Implantable cardioverter defibrillator treatment : benefits and pitfalls in the currently indicated population

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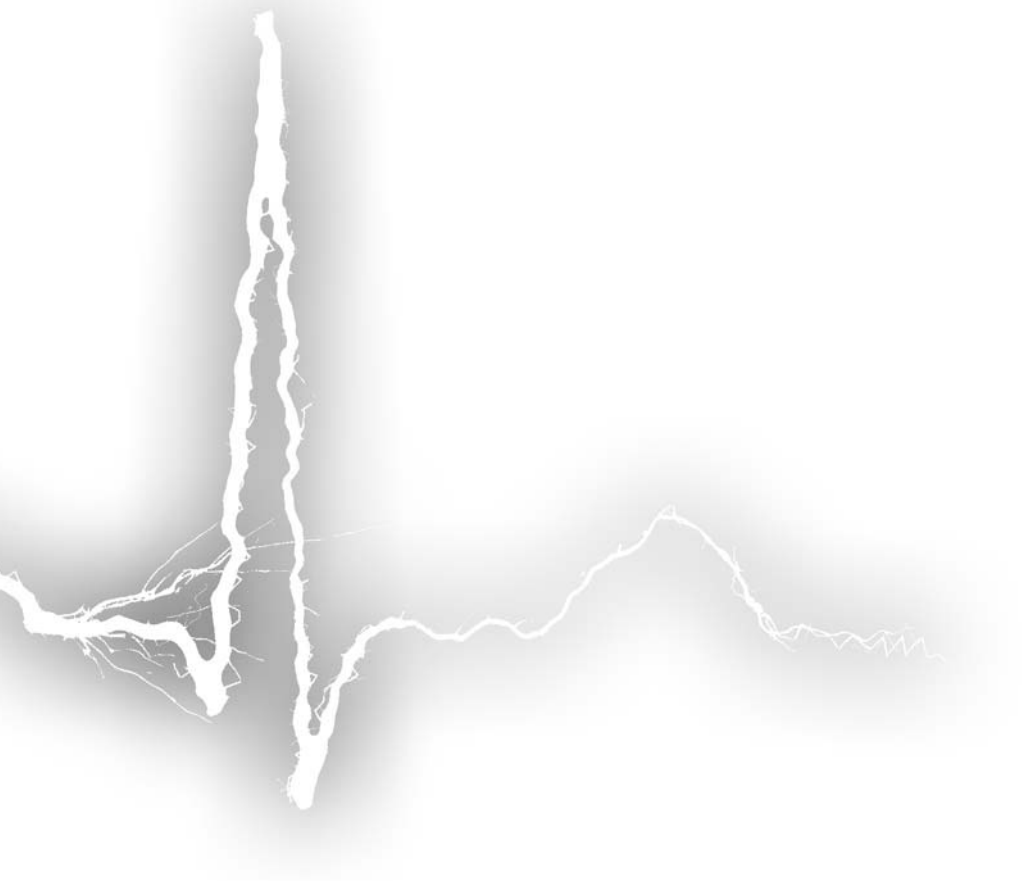
Summary, conclusions and future perspectives



Summary

The general introduction (**Chapter 1**) of this thesis describes aspects of sudden cardiac death (SCD), ventricular arrhythmias, substrates for ventricular arrhythmias, and the relevant treatment options for ventricular arrhythmias, amongst others implantable cardioverter defibrillator (ICD) therapy. **Chapter 1** further specifies on the history of ICDs, the studies leading to the construction of the international guidelines, and questions still arising about ICD treatment.

The aim of this thesis was to improve understanding of several important clinical issues concerning ICD treatment in daily clinical care by studying a large population of ICD patients outside the setting of a clinical trial. Firstly, the population currently receiving ICD treatment was assessed and long-term follow-up, as well as possibilities for baseline risk stratification, were evaluated (**Part I**). To improve risk stratification within the population, currently treated with an ICD, the added value of new parameters was studied (**Part II**). Finally, complications accompanying ICD treatment were studied (**Part III**).

