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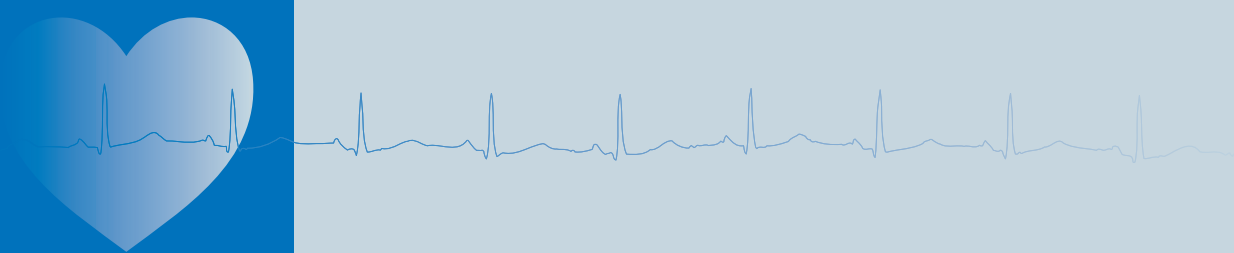
Chapter 1

General Introduction, Aim and Outline of the Thesis

Based on:
Improvements in 25 Years of Implantable Cardioverter Defibrillator Therapy



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Neth Heart J 2011;19:24-30

INTRODUCTION

Sudden cardiac death

Sudden cardiac death (SCD) is defined as an unexpected circulatory arrest, mostly due to a cardiac arrhythmia, resulting into death.[1-3] Especially patients with coronary heart disease are at risk for SCD, whereof approximately 50% dies unexpectedly shortly after symptoms. Previous studies demonstrated that the incidence of SCD is strongly correlated with the prevalence of coronary heart disease.[4, 5] Consequently, the high number of patients with coronary heart disease in the United States of America, results in massive numbers of patients who die of SCD each year, with estimates ranging from 300 000 to 350 000.[4, 6-9] As numbers are comparable in Europe, more then 700 000 patients die yearly of SCD in the Western world.[5] Of concern is that the majority of patient who died following sudden cardiac arrest, were unidentified to be affected by ischemic heart disease.[2, 3, 8, 10] Although prodromal symptoms are often non-specific, they include chest pain (ischemia), palpitations (tachyarrhythmia), or dyspnea (congestive heart failure) and if present can be related to SCD. Major risk factors, increasing the risk of SCD include (risk factors for) coronary heart disease, prior coronary events, prior ventricular arrhythmia, poor left ventricular systolic function and symptoms of advanced heart failure.[2] Unfortunately, an inverse relationship exists between the risk and total number of SCD in sub-groups of patients at increased risk (Figure 1).[10]

It is reported that 75-80% of SCD cases originate from ventricular fibrillation (VF) whereas in the remaining a bradyarrhythmia, including asystole and complete atrioventricular block is recorded.[11] However, one should note that both causes of sudden death can intertwine: in other words, although the initial rhythm disorder can be VF, after some time VF extinguishes and asystole becomes the presenting rhythm when a first ECG is documented. Conversely,

