programming device and leads of an implantable cardioverter-defibrillator in the thorax; the right image is an X-thorax of a patient with an implantable cardioverter defibrillator in situ.

in 1980.[14] However, these first ICDs were large, plain devices with epicardial patches. Further developments resulted in the smaller devices with endocardial leads and complex programming options, implanted nowadays.

ICD for secondary prevention of sudden cardiac death

Survivors of SCD are at increased risk of recurrent sustained VT, the incidence of VT or SCD reaches up to 33% in 3 years.[15] ICD treatment is beneficial in the management of recurrent VT and prevention of SCD (secondary prevention).[16]

In 1995, de Wever et al. published the results of the first randomized trial in which 60 cardiac arrest survivors were randomized to receive ICD or AAD therapy.[17] After a median follow-up of 24 months, ICD recipients were 73% less likely to experience death, recurrent cardiac arrest or cardiac transplantation.[17] This study was followed by 3 pivotal large-scale randomized controlled trials, demonstrated in table 1, which together form the basis of the current clinical guidelines.

The Anti-arrhythmic versus Implantable Defibrillator (AVID) trial was the first large trial to assess the benefit of ICD treatment in patients either resuscitated from VF or with symptomatic VT.[18] A total of 1016 patients were randomly assigned to amiodarone or ICD treatment, after 18 months follow-up ICD treatment was associated with 27% relative reduction of all-cause mortality.

The AVID trial was followed by the Cardiac Arrest Study Hamburg and the Canadian Implantable Defibrillator Study (CIDS), both studies randomized a smaller amount of patients, these were however, followed over a longer period of time.[19 20] In addition to patients resuscitated from VF or with symptomatic VT, the CIDS investigators also included patients with unmonitored syncope and inducible VT. Individually, both trials did not observe a statistical significant difference between AAD or ICD therapy, although all-cause mortality tended to be 20-23% lower in ICD recipients. However, a meta-analysis by Connolly et al. including all 3 pivotal trials demonstrated that secondary prevention ICD therapy was associated with a 28% reduction of all-cause mortality.[16]

Table 1. Clinical trials on Secondary and Primary prevention ICD therapy

	Follow-up, months	Patients, N	Inclusion criteria	All-cause mortality Control	ICD	Relative risk reduction with ICD	
Secondary prevention							
AVID[18]	18	1016	Resuscitated from VF, sustained VT with syncope or sustained VT with LVEF ≤40%	24%	16%	27%	p=0.02
CASH[20]	57	288	Resuscitated from VF or VT	44%	36%	23%	p=0.08
CIDS[19]	36	659	VF, resuscitated from VF or VT, symptomatic VT with LVEF ≤35%, unmonitored syncope with inducible VT	10%/yr	8%/yr	20%	p=0.14
Primary prevention in ischaemic cardiomyopathy							
MADIT[23]	27	196	NYHA class I-III, prior MI with LVEF ≤35%, nsVT and inducible VT	39%	16%	54%	p=0.01
CABG-Patch[26]	32	900	Undergoing CABG with LVEF ≤35% and abnormal signal averaged ECG	21%	23%	-7%	p=0.64
MUSTT[24]	39	704	CAD with LVEF ≤40%, nsVT and inducible VT	55%	24%	58%	p<0.001
MADIT-II[25]	20	1232	prior MI with LVEF ≤30%	20%	14%	31%	p=0.02
DINAMIT[27]	30	674	6-40 days post MI with LVEF ≤35% and impaired cardiac autonomic function	17%	19%	-8%	p=0.66
Primary prevention in non-ischaemic cardiomyopathy							
DEFINITE[31]	29	458	NICMP in NYHA I-III with LVEF ≤35% and PVC or nsVT	18%	12%	35%	p=0.08
Primary prevention in ischaemic and non-ischaemic cardiomyopathy							
SCD-HeFT[32]	46	2521	NYHA II-III with LVEF ≤35%	29%	22%	23%	p<0.001

AVID = Antiarrhythmic versus Implantable Defibrillator; CABG-Patch = Coronary Artery Bypass Graft Patch Trial; CAD = coronary artery disease; CASH = Cardiac Arrest Study Hamburg; CIDS = Canadian Implantable Defibrillator Study; DEFINITE = Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT = Defibrillator in Acute Myocardial Infarction Trial; ECG = electrocardiogram; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MADIT = Multicentre Automatic Defibrillator Implantation Trial; MADIT-II = Multicentre Automatic Defibrillator Implantation Trial; MI = myocardial infarction; MUSTT = Multicentre Unsustained Tachycardia Trial; nsVT = non-sustained ventricular tachycardia; NICMP = non-ischaemic cardiomyopathy; NYHA = New York Heart Association functional class; PVC = premature ventricular beat; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial; VF = ventricular fibrillation; VT = ventricular tachycardia.

ICD for primary prevention of sudden cardiac death

Prophylactic ICD implantation is recommended in selected patients at high risk of sudden cardiac death.[7] Numerous studies have demonstrated that systolic heart failure is associated with an increased risk of SCD.[21] Heart failure patients with prior myocardial infarction and non-sustained ventricular arrhythmias have a 30% increased risk of mortality.[22] This instigated the evaluation of the efficacy of primary prevention ICD treatment in patients with ischemic cardiomyopathy.

ICD in ischemic cardiomyopathy

The Multicentre Automatic Defibrillator Implantation Trial (MADIT), was the first large scale trial assessing prophylactic ICD implantation in post-myocardial infarction patients with left ventricular ejection fraction (LVEF) ≤35% and inducible VTs (N=196).[23] The investigators demonstrated that ICD therapy, in this population, had led to an astonishing reduction of all-cause mortality of 54% after 27 months. Similarly, the Multicenter Unsustained Tachycardia Trial demonstrated a 58% reduction of all-cause mortality by ICD therapy.[24] This trial included 704 patients with coronary artery disease, LVEF≤35% and inducible VTs (Table 1).

These trials were followed by the second MADIT trial, as in the first MADIT study patients were included with prior myocardial infarction and reduced systolic heart function (LVEF ≤30%), however inducible VT was not required.[25] After 20 months follow-up of 1232 patients, the study showed that ICD therapy was associated with a 31% reduction of all-cause mortality.

Additional trials demonstrated that prophylactic ICD treatment is not deemed beneficial when the ICD is implanted within the first month after myocardial infarction nor in patients undergoing coronary artery bypass graft surgery.[26 27]

ICD in non-ischaemic cardiomyopathy

Increased risk of SCD in not limited to patients suffering from ischemic cardiomyopathy. In patients with non-ischaemic cardiomyopathy SCD accounts for approximately 28% of the all deaths.28 Unexpectedly, the first small ICD studies in patients with non-ischaemic cardiomyopathy failed to show any survival benefit.[29 30] Latter, the Defibrillators in Non-ischaemic Cardiomyopathy Treatment Evaluation assessed ICD therapy in 458 patients with non-ischaemic cardiomyopathy with LVEF ≤35% and non-sustained VTs or premature ventricular contractions. After 29 months, all-cause mortality was 12% in the ICD arm compared to 18% in the control arm, however statistical significance was not reached.[31] The pivotal study assessing the benefit of ICD in non-ischemic heart failure patients was the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT).[32] A total of 2521 patients with LVEF ≤35% and NYHA II-III were included where of 48% suffered from non-ischaemic heart disease. Overall, ICD decreased the risk of death by 23%. ICD benefit was comparable in patients with ischemic and non-ischaemic heart failure. Mortality rates in the subpopulation with non-ischaemic heart disease were 21% in the ICD recipients and 29% in patients on placebo, however on their own these differences were not significantly different (Table 1).

Subgroups underexposed in ICD trials

Evidence of both the secondary and primary prevention ICD trials, has resulted in immediate and widespread deployment of ICD therapy.[7 33] The astonishing results of the primary prevention ICD trials have led to a generalized LVEF-based recommendation for prophylactic ICD therapy. However, in many subgroups the survival benefit of prophylactic ICD treatment has not been consistently demonstrated. In the major clinical trials, women, non-Caucasians, elderly, or patients suffering from comorbidities were underrepresented, and subgroup analyses, thus far, have shown conflicting results.[34]

Women

Sudden Cardiac Death occurs approximately 50% less frequent in women as in men.[34] Although the pathophysiology of SCD is mostly similar in men and women, the arrhythmogenic substrate differs. An autopsy study demonstrated that only 37% of females deceased to SCD had coronary artery disease as compared to 56% in men.[35] Because of this higher rate of non-ischemic cardiomyopathy, in case of cardiac arrest, women are more likely to present with asystole or pulseless electrical activity, both rhythms in which an ICD is ineffective.[36] In addition, women do have a 1.5 times increased risk at device-related complications.[37] Currently, ICDs are routinely implanted in women, as they comprise 16%-27% of all ICD recipients in clinical practice.[37] Nonetheless, evidence for the efficacy of ICD treatment in women is limited and results of subgroups analyses have been conflicting.