Part I: Long-term follow-up and baseline risk stratification of ICD patients

Chapter 2 we assessed the frequency of patients in daily clinical practice who meet criteria for implantation of an ICD following acute myocardial infarction (MI) using a pre-hospital, in-hospital and out-patient clinical framework aimed at the prevention of SCD. A total of 676 consecutive acute MI patients (78% male, mean age 59±12 years) were included in this analysis. Left ventricular ejection fraction (LVEF) at 3 months was 54±10%. Only 39 (6%) patients met criteria for implantation of an ICD <1 year post-MI. These patients suffered more extensive infarctions as indicated by higher peak troponin T values (mean 14.5±8.3μg/l vs. 6.5±14.7μg/l; $p<0.001$) and had more LAD related infarctions (79% vs. 46%; $p<0.001$). Cumulative first appropriate therapy rate was 15% (95% CI 4-27%) at 3 years follow-up. No sudden cardiac death was observed in the study population.

This study indicates that with the implementation of an aggressive optimized treatment protocol for acute MI patients, prophylactic ICD implantation was warranted in only 6% of patients. Additionally, this easy-to-use guideline-based protocol is able to reduce the occurrence of SCD substantially.

The aim of **Chapter 3** was to assess the long-term mortality rate and the recurrence of potentially life-threatening ventricular arrhythmias in secondary prevention ICD patients and to construct a model for baseline risk stratification. For this purposes, 456 patients with ischemic heart disease, receiving ICD therapy for secondary prevention of sudden cardiac death were evaluated at implantation and during 54±35 months follow-up. During follow-up, 100 (22%) patients died and appropriate ICD therapy was noted in 216 (47%) patients of whom 138 (30%) for fast, potentially life-threatening ventricular arrhythmias.

Multivariate analysis revealed a history of atrial fibrillation (AF) or flutter, ventricular tachycardia (VT) as presenting arrhythmia, wide QRS and poor left ventricular ejection fraction as independent predictors of life-threatening ventricular arrhythmias. The strongest predictor was atrial fibrillation with a hazard ratio of 2.1 (95% CI: 1.3-3.2). Based on the available clinical data it was not possible to identify a group which exhibited no risk of recurrence of potentially life-threatening ventricular arrhythmias.

This study demonstrates the high recurrence rate of life-threatening arrhythmias in secondary prevention patients. Although factors correlating to an increased risk can be identified, no recurrence-free group could be distinguished. This stresses the importance of ICD treatment in this population.

In **Chapter 4** the presence of a history of AF (paroxysmal, persistent or permanent) was evaluated in 913 ICD patients. Furthermore, the effect of AF on the occurrence of appropriate or inappropriate device therapy, as well as mortality was noted. At implantation, 73% of patients had no history of AF, 9% had a history of paroxysmal AF, 7% had a history of persistent AF and 11% had permanent AF. During 27±13 months follow-up, 117 patients (13%) died, 228 patients (25%) experienced appropriate device discharge and 139 patients (15%) received inappropriate shocks. Patients with permanent AF exhibited more than double the risk of mortality, ventricular arrhythmias triggering device discharge, and inappropriate device therapy. Patients with paroxysmal or persistent AF did not show a significantly increased risk of mortality or appropriate device therapy but demonstrated an almost threefold increased risk of inappropriate device therapy.

This study clearly demonstrates prognostic importance of this common arrhythmia in ICD treated patients.

Chapter 5 described the importance of new-onset AF in 223 ICD patients without a history of AF with symptomatic heart failure, who received a cardiac resynchronization therapy-defibrillator device. Defining new-onset AF as atrial high-rate episodes >180 bpm during >10 minutes/day as detected by the device resulted in 55 patients (25%) who develop new-onset AF during a mean follow up of 32±16 months. When compared to the patients who maintained sinus rhythm during follow-up, patients developing AF showed less LV reverse remodeling (ΔLV end systolic volume 37±53 vs. 19±37 ml, $p<0.05$) and less improvement in LV function (ΔLV ejection fraction 6.7±8.9 vs. 3.5±10.3%, $p<0.05$). Importantly, patients developing AF experienced more appropriate ICD shocks for ventricular arrhythmias, more inappropriate shocks and more hospitalizations for heart failure.

This study shows the importance of new-onset AF in this symptomatic population. Furthermore, it demonstrates the possibilities for device-based diagnostics.

Chapter 6 assessed survival in 1036 primary prevention ICD patients with non-ischemic or ischemic heart disease and constructed a baseline mortality risk score. Non-ischemic and ischemic patients demonstrated similar survival but exhibited different factors that influence risk for mortality. A risk score, consisting of simple baseline variables could stratify patients in low, intermediate and high risk for mortality. In non-ischemic patients, annual mortality was 0.4% (95% CI 0.0-2.2%) in low risk and 9.4% (95% CI 6.6-13.1%) in high risk patients. In ischemic patients, annual mortality was 1.0% (95% CI 0.2-3.0%) in low risk and 17.8% (95% CI 13.6-22.9%) in high risk patients.

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

In an attempt to identify patients who do not benefit from ICD treatment, **Chapter 7** defined non-benefit from ICD treatment as death, prior to appropriate ICD therapy. Out of a number of different routinely acquired baseline variables such as age, ejection fraction and diabetes, a baseline risk score was constructed to estimate risk for non-benefit in 900 ischemic primary prevention ICD recipients. Stratification for non-benefit resulted in risk categorization of patients as low, intermediate or high-risk. Advanced age was the strongest predictor of non-benefit. Five-year cumulative incidence for non-benefit ranged from 12% (95%CI 5–18%) in low-risk patients to 49% (95%CI 38–60%) in high-risk patients.

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

Part II: New parameters for risk stratification

Chapter 8 evaluated the relation between infarct tissue heterogeneity on contrast-enhanced magnetic resonance imaging (MRI) and the occurrence of spontaneous ventricular arrhythmia in patients with previous myocardial infarction. For this study, 91 patients with previous MI scheduled for ICD implantation underwent cine-MRI to evaluate left ventricular function and volumes and contrast-enhanced MRI for characterization of scar tissue (infarct gray zone as measure of infarct tissue heterogeneity, infarct core and total infarct size). Appropriate ICD therapy was documented in 18 patients (20%) during a median follow-up of 8.5 months (interquartile range 2.1-20.3). Multivariable Cox proportional hazards analysis revealed that, out of all MRI parameters, the amount of infarct gray zone was the strongest predictor of the occurrence of spontaneous ventricular arrhythmia with subsequent ICD therapy (hazard ratio 1.49/10g, confidence interval 1.01-2.20).

This study established the correlation between infarct tissue heterogeneity on contrast-enhanced MRI and the occurrence of ventricular arrhythmias in patients with previous MI.

In **Chapter 9**, the value of cardiac sympathetic denervation, measured with 123-iodine metaiodobenzylguanidine (123-I MIBG) imaging, was tested for the prediction of ventricular

arrhythmias causing appropriate ICD therapy (primary endpoint) and the composite of appropriate ICD therapy or cardiac death (secondary endpoint). Before ICD implantation, 116 patients underwent 123-I MIBG and myocardial perfusion imaging. Early and late 123-I MIBG (planar and SPECT) imaging was performed to assess cardiac innervation (heart-to-mediastinum ratio, cardiac washout rate and 123-I MIBG SPECT defect score). Stress-rest myocardial perfusion imaging was performed to assess myocardial infarction and perfusion abnormalities (perfusion defect scores). During 23±15 follow-up, appropriate ICD therapy and cardiac death were documented. Late 123-I MIBG SPECT defect score demonstrated to be an independent predictor for both endpoints. Patients with a large late 123-I MIBG SPECT defect (summed score >26) showed significantly more appropriate ICD therapy (52% vs 5%, $p<0.01$) and appropriate ICD therapy or cardiac death (57% vs 10%, $p<0.01$) than patients with a small defect (summed score ≤26) at 3-year follow-up.

The study underscores the potential strong value of 123-I MIBG imaging in the stratification for ventricular arrhythmia and SCD.

Chapter 10 described the value of the ECG derived QRS-T angle for prediction of ICD therapy and mortality in primary prevention patients with ischemic heart disease. For this, 412 ICD patients with ischemic heart disease and a left ventricular ejection fraction ≤ 40% were included. After device implantation, the occurrence of appropriate ICD therapy and mortality was noted. A survival analysis was performed comparing patients with a planar QRS-T angle ≤ 90º (n=124, 30%) to patients with a planar QRS-T angle > 90º before device implantation. Furthermore, patients with a spatial QRS-T angle ≤ 100º (n=56, 14%) were compared to patients with a spatial QRS-T angle > 100º, prior to implant. For patients with a planar QRS-T angle >90º as compared to ≤ 90º, the adjusted hazard ratio for the occurrence of appropriate device therapy was 2.4 (95% CI 1.1-5.2); a spatial QRS-T angle > 100º was associated with an adjusted hazard ratio of 7.3 (95% CI 1.0-53.8). Furthermore, a spatial QRS-T angle ≤ 100º exhibited a positive predictive value of 98% (95% CI 95-100%) for the prediction of an appropriate therapy-free follow-up.

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

Chapter 11 evaluated the prognostic value of myocardial excitability, as assessed by right ventricular stimulation threshold testing in 689 consecutive primary prevention ICD recipients with ischemic heart disease. Best dichotomous separation was reached at a cut-off of 1V. Cumulative appropriate shock incidence for patients with right ventricular threshold ≥1V (n=166) was 16% at 1 year, 24% at 3 years and 34% at 5 years compared to 4%,

11% and 17% for patients with a right ventricular threshold <1V (n=523). Adjusted HR of right ventricular threshold ≥1V was 1.8 (95% CI 1.3-2.6) for appropriate therapy, 3.3 (95%CI 2.0-5.4) for appropriate shocks and 1.6 (95%CI 1.1-2.5) for mortality.

This study shows that right ventricular stimulation threshold at ICD implant has a strong independent prognostic value for the occurrence of ventricular arrhythmias triggering appropriate ICD therapy, appropriate shocks and mortality.

Part III: Mechanical aspects and complications of device therapy

The incidence, predictors and outcome of inappropriate shocks in 1544 ICD patients was assessed in **Chapter 12**. During a follow-up period of 41 ± 18 months, 13% experienced one or more inappropriate shocks. The cumulative incidence steadily increased to 18% at 5 years follow-up. Independent baseline predictors for the occurrence of inappropriate shocks consisted of history of atrial fibrillation (HR 2.0, p<0.01) and age below 70 years (HR 1.8, p<0.01). Experiencing a single inappropriate shock resulted in an increased risk for all-cause mortality (HR 1.6, p=0.01). Mortality risk increased with every subsequent shock, up to a HR of 3.7 after 5 inappropriate shocks.

This study stresses the importance of inappropriate shocks in this population. Most important finding is the association between inappropriate shocks and mortality.

The occurrence and cause of failure of 568 coronary sinus leads and 2161 defibrillation leads were assessed in **Chapter 13** and **Chapter 14** respectively.

During follow-up, 7% of patients required a coronary sinus lead intervention. Cause of the intervention was an elevated threshold (n=13), loss of capture (n=20), or intractable phrenic nerve stimulation (n=6). Fifteen patients (38%) required a coronary sinus lead intervention before first scheduled follow-up (two months after implantation). Thirteen patients (33%) warranted a coronary sinus lead intervention more than six months after implantation. The first endovascular replacement was successful in 86% (32 out of 37), while a second endovascular approach failed in 66% (2 out of 3).

During follow-up, 82 (3.8%) cases of defibrillation lead failure were identified. Cumulative incidence of lead failure at one year was 0.6%, at five years 6.5% and 16.4% at ten years. The highest risk of lead failure was found in small-diameter leads. Adjusted hazard ratio was 6.4 (95% CI 3.2-12.8) for Medtronic 7 Fr leads, when compared to all other leads.

These studies provide insight in the occurrence of adverse events, accompanying ICD treatment.

Since the Medtronic Sprint Fidelis defibrillation lead has a higher than expected failure rate (**Chapter 14**), Medtronic announced two advisories consisting of (1) adjustments in device settings (October 2007) and (2) installation of a lead integrity algorithm (May 2008). The

objective of **Chapter 15** was to evaluate the effect of these advisories on patient safety in 372 implanted leads. Three periods were distinguished in the comparison of event rates: lead implantation to advisory 1 (period A), in-between both advisories (period B) and advisory 2 to follow-up (period C). Overall cumulative incidence rate of lead failure was 3.6% (95%CI 1.6 – 5.6%) at 21 months and increased to 11.0% (95% CI 6.1 – 15.9%) at 42 months. After implementation of both advisories, the occurrence of inappropriate shocks due to lead failure decreased from 1.5 (95% CI 0.6 – 3.0) per 100 lead-years in period A to 0.8 (95% CI 0.0 – 4.3) per 100 lead-years in period C.

This study demonstrated that, despite an increasing risk for Sprint Fidelis lead failure, implementation of the advisories decreased the occurrence of inappropriate shocks due to lead failure.

In **Chapter 16**, the requirement for pocket related surgical re-interventions following 3161 ICD implantations was evaluated and the effect of device replacement on the occurrence of re-interventions was assessed. In total, 145 surgical re-interventions were required in 122 (3.9%) patients, with a median time to first re-intervention of 75 days. The three year cumulative incidence of first re-intervention was 4.7% (95% CI 3.9-5.5%) and the incidence of re-intervention was 1.9 (95% CI 1.6-2.2) per 100 ICD-years. Event rate comparison of replacement ICDs versus first implanted ICDs showed a more than doubled need for re-interventions in replacement ICDs (rate ratio 2.2 [95% CI 1.5-3.0]). Further sub-division by the consecutive number of ICD replacements, shows an increase in the annual need for surgical re-intervention, ranging from 1.5% (95% CI 1.2-1.9%) in the first implanted ICD, to 8.1% (95% CI 1.7-18.3%) in the fourth implanted ICD.

This study showed the effect of ICD replacement on the requirement of pocket related surgical re-interventions.

Conclusions and future perspectives

Despite undisputed beneficial effects of ICD therapy in selected patients, as shown in large randomized trials, much remains unclear about ICD recipients in daily practice, outside the setting of a clinical trial. The current thesis clarified a few aspects of this increasing and important population of cardiac disease patients. Firstly, long-term follow-up has been assessed in different subgroups of ICD recipients, demonstrating rates of all-cause mortality, the occurrence of appropriate ICD therapy, triggered by ventricular arrhythmia, and the incidence of adverse events such as inappropriate device shocks. Secondly, the thesis has explored the possibilities for risk estimations using routinely acquired clinical variables (age, sex, clinical history, findings on ECG and echocardiography) without additional, less commonly applied modalities. Subsequently, the important role of atrial fibrillation

at baseline and during follow-up has been more thoroughly assessed. Thirdly, the value of novel parameters, acquired by additional modalities (MRI, MIBG, vector ECG) has been assess for the prediction of ventricular arrhythmia to improve baseline risk stratification. More importantly, these novel parameters could prove valuable in the identification of patients who, although currently indicated for ICD treatment, have a very low occurrence of ventricular arrhythmia during follow-up and should possibly be reconsidered for implantation. Additionally, clinically applicable risk scores have been proposed to make patient-tailored estimations of mortality risk and of the risk for mortality, prior to a first ICD discharge. Finally, the thesis has eluded on the occurrence of important drawbacks of ICD treatment such as inappropriate shocks and their prognostic importance, LV lead failure and the success rate of endovascular replacement, and RV lead failure and the effect of lead advisories on patient safety.