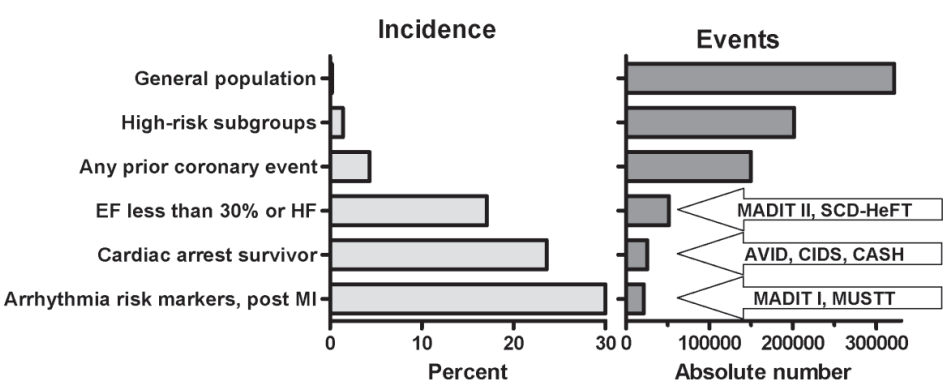

Figure 1. Absolute numbers of events rates of sudden cardiac death in the general population and in specific subpopulations over 1 year. Clinical trials that included specific subpopulations of patients are shown in the right side of the Figure.
AVID = Antiarrhythmics Versus Implantable Defibrillator; CASH = Cardiac Arrest Study Hamburg; CIDS = Canadian Implantable Defibrillator Study; EF = ejection fraction; HF = heart failure; MADIT = Multicenter Automatic Implantation Trial; MI = myocardial infarction; MUSTT = Multicenter UnSustained Tachycardia Trial; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial.

bradycardia or atrioventricular conduction delay can trigger VF, which makes a correct estimation of incidences difficult.[6] Further research on the initial rhythm, causing SCD, conducted in 157 patients experiencing SCD during ambulatory Holter monitoring demonstrated VF in 62.4% of patients, a bradyarrhythmia in 16.5% of patients, an episode of *torsades de pointes* in 12.7% of patients, and a ventricular tachycardia (VT) in 8.3% of patients.[12]

Implantable cardioverter defibrillators

Since 40% of all cases of SCD are not witnessed, immediate and adequate treatment is difficult, resulting in high mortality rates.[13] However, if witnessed, cardiac defibrillation can be life-saving. This experience dates back to 1947 when Dr. Claude Beck was correcting a pectus excavatum in a 14-year old boy. When during surgery VF occurred, Dr Beck initiated direct cardiac massage through the opened chest and, after more than a half hour of cardiac massage, used an animal cardiac defibrillator which he had developed while working in an animal laboratory many years earlier. The electrical defibrillation was successful and the rhythm restored to sinus rhythm.[14]

Although this success immediately led to the general acceptance of electrical defibrillation for life-threatening arrhythmias, the development of an implantable cardioverter defibrillator (ICD) took some time. It was Dr. Michel Mirowski, whose friend died due to several bouts of a ventricular tachycardia in 1967, influencing him to pursue the implantable defibrillator. In 1980, he and his team implanted the first implantable cardioverter defibrillator (ICD) in patients and successfully defibrillated VF.[15]

Secondary prevention

The invention of the ICD raised the question if patients would benefit from ICD therapy and how to properly select them. Based on epidemiological studies, patients with life-threatening ventricular arrhythmias were found to have a two-year recurrence rate of 30-50%.[16, 17] Accordingly, this population was the first in which the effect of ICD treatment was evaluated and eligibility for ICD treatment was based on the survival of at least one-life-threatening ventricular arrhythmia such as VF or sustained VT (secondary prevention).[15, 18-24] Wever et al. ,working in Utrecht the Netherlands, performed the first study in which fifty patients who survived a cardiac arrest were randomized to be treated with antiarrhythmic drugs or an ICD.[24] After a median follow-up of 24 months, it was demonstrated that the ICD treated group had lower rates of major outcome events such as death, recurrent cardiac arrest or cardiac transplantation, underwent fewer invasive procedures, and were hospitalized less frequently.[24] Thereafter, the effectiveness of ICD therapy was further assessed in three larger trials: the Antiarrhytmics Versus Implantable Defibrillator (AVID), the Canadian Implantable Defibrillator Study (CIDS), and the Cardiac Arrest Study Hamburg (CASH).[18-20] Patients included in these trials survived an episode of cardiac arrest or had a documented episode of sustained VT and were randomized to optimal pharmacological antiarrhythmic therapy or ICD treatment (Table 1). Although only AVID demonstrated a significant reduction in mortality, a meta-analysis of these three trials, demonstrated a significant 28% reduction in all-cause mortality in favor of ICD treatment and, with these results, the survival benefit of the ICD was proven and ICD therapy for secondary prevention was generally accepted.[25]

Table 1. Major secondary prevention implantable cardioverter defibrillator (ICD) Trials.