Non-Caucasians

Ethnicities as African Americans, Hispanic, Asian and others were underrepresented in the landmark trials for ICD treatment. Differences in genetic profile and socioeconomic circumstances may affect the survival benefit of ICD treatment.[7] The SCD-HeFT trial included the largest amount of non-Caucasian patients.[38] Among the 2521 patients randomized in the trial, 589 (23%) were non-Caucasian, these included 425 (72%) African Americans, 111 (19%) Latin Americans, and 53 (9%) other ethnic minorities. Survival with ICD therapy was found not dependent on race. No evidence was found that ICD therapy was less effective in African Americans as compared to Caucasians. Numbers of other ethnic minorities were small and additional studies lack.

Elderly

Whether the initial survival benefit associated with ICD treatment persists in patients with a shorter life expectancy, namely the elderly, is doubtful. Although the risk of sudden cardiac death increases with age, this increase may be inferior to the higher risk of non-sudden cardiac death.[39] Yet, the number of elderly patients qualifying for ICD treatment is rapidly increasing due to the aging of the population. Nowadays, 42% of the ICD recipients are aged ≥70 years old.[40]

In a meta-analysis of the pivotal primary prevention trials, performed by Kong et al. 597 elderly patients were included aged ≥75 years.[41] Although the survival benefit was smaller, when compared to their younger peers, even in the elderly patients ICD treatments was associated with a 27% reduction of all-cause mortality (p=0.03). Despite these beneficial outcomes, patients at a higher age (>79 years) are more frequently excluded for ICD treatment.[42]

Patients suffering from comorbidities

Landmark randomized trials often constitute of highly selected individuals and as a consequence, patients receiving treatment in routine clinical practice have a higher burden of comorbidities. In a large community-based study, Lee et al. demonstrated that 29% of ICD recipients suffer from ≥1 cardiac and non-cardiac comorbidities.[39] The most common non-cardiac comorbidities were diabetes (20%), chronic obstructive pulmonary disease (13%), renal insufficiency (8%) and peripheral vascular disease (8%). Individually these comorbidities all increase the risk of all-cause mortality by approximately 150-230%. These findings suggest that ICD survival benefit is associated with non-cardiac comorbidities. Although randomized studies lack, these data suggest that the presence of non-cardiac comorbidities should be taken in consideration when evaluating appropriate ICD allocation.

Drawbacks of contemporary ICD treatment

ICD treatment still has some important drawbacks whereupon the contemporary ICD research is focusing. Firstly, the device implantation is associated with a number of complications such as pneumothorax, pocket hematoma or lead dislodgement.[43] Other complications including inappropriate shocks, device infection or lead-related complications occur during follow-up.[44]
Secondly, the population currently eligible for ICD implantation according to international guidelines comprises too many patients not benefitting from ICD therapy.[45] In addition, provision of ICD treatment to all patients eligible, might strain financial resources and the pool of trained personnel financial.[46] Therefore selection criteria for ICD treatment need to be refined.

Implantation-related device complications

ICD leads are transvenously positioned in the right atrium and ventricle, venous access is obtained via the cephalic, subclavian or axillary vein. In approximately 1% of ICD recipients, the gain of venous access provokes a pneumothorax.[43] Blind puncture via the subclavian vein approach raises the highest risk of pneumothorax.[47]
During the implantation procedure the generator device in positioned subcutaneously for which a device pocket needs to be created often by blunt dissection. Pocket hematomas, requiring re-intervention occur in approximately 2% of all ICD recipients.[43] Although pocket hematomas on their own are not life-threatening, the required early re-interventions are associated with a 15 times increased risk of device infection.[48]
On average, acute lead dislodgement occurs in 0.6% of the single chamber ICDs and in 1% of dual chamber ICDs.[49]