Future research will primarily focus on the optimal allocation of ICD treatment. On one hand, patients at high risk for SCD but without an indication for ICD treatment according to the current guidelines will have to be identified. On the other hand, within the population presently being considered for an ICD, a large portion does not receive potentially lifesaving ICD therapy during long-term follow-up and should therefore be recognized prior to implantation and reconsidered. Furthermore, the occurrence of potential drawbacks of ICD treatment will have to be further assessed and options for its minimization tested.

Sudden cardiac death in the general population

According to the Maastricht data, SCD is the first manifestation of heart disease in approximately 50% of all cases. Of all cases of SCD in patients with prior myocardial infarction and echocardiographic data, 50% had an LVEF higher than 30% and 20% of patients had an LVEF higher than 50%,[1] which is in line with the data from our own Leiden out-of-hospital cardiac arrest study.[2, 3] Taken in consideration that, in general, the ICD treated patients will show survival benefit as long as the tested population has high enough risk for arrhythmia (as stated by Dr. Mower, co-developer of the ICD)[4] one could conclude that the majority of the population needing defibrillator backup is not indicated according to the current international guidelines.[5] Future research will therefore initially have to focus on the detection of this “unknown” population of patients at high risk for SCD and on the prevention and early identification of substrate development (e.g. prevention of acute myocardial infarction, identification of dilated cardiomyopathy).

Since prior studies have proven the effect of ICD treatment for the primary prevention of SCD in patients with a poor left ventricular function, the extension of the indicated population could aim at patients with known heart disease and a preserved LVEF or at patients without known heart disease but with higher risk for substrate for ventricular arrhythmia (e.g. positive family history for SCD) or a provocative lifestyle (e.g. competitive sports). Parameters identifying this “new” population at high risk will have to be applicable in a

large population and, therefore, should be non-invasive and easily acquirable. Parameter derived from basic clinical assessment and ECG recording would fit these demands.

Currently ICD treated population

Large trials have clearly shown the potential of defibrillator treatment for the primary prevention of SCD in a large population at high risk. However, the relatively low rate of appropriate and potentially life-saving ICD therapy during long-term follow-up does cause the efficacy of ICD allocation to be questioned. Although the studied groups as a whole have clearly demonstrated survival benefit, this does not mean that all individual included patients have equal gain from ICD treatment. Within the indicated population, patients who can be assumed to have little benefit from ICD treatment can be distinguished by the following factors: 1) a poor prognosis, regardless of defibrillator backup (e.g. high rate of heart failure or non-cardiac death); 2) none or low occurrence of potentially life-saving appropriate ICD therapy during follow-up; 3) a combination of both factors (death prior to appropriate ICD therapy). In order to more efficiently allocate ICD treatment, these patients should be identified, prior to implantation. Since the currently indicated ICD population is characterized by high age (50% > 65 years; 14% > 75 years) and severe co-morbidity, the identification of patients with little benefit should at first focus on these patients.

The assessment of the effect of withholding a portion of the indicated population from ICD treatment would interfere with the guidelines and, therefore, is difficult. However, 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 provision of ICD therapy will strain financial resources and the pool of trained personnel.[6] If this is the case, clinicians should be guided in the differentiation between patients at high probability to benefit from ICD treatment (good prognosis, high risk for ventricular arrhythmia) and patient in whom the positive effects of implantation might not outweigh the risk for adverse events, related to device implantation.

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