	AVID[18]	CIDS[19]	CASH[20]
Sample size	1016	659	288
Design	ICD vs. antiarrhythmic drugs	ICD vs. amiodarone	ICD vs. amiodarone vs. metoprolol
Patients	Resuscitated VF or postcardioversion from sustained VT	Resuscitated VF or VT with unmonitored syncope	Survivors of cardiac arrest secondary to documented ventricular arrhythmias
Follow-up, months	18	36	57
Risk reduction with ICD	28% (p = 0.02)	20% (p = 0.14)	23% (p = 0.08)

ICD = implantable cardioverter defibrillator; VF = ventricular fibrillation; VT = ventricular tachycardia.

Primary prevention

Although secondary prevention ICD therapy was proven to be beneficial, the most important limitation is that only 6% of patients survive an episode of cardiac arrest and therewith becomes eligible for ICD therapy.[13] Accordingly, focus shifted to the identification of patients at high risk for life-threatening ventricular arrhythmias (primary prevention). Previous trials demonstrated that a left ventricular ejection fraction (LVEF) below 40% and frequent (runs of) premature ventricular beats were risk factors for SCD.[26, 27]

Accordingly, patients included in the first small primary prevention trials were selected based on a reduced LVEF due to prior myocardial infarction and the presence of non sustained VT on 24-hour Holter monitoring in patients or inducible non-suppressible (by pharmacological treatment) sustained VT/VF on electrophysiological study.[28, 29] Later on, multiple large randomized control trials were performed to assess if primary prevention ICD therapy was beneficial in selected populations (Table 2).[30-37] [30-32, 34-37] One of these was the Multicenter Automatic Defibrillator Implantation Trial (MADIT) which enrolled patients with a prior myocardial infarction, LVEF less than 35%, documented non sustained VT, and inducible/non-suppressible VT/VF during electrophysiological study.[35] Subsequently, patients were randomized to either ICD treatment or optimal medical therapy. During a follow-up of 27 months and with the inclusion of only 196 patients, the study demonstrated a 54% mortality reduction in the ICD group. Important limitations of this trial were the relatively small cohort of patients and the significantly higher use of beta blockers in the ICD treatment group when compared with the optimal medical therapy group. Additional subgroup analysis of survival benefit demonstrated that the highest benefit was reached in patients with a LVEF less than 26%.[38]

Accordingly, this observation led to a simplified design, the MADIT II trial, randomizing patients post infarction with a LVEF less than 30% to either an ICD or no ICD without additional electrophysiological testing. The study required premature closure since the efficacy boundary had been reached. During an average follow-up of 20 months, a mortality reduction of 28% was observed in patients treated with an ICD.[36]

With publication of the results of the MADIT trials, it became clear that patients with a poor left ventricular systolic function are at risk for sudden cardiac death due to a

Table 2. Major primary prevention implantable cardioverter defibrillator (ICD) trials.

	MADIT[35]	MUSTT[32]	MADIT II[36]
Sample size	196	704	1232
Design	ICD vs AAD	EPS-guided: ICD vs AAD vs no AAD	ICD vs AAD
Patients	Prior MI, EF ≤0.35, nsVT, EPS+	Prior MI, EF ≤0.40, EPS+	Prior MI, EF ≤0.30
Follow-up, months	27	39	20
Risk reduction with ICD vs AAD	54% (p = 0.01)	58% (p < 0.001)	31% (p = 0.02)

AAD = antiarrhythmic drugs; CRT-D = cardiac resynchronization therapy-defibrillator; EF = ejection fraction; EPS = electrophysiological study; HR = heart rate; ICD = implantable cardioverter defibrillator; I = ischemic; MI = myocardial infarction; NICM = non-ischemic cardiomyopathy; nsVT = non sustained ventricular tachycardia.

ventricular arrhythmia, which risk is high enough to warrant ICD treatment. And with this proven reduction in mortality, additional trials were designed in populations at high risk for life-threatening ventricular arrhythmias. Earlier studies and daily clinical practice had shown that patients are at very high risk for hemodynamically compromising ventricular arrhythmias in the period following acute myocardial infarction.[10, 28, 39-41] Therefore, Hohnloser and coworkers started the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT), including patients with a reduced left ventricular ejection fraction 6 to 40 days after acute myocardial infarction and randomizing between ICD treatment and optimal medical therapy alone.[33] During a mean follow-up period of 30 months, no over-all mortality difference was observed between the two treatment groups. Further classification by cause of death showed that ICD treated patients were 58% less likely to experience arrhythmic death but had a 75% higher risk for non-arrhythmic death. These results imply that ICD treatment following recent myocardial infarction does not improve patient outcome, but merely changes the mode of death in this vulnerable population. More recently, a similar trial (Immediate Risk Stratification Improves Survival (IRIS)) was conducted randomizing 898 patients 5 to 31 days after myocardial infarction.[37] Additional inclusion criteria were a left ventricular ejection fraction ≤40% and a heart rate of 90 or more beats per minute or nonsustained ventricular tachycardia. During a mean follow-up of 37 months, overall mortality was not reduced in the ICD treated group. However, risk of sudden cardiac death was 45% lower in the ICD group, but the risk of nonsudden cardiac death was 92% higher. These results confirmed the conclusions stated by DINAMIT that following recent myocardial infarction, patients do not benefit from ICD treatment.

Based on all previously described primary prevention trials, Nanthakumar and co-workers conducted a meta-analysis, which demonstrated a 25% mortality reduction in favor of ICD patients and, consequently, these findings led to the inclusion of primary prevention ICD treatment in the current guidelines.[42, 43]

COMPANION[31]	DEFINITE[34]	SCD-HeFT[30]	DINAMIT[33]	IRIS[37]
1520	458	2521	674	898
CRT-D vs CRT vs AAD	ICD vs AAD	ICD vs AAD vs AAD + amiodarone	ICD vs AAD	ICD vs AAD
I & NICM, EF ≤0.35, QRS >120ms	NICM, EF ≤0.35	I & NICM, EF ≤0.35	Prior MI, EF ≤0.35, HR ≥80	Prior MI, EF ≤0.40, HR ≥90
14	29	46	30	37
40% (p < 0.001)	35% (p = 0.08)	23% (p = 0.007)	-8% (p = 0.66)	-4% (p = 0.78)

Cardiac resynchronization therapy

Following the inclusion of primary prevention in the guidelines, a shift occurred in the population receiving an ICD device. Firstly, in 1996 only patients with a survived cardiac arrest received an ICD (secondary prevention), however in 2008 already 80% of ICD recipients had a primary prevention indication.[44] As a result, an increasing part of ICD recipients suffered from a more advanced stage of heart disease with a reduced LVEF.[45] Importantly, left ventricular failure is associated with conduction disturbances causing mechanical dyssynchrony which further contributes to a reduction in the LVEF.

Consequently, cardiac resynchronization therapy (CRT) devices were designed to improve LV performance by restoring the atrio-ventricular, interventricular en intraventricular synchronicity and therewith increase LV filling time, reduce MR, and correct septal dyskinesis.[46] In numerous randomized and multicenter trials, CRT has shown to improve the systolic LV function and clinical prognosis of patients with end-stage, drug refractory heart failure (Table 3).[31, 47-61] For instance, in the CARE-HF trial, patients with severe NYHA functional class ≥III heart failure due to a reduced LVEF (≤35%) and cardiac dyssynchrony (QRS ≥120msec) were randomly assigned to receive medical therapy alone or in combination with CRT.[53] During follow up, CRT demonstrated to be beneficial with a hazard ratio of 0.63 (95% CI 0.51 – 0.77) for the primary endpoint (a composite of death from any cause or an unplanned hospitalization for a major cardiovascular event) in patients treated with CRT as compared with patients treated with medical therapy only. Almost simultaneously, the COMPANION trial reported results of advanced heart failure patients (NYHA III or IV) with a depressed LVEF (≤35%) and a wide QRS complex (≥120ms) who were randomly assigned to receive optimal medical therapy alone or in combination with CRT with either a pacemaker or a pacemaker defibrillator (CRT-D).[31]Again, the risk of the combined endpoint of death from or hospitalization for heart failure was significantly reduced by 34% and 40% in the CRT and CRT-D respectively if compared with the conventionally treated group. In addition, CRT-D therapy also significantly reduced mortality with 36% when compared with the pharmacologic-therapy group.

Table 3. Overview of inclusion criteria and main findings of randomized clinical trials evaluating cardiac resynchronization therapy in heart failure patients.

	Sample size	NYHA class	LVEF (%)	QRS (ms)	ICD	Main findings
MUSTIC-SR[52]	58	III	≤35	≥150	No	· Reduction in hospitalization · Improvement in 6 MWT, NYHA class, QoL, and Peak VO_2 · Reduction in LV volumes and MR
MIRACLE[47]	453	III, IV	≤35	≥130	No	· Improvement in 6 MWT, NYHA class, and QoL · Reduction in LVEDD, MR, increase in LVEF
PATH-CHF[49]	41	III, IV	≤35	≥120	No	· Reduction in hospitalization · Improvement in 6 MWT, NYHA class, and QoL
MUSTIC-AF[57]	59	III	≤35	≥200	No	· Reduction in hospitalization · Improvement in 6 MWT, NYHA class, QoL, and Peak VO_2
MIRACLE-ICD[61]	369	III, IV	≤35	≥130	Yes	· Improvement in NYHA class, QoL, and Peak VO_2
CONTAK-CD[56]	490	II-IV	≤35	≥120	Yes	· Improvement in 6 MWT, NYHA class, and QoL · Reduction in LV volume, increase in LVEF
PATH-CHF II[50]	86	III, IV	≤35	≥120	Yes/No	· Improvement in 6 MWT, QoL, and Peak VO_2
COMPANION[31]	1520	III, IV	≤35	≥120	Yes/No	· Reduction in all-cause mortality or hospitalization
MIRACLE-ICD II[48]	186	II	≤35	≥130	Yes	· Improvement in NYHA class · Reduction in LV volumes, increase in LVEF
CARE-HF[53, 54]	813	III, IV	≤35	≥120	No	· Reduction in all-cause mortality or hospitalization · Improvement in NYHA class, QoL
RETHINQ[51]	172	III	≤35	<130	Yes	· Improvement in NYHA class
REVERSE[55, 58]	610	I, II	≤40	≥120	Yes/No	· Reduction in hospitalization · Reduction in LVESV
MADIT-CRT[59]	1820	I, II	≤30	≥130	Yes	· Reduction in all-cause mortality or heart failure event · Reduction in LVESV
RAFT[60]	1798	II, III	≤30	≥130	Yes	· Reduction in all-cause mortality or heart failure hospitalization

6 MWT = 6 minutes walk test; ICD = implantable cardioverter defibrillator; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVESV = left ventricular end-systolic volume; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NYHA = New York Heart Association; QoL = quality of life

Accordingly, these findings resulted in the American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines to consider CRT a class I indication in patients with end-stage heart failure (NYHA III-IV) with an LVEF ≤35% and a QRS complex duration of ≥120ms.[62] Similar recommendations were provided by the European Society of Cardiology in 2007.[63]

Despite the widely proven beneficial effects of CRT therapy, 20-30% of CRT recipients do not show any clinical or echocardiographic improvement and are considered CRT non responder.[46] Already several factors such as LV dyssynchrony, extent and location of scarred

tissue and position of the LV pacing lead have demonstrated to determine the response to CRT.[64-70] However, it is of interest if patients who respond to CRT, and therewith have a decreased myocardial wall tension, have less ventricular arrhythmias if compared to CRT non-responders.

Complication of device treatment

With expending indications for ICD treatment, worldwide implantation rates increased to an estimated 275.000 units in 2008.[62, 71] Although the beneficial effect on mortality has been thoroughly proven in a selected population, some serious drawbacks of ICD therapy should not be overseen.

Firstly, device implantation is associated with a number of complications, such as pneumothorax and endovascular lead related complications such as right ventricular perforation and coronary vein dissection (Table 4).[72-79] The first days following implantation can be accompanied by pocket hematoma and lead dislodgement.

Secondly, during longer follow-up, other complications can occur, such as defibrillation lead failure,[72-77, 80] pocket infections,[79, 81-83] and inappropriate device discharge[18, 30, 32-34, 36, 84]. An important difficulty is the limited service life of the pulse generator, resulting in device replacement approximately every 4-5 years.[85, 86] With increased survival of patients it is estimated that over 70% of implanted patients require an ICD replacement due to end-of-life of the device and 40% even require a second replacement.[86] These figures imply that the number of replacements can be expected to outnumber first implantations in the

Table 4. Implantation related complications of implantable cardioverter defibrillators and cardiac resynchronization therapy-defibrillators in major randomized clinical trials.

	Number of Patients implanted	Duration in Months	Pneumo-thorax, n (%)	In-Hospital Mortality, n (%)	Hematoma or bleeding, n (%)	Lead dis-lodgement, n (%)	Coronary vein Com-plications, n (%)
AVID[18, 76]	539	27	6 (1.1)	NR	8 (1.5)	8 (1.5)	NA
MADIT II[36]	742	20	NR	0 (0.0)	NR	NR	NA
DINAMIT[33]	312	30	NR	0 (0.0)	NR	NR	NA
DEFINITE[34]	229	29	2 (0.9)	0 (0.0)	NR	6 (2.6)	NA
SCD-HeFT[30]	829	46	NR	NR	NR	NR	NA
IRIS[37]	445	37	NR	5 (0.8)	NR	NR	NA
MADIT-CRT[59]	1829	29	24 (1.3)	1 (0.1)	54 (3.0)	44 (4.4)	5 (0.5)
MIRACLE[47, 79]	571	6	1 (0.2)	2 (0.4)	NR	31 (5.9)	35 (6.2)
MIRACLE ICD[61, 79]	429	6	3 (0.7)	0 (0.0)	NR	11 (2.9)	19 (4.5)
COMPANION[31]	1212	16	NR	8 (0.6)	NR	NR	22 (1.8)
CARE-HF[53, 78]	409	29	2 (0.5)	0 (0.0)	NR	11 (2.8)	6 (1.5)
RethinQ[51]	250	6	2 (1.1)	0 (0.0)	2 (1.2)	13 (7.6)	1 (0.6)
REVERSE[58]	684	12	4 (0.6)	NR	5 (0.8)	66 (10.6)	3 (0.5)

near future.[87] Previous studies have demonstrated that surgical re-interventions, such as device replacements, are correlated to an increased occurrence of device infections.[82, 83] Additionally, Gould and Krahn reported that the consequences of an early re-intervention for a non-infectious cause can be considered more harmful than the underlying complication itself.[88] However, the effect of replacement on non-infectious pocket related complications and the effect of additional replacements has not yet been assessed.

Socio-economic implications

As already discussed, ICDs have shown to be an effective treatment modality in the prevention of sudden cardiac death in selected patients.[18-20, 30, 32, 35, 36] However, it has been recognized that ICD recipients have an ongoing risk of sudden cardiac incapacitation that might cause harm to others when driving a car. Although numerous recommendations exist, thus far evidence is scarce to justify them and large variation exist between different countries concerning the legislation of driving restriction after ICD implantation (Table 5).[89, 90] Keeping in mind that driving restrictions are often being perceived as difficult for patients and their families, clear evidence on the necessity of these restrictions is vital.

Furthermore, with increased implantation rates, clinicians have expressed concern that the number-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 ICD therapy will strain financial resources and the pool of trained personnel.[91, 92] Concomitantly, it is essential to assess the cost-effectiveness of ICD therapy in different subgroups in order to specify which patients would have a reasonable cost to benefit ratio if treated with an ICD. It is therewith important to realize that the accepted cost-effectiveness ratio per gained quality-adjusted life year vary widely per country. In the Netherlands a cost-effectiveness ratio below €40,000 per gained quality-adjusted life year is accepted whereas in the United States of America a threshold of $60.000 is accepted.[93, 94]

Previously, several studies have assessed the cost-effectiveness of the prophylactic use of ICDs and showed a wide diversity in the cost and benefit ratio if the current guidelines are followed (Table 6).[95-100] However, these dissimilarities in the beneficial effect of ICD therapy,

Table 5. Overview of the recommendations by the American Heart Association (AHA) and the European Heart Rhythm Association (EHRA) for ICD patients with private driving habits.