Inappropriate shock

Inappropriate device therapies are the most common adverse event of defibrillator treatment which may result in pro-arrhythmic risk, heart failure progression, reduction of battery-life and psychological distress.[50] Misdiagnosis of supraventricular arrhythmias is the leading cause of inappropriate ICD discharges.[50] Initial clinical trials have reported an incidence of inappropriate shocks of 13-22% after a follow-up of 2-2.5 years.[31 51] Through implementation of ATP, adjustments in zone cut-offs and SVT discrimination algorithms the occurrence of inappropriate defibrillator shocks can be reduced.[52 53] Recently, Moss et al. reported a method to further reduce inappropriate shock in primary prevention patients by delayed therapy (first ICD shock delayed by 60s) or high

rate therapy (ICD shock is initial therapy in ventricular arrhythmias > 200 b.p.m.), which resulted in a 50% reduction of inappropriate shocks, without increased occurrence of syncope.[54] This emphasizes the importance of adequate device programming.

Device infection

Large registries have described an annual incidence of device-related infections of 1.5–2.4%, which is strongly associated with generator replacement.[55 56] The burden of device infection has risen disproportionally, with the increased rate of ICD implantations.[33] Several mechanisms may explain the increased incidence of device infection; firstly, as a consequence of the increased rate of ICD implantations also the rate of ICD replacements, highly associated with device infection, has increased.[57] Secondly, the populations currently receiving ICDs might be more prone to ICD infections since risk factors like renal failure and diabetes are more common.[58] Thirdly, implantation procedures have become more complex and time-consuming with introduction of CRT, the duration of the implantation procedure is a known risk factor of device infection.[59]

ICD recipients that suffer from device infection have a 2 times increased risk of mortality.[56] To adequately treat device infections, device and lead extraction is of utmost importance. In addition, device infections can be prevented by reducing the number of device replacements. In the last decades battery longevity has already been extended from 5 to more than 10-12 years for ICDs and CRT-Ds.[60 61] This will hopefully lead to a lower incidence of device infections and in addition an improvement of cost-effectiveness of ICD treatment.

Lead-related complications

As the knowledge of long-term ICD treatment expands, the reliability of transvenous ICD leads have become a prominent issue.[62] Causes of lead failure can be lead-related (technical factors as insulation defect), patient-related (clinical factors as excessive activity of the upper body) or implantation-related (procedural factors as kinking of the lead).[63] Especially on the long term lead failure rates are disturbing, Kleeman et al. reported a cumulative lead survival was only 60% after 8 years.[62] Leads aged ≥10 years had an annual failure rate of 20%.

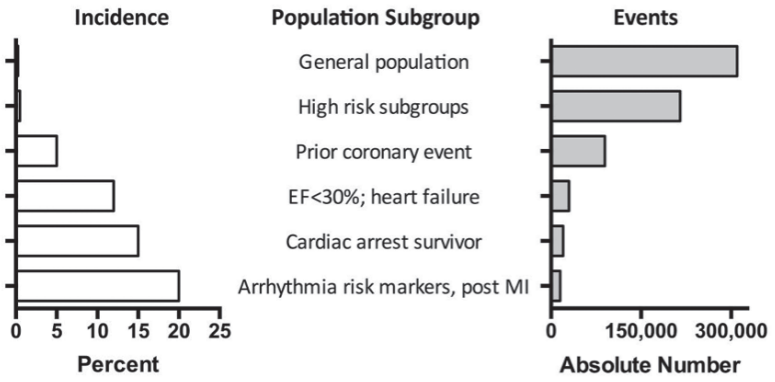
As a consequence of lead failure and the increasing rate of device infections, the need for safe and successful transvenous lead extraction increased.[64] Currently, a vast number of extraction tools are available in order to allow successful extraction ICD leads and numerous studies have been published describing and comparing the different extraction tools, methods and approaches, although clear directives lack.[65]

Risk stratification

The landmark clinical trials have demonstrated that ICD treatment significantly reduces mortality in patients with ischemic or non-ischemic heart disease and LVEF <35%. However, figure 3 illustrates that the majority of the sudden cardiac death events occurs in the general population, thus without ischemic or non-ischemic heart disease and LVEF <35%. Furthermore, from the patients eligible for primary prevention ICD implantation according to the current guidelines, 63% did not require ICD interventions for potentially life-threatening ventricular arrhythmias the first 5 years after device implantation.[45]

To date, no validated criteria exist for exclusion or selection of patients with reduced LVEF for prophylactic ICD implantation. ECG characteristics, non-sustained ventricular tachycardias,

Figure 3. Incidence and total population burden of sudden cardiac death.



