Improvements in implantable cardioverter defibrillator patient stratification

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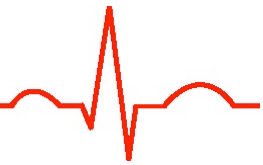
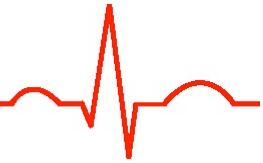


Summary, conclusions and future perspectives



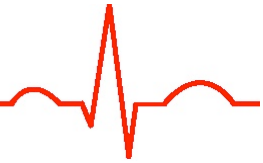
Summary

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

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

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

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



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

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

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

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

Part II: Improvements in risk stratification

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

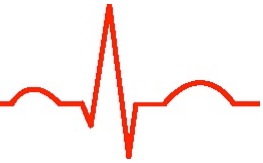


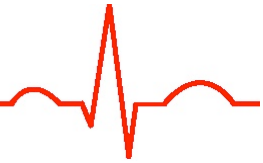
exhibit different factors that influence the risk for mortality. A risk score, consisting of simple baseline variables could stratify patients in low, intermediate and high-risk for mortality. In non-ischemic patients, annual mortality was 0.4% (95% CI 0.0-2.2%) in low-risk and 9.4% (95% CI 6.6-13.1%)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

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

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

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

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

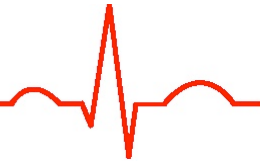


a baseline risk score was constructed to estimate the risk for non-benefit in 900 ischemic primary prevention ICD recipients. Stratification for non-benefit resulted in risk categorization of patients as low, intermediate or high-risk. Advanced age was the strongest predictor of non-benefit. Five-year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

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

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

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

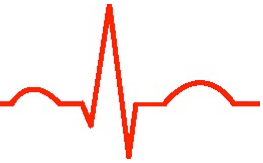


In **Chapter 8** we provided an update on the lead failure and cardiac perforation rate of Medtronic's Sprint Fidelis ICD lead and St. Jude Medical's Riata ICD lead in comparison to a large benchmark cohort. For this, data on 396 Sprint Fidelis leads (follow-up 3.4±1.5 years), 165 8-French (F) Riata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

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

Conclusions and future perspectives

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

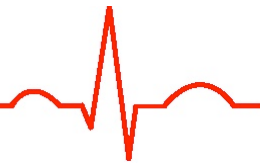


ICD implantation indications (primary vs. secondary). As expected, patients treated for secondary prevention are at increased risk for appropriate therapy. However, similar event-rates of all-cause mortality were observed between both groups. Furthermore, insight was given in the actual need for device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

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

Sudden cardiac death

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



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

Death, prior to first appropriate ICD therapy

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

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

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

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