	AHA[89]	EHRA[90]
ICD for secondary prevention	6 months	3 months
ICD for primary prevention	1 week	4 weeks
Following appropriate ICD therapy	6 months	3 months
Following inappropriate ICD therapy	None	Until measures are taken
Following ICD replacement	None	1 week
Following lead replacement	None	4 weeks

ICD = implantable cardioverter defibrillator.

Table 6. Results of increased costs, increased life years, increased quality-adjusted life years, and incremental cost-effectiveness ratios for implantable cardioverter defibrillators compared with control therapy in different primary prevention ICD trials.

	Increase in Cost ($)	Increase in LY	Increase in QALY	ICER ($/LY)	ICER ($/QALY)
MADIT I[35, 98]	92,100	3.64	2.64	25,300	34,900
CABG Patch[98, 101]	55,700	(0.40)	(0.29)	Dominated	Dominated
MUSTT[32, 98]	101,500	4.14	2.99	24,500	34,000
MADIT II[36, 98, 100]	79,400	2.03	1.47	39,000	54,100
DEFINITE[34, 98]	100,500	2.73	1.96	36,800	51,300
DINAMITE[33, 98]	58,800	(0.48)	(0.34)	Dominated	Dominated
COMPANION[31, 98]	68,300	1.87	1.36	36,500	50,300
SCD-HeFT[30, 98]	71,000	1.40	1.01	50,700	70,200

ICER = incremental cost-effectiveness ratio; LY = life years; QALY = quality-adjusted life year

based on results from clinical trials, are difficult to extrapolate to routine clinical practice since these studies mainly used experts' opinions for complication rates, device longevity, and costs. Furthermore, differences in study population and patient characteristics in previous analysis presumably had a large effect on the final cost-effectiveness of ICD therapy. Consequently, it is important to determine the cost-effectiveness of ICD therapy, based on clinical data and detailed costs derived from routine clinical practice.

Furthermore, the effect on the cost-effectiveness of ICD therapy should be calculated for various clinical circumstances as for instance an older age at implantation, higher rate of complications, and the obtained quality of life. Hence, based on these results one is able to allocate the limited financial resources and trained personnel in the most efficient manner for the health care system.

AIM AND OUTLINE OF THE THESIS

In large clinical trials, ICD therapy and CRT-D have been proven to be an effective treatment in selected patients. However, the population assessed in these trials does not reflect the population receiving an ICD or CRT-D in the "real world". Therefore the aim of the current thesis was to evaluate the clinical aspects and socio-economic implications of ICD and CRT-D treatment in the population presently receiving device therapy.

In **Part I**, the clinical characteristics and outcomes of the population indicated for defibrillator treatment in routine clinical practice were studied. Chapter 2 describes the mode of death and prognosis for different subgroups of device recipients outside the setting of a clinical trial. The increasing risk for pocket-related complications with recurrent device replacements is evaluated in chapter 3. Chapter 4 studied the effect of CRT on the occurrence of ventricular arrhythmias in patients who underwent upgrade from ICD to CRT-D. Finally, in chapter 5, the suitability and predictors of the unsuitability for an entirely subcutaneous ICD system were established.

In **Part II**, the social and economic implications of ICD and CRT-D therapy are examined. In chapter 6, lifetime cost and gained quality-adjusted life years were estimated for primary prevention ICD recipients. Device longevity and reasons for defibrillator replacement were studied in chapter 7. In chapter 8, an evidence based approach for driving restrictions in defibrillator patients was based on real-world incidences of appropriate and inappropriate device shocks. Finally, in chapter 9, strategies to identify those patients most likely to benefit from primary prevention ICD therapy are discussed.

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