Event rates are compared with total numbers of events for the general population and for specific subgroups with coronary artery disease. Note the inverse relationship between incidence and absolute numbers of events. EF = Ejection fraction; MI – myocardial infarction. Adapted from Myerburg et al, Circulation 2012

advanced NYHA functional class, cardiac MRI, and inducibility with electrophysiological testing have all been associated with ICD survival benefit, but have limited value in patients selection for prophylactic ICD implantation.[66]

In a substudy of the MADIT-II trial, Barsheshet et al. demonstrated that ICD benefit is most pronounced in the low, and moderate risk population, whereas high risk patients (3 risk factors or severe renal disease) did not experience any ICD survival benefit. The risk factors included Age >70 years, NYHA functional class > II, Atrial fibrillation, QRS duration > 120ms and, Blood Urea Nitrogen > 20mg/dl. These results imply that the less sick patients benefit most from ICD treatment and the sick patients might not benefit from ICD implantation at all. This suggest that their risk of non-SCD is disproportionally higher than their risk of SCD, resulting in a higher early mortality. The less sick patients however, have longer life expectancy, and therefore are exposed to the risk of SCD for a longer period of time. Thus, the risk of sudden cardiac death is not equivalent to benefit of ICD treatment. On the one hand, ICD survival benefit depends on the risk of sudden cardiac death, but on the other hand it depends on the risk of non-sudden cardiac death, which should be taken into account in ICD allocation.

ICD implantation in all patients currently eligible for prophylactic ICD treatment might strain financial recourses and the pool of trained personnel.[46] Hence, better methods are required to identify patients who will actually benefit from ICD treatment.

Cardiac Resynchronization Therapy

Cardiac Resynchronization Therapy (CRT) is an additional treatment for which more than 30% of contemporary ICD recipients are eligible.[67] CRT devices were designed to improve LV performance by restoring atrio-ventricular, interventricular and intraventricular synchronicity.[68] Numerous major randomized studies have demonstrated that CRT is effective in relieving symptoms of heart failure, in decreasing the number of heart failure related hospitalizations and in reducing mortality.[69-73] To date, the Multicentre Automatic Defibrillator Implantation Trial with CRT (MADIT-CRT) was the largest trial that assessed the beneficial effect of CRT in addition to ICD treatment.[69] A total

of 1820 patients with LVEF≤30%, functioning in NYHA I or II and prolonged QRS≥130ms were randomized to receive ICD or CRT-D treatment. The MADIT-CRT investigators demonstrated that CRT combined with ICD was associated with a 34% reduction of heart failure hospitalizations and all-cause mortality. In addition, LVEF was significantly increased in patients receiving CRT.
The current international guidelines recommend CRT treatment in patients with advanced systolic heart failure and prolonged QRS duration >120ms.[74] In clinical practice, there is however a wide variability in the extent of response to CRT among patients. Of all CRT recipients, 9-47% experience major improvements with extensive left ventricular reverse remodelling resulting in a significant improvement of LV function (super-responders), whereas approximately 30% show unchanged or even increasing cardiac volumes and deteriorating LV function (non-responders and negative responders)[75-77]
Patient characteristics predictive for pronounced response are a shorter period of symptomatic heart failure, non-ischemic cardiomyopathy, prolonged QRS duration, left bundle branch block, or echocardiographic mechanical dyssynchrony.[75 76]

Aim of thesis

Although the beneficial effect of ICD treatment has evidently been demonstrated in selected patients, the population included in the landmark randomized trials does not reflect the population that received ICD treatment in contemporary routine clinical practice. Therefore the aim of the current thesis is to evaluate the long-term follow-up in routine clinical practice and improve the strategies for risk stratification, for more targeted ICD allocation.
Part I describes the clinical outcomes of the population currently indicated for ICD treatment. The clinical characteristics and clinical outcome of the general population that received an ICD for primary or secondary prevention were evaluated after extended follow-up. Additionally, clinical characteristics and outcome of populations underrepresented in the trials are described.
Part II focuses on risk stratification of ICD and CRT-D recipients. Pre-existing prediction models developed to anticipate individual ICD survival benefit are compared and adapted to the 'real world' ICD population.
Part III highlights the programming of ICD devices and the association of ICD programming with clinical outcome. Furthermore, methods for adequate transvenous lead extraction are described.

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