Invasive therapy for inherited cardiac arrhythmias: towards a better benefit-risk equilibrium
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Invasive therapies, especially the implantable cardioverter-defibrillator (ICD), have become important treatment options for patients with inherited cardiac arrhythmia syndromes who are at risk for sudden cardiac death (SCD). In the introductory **CHAPTER 1**, a review on the current risk stratification and indications for invasive treatment in this group of patients is presented. It demonstrates that ICDs are effective in preventing SCD in selected patients. However, it also shows that these invasive therapies are accompanied by treatment-related complications, while a substantial part of the patients have no treatment benefit. The aim of the current thesis was to provide evidence for the optimization of the benefit-harm equilibrium of treatment in patients with inherited cardiac arrhythmia syndromes who are at risk for SCD by refining therapy indications, evaluating current treatment strategies and testing new treatment options which aim to minimize therapy harm.

**PART I: PREVENTING TREATMENT HARM BY ADEQUATE SYNCOPE RISK STRATIFICATION**

Syncope is the presenting symptom of various clinical disorders, ranging from benign reflex syncope to potentially lethal ventricular arrhythmias. The various causes imply different types of treatment. **CHAPTER 2** describes the prevalence and causes of syncope in the general population compared to the general practice and emergency unit. In this study, 0.94% of all the patients visiting the emergency unit presented with transient loss of consciousness, of which half of the patients were diagnosed with syncope. Reflex syncope was the most prevalent cause of syncope and is more common in patients younger than 40 years than in patients older than 60 years. Cardiac syncope was only rarely diagnosed in patients younger than 40 years. The event rate for syncope in the general population is much higher than the presentation rate in general practice, which exceeds the presentation rate in the emergency unit by far, indicating a strong selection in the referral of patients with syncope. Earlier studies have already demonstrated that reflex syncope is by far the most frequent cause of syncope in the general population. The epidemiological knowledge from this study underscores that benign reflex syncope is the most commonly occurring type of syncope, also in the emergency units and especially in young patients.

**CHAPTER 3** is a letter-to-the-editor in response to a study performed by Liu et al. on the occurrence of syncope in patients diagnosed with long QT syndrome (LQTS). Liu and co-workers demonstrated that the risk of recurrent syncope episodes after the occurrence of a first syncope event is increased in these patients, regardless of other LQTS risk factors. Moreover, they demonstrated that recurrent syncope is a powerful predictor of future aborted cardiac arrest or SCD. In this letter-to-the-editor we responded that not all syncope does equate to torsades de pointes – the rhythm disturbance associated with SCD in LQTS patients –, especially not in the young, since reflex syncope is very common in the general popula-
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...tion with a life-time cumulative incidence of up to 40% at the age of 21 years. We therefore emphasized that careful history taking remains the cornerstone of adequate diagnosis and subsequent treatment in these LQTS patients with syncope.

To proof that benign non-arrhythmic syncope frequently occurs in young patients with inherited cardiac arrhythmia syndromes, syncope events in families with inherited arrhythmia syndromes were studied. Firstly, in CHAPTER 4 we hypothesized that syncope events in family members are simple reflex syncope events and we aimed to support this hypothesis by analyzing the characteristics of the syncope events. We therefore studied family members of LQTS patients enrolled in the International LQTS Registry who were genetically tested and found negative for the family proband’s LQTS-causing mutation. We found that 11% of them had a history of one or more episodes of syncope, opposed to a near-zero rate of aborted cardiac arrest or SCD. These syncope events were likely to be reflex syncope, since the clinical characteristics of these syncopal events were similar to the characteristics of reflex syncope as reported in the literature. Syncope events mainly occurred in female family members during mid-adolescence. Syncope triggered by exercise and loud noise identified LQT1 and LQT2-related syncope, respectively. Syncope caused by other triggers (often typical vasovagal triggers) was more prevalent in genotype negative family members. Moreover, syncope was not a predictor of adverse outcome in this population, since none of the family members experienced a life-threatening event after the first syncope episode.

Subsequently, in CHAPTER 5 we demonstrated that syncope is also very prevalent in Brugada syndrome (BrS) patients. As many as 34% of the patients with BrS had a history of syncope at the time of diagnosis, of whom 28% had suspected arrhythmic syncope and 57% suspected non-arrhythmic syncope. Clinical and historical features that suggesting ventricular arrhythmias were male gender, presence of urinary incontinence, absence of typical prodromes, and, most specific, absence of typical triggers. These features may therefore be used to distinguish arrhythmic from non-arrhythmic syncope. Moreover, the risk for future arrhythmic events was zero in a 9-year follow-up period in patients with non-arrhythmic syncope, confirming that the diagnosis, which was based on the ESC guidelines, was correct.

The results from CHAPTER 4 and CHAPTER 5 demonstrate that benign non-arrhythmic syncope, mostly reflex syncope, is a frequent cause of syncope also in young patients with inherited arrhythmia syndromes and their family members. It is important to distinguish arrhythmic and non-arrhythmic syncope since all, including the most recent, consensus statements about diagnosis and management of patients with inherited arrhythmia syndromes recommends ICD implantation only in BrS patients with syncope judged to be likely caused by ventricular arrhythmias. Therefore, the high prevalence of non-arrhythmic syncope, corresponding with the background prevalence of reflex syncope in the general population, must be taken into account during risk stratification to prevent device over-utilization in the future. Patients with inherited arrhythmia syndromes and their unaffected family members who suffered syncope episodes should not be invasively treated by default.
PART II: BENEFIT VERSUS HARM OF CURRENT INVASIVE THERAPIES

The ICD is effective in preventing SCD in patients with inherited arrhythmia syndromes, although selection criteria for ICD implantation are ill-defined due to the lack of randomized trials. While the profound benefit of ICD therapies is emphasized in the consensus statements, the associated harm received less attention so far. Patients with inherited arrhythmia syndromes often are young and active and therefore more likely to encounter device complications during the course of many decades of expected use, including inappropriate shocks and lead-related problems. This subsequently might lead to morbidity and reduced quality of life. It is unknown whether the potential adverse effects on morbidity outweigh the efficacy in this population. CHAPTER 6 reports the ICD indications, efficacy and safety in 354 patients with inherited arrhythmia syndromes implanted for primary or secondary prevention in the Academic Medical Center in Amsterdam. We found that among various arrhythmia syndromes, indications for primary prevention were not predictive for appropriate shock therapy, although the low event rates in a relatively small and heterogeneous study population make drawing definite conclusions regarding predictors of future events difficult. Moreover, we found that the risk of appropriate shocks in BrS, LQTS, and DPP6 patients implanted for primary prevention is close to zero (cumulative: 1 appropriate shock in 259 patient-years), while in the entire cohort 35% of the study population had ICD-related morbidity. The absolute risk of ICD-related complications therefore outweighs the mere chance of any appropriate shock in BrS, LQTS, and so far, in DPP6. In patients with ICDs implanted for secondary prevention, there was no such discrepancy between efficacy and harm. Our data do not imply that ICDs should not be implanted for primary prevention in patients with a genetic predisposition of SCD since complications are almost always manageable, while SCD is irretrievable. This notwithstanding, a patient-tailored risk stratification for ICD implantation for primary prevention seems underdeveloped in this rapidly increasing ICD treated population. Future studies should therefore primarily focus on improving risk assessment strategies for primary prevention of SCD.

CHAPTER 7 is a systematic review quantifying the occurrence of ICD harm in young patients with inherited arrhythmia syndromes at increased risk for SCD worldwide. In this meta-analysis of data from 63 study populations comprising 4,916 patients with a genetic predisposition for SCD and a mean age of 39±15 years, inappropriate shocks occurred in 20% of the patients (crude annual rate of 4.7% per year). A variety of other types of ICD-related complications occurred in 22% of the patients (4.4% per year) and ICD-related mortality was 0.5% (0.08% per year). This knowledge on the safety of ICD therapy in this patient population can be used to create a reasonable expectation of procedural and long-term risk-benefit for patients and physicians and therefore facilitates shared decision making. Unfortunately, most studies included in this review did not report ICD harm as the primary finding, but merely
focussed on appropriate therapy. Structural reporting of ICD harm is therefore warranted to draw more definitive conclusions.

Although ICDs are effective in terminating ventricular arrhythmias, ICDs do not prevent ventricular arrhythmias. Left cardiac sympathetic denervation (LCSD) has the potential to actually prevent ventricular arrhythmias and has been increasingly used in therapy-resistant LQTS and catecholaminergic polymorphic ventricular tachycardia (CPVT) patients. In Chapter 8 the results of LCSD in the Netherlands are reported. Seventeen patients, of whom 12 LQTS patients and 5 CPVT patients, underwent LCSD. Most patients (94%) were referred because of therapy refractory cardiac events. In 87% of the symptomatic patients, the annual cardiac event rate decreased. However, after 2 years the probability of cardiac event-free survival was still 59% in LQTS and 60% in CPVT patients. There were four patients (24%) with minor reversible complications following LCSD who did not require any intervention and one patient (5.9%) with a non-reversible post-procedural Harlequin face. Also, one LQT8 patient (5.9%) died secondary to surgery-related issues. Although the procedure is not without risk, LCSD seems a viable treatment for patients with inherited arrhythmia syndromes without other options for therapy. Future studies need to determine whether LCSD can be used as first line therapy or replace the ICD in patients with therapy refractory ventricular arrhythmias. Also the role of LCSD in other inherited arrhythmia syndromes needs to be studied further, after promising results from the Mayo Clinic. Moreover, percutaneous renal sympathetic denervation has emerged as a therapeutic option for patients with hyperactivity of the sympathetic system such as therapy-resistant hypertension, and in animal models renal denervation suppressed ventricular arrhythmias. These findings support the hypothesis that renal denervation might be useful in reducing sympathetic activity in highly symptomatic patients with inherited arrhythmia syndromes and thereby reducing cardiac event rate, although this needs to be studied in the future.

PART III: REDUCING TREATMENT HARM WITH THE SUBCUTANEOUS ICD

With current transvenous ICD technology, many complications are attributable to the endovascular position of the leads and problems related to structural integrity of transvenous leads over the long term. Transvenous leads are therefore increasingly being recognized as the weak link in SCD prevention. In 2010, an entirely subcutaneous ICD (S-ICD) has been introduced, which was designed to avoid the need for the placement of sensing and therapy electrodes within or on the heart. The S-ICD was developed because of its perceived benefits over transvenous (TV)-ICD systems. It is likely that the eliminated need for transvenous lead placement reduces or eliminates problems such as failure to achieve vascular access, intravascular injury, and lead failure requiring difficult procedures for extraction and replacement. Additional potential benefits of such a device include the preservation of venous access for
other uses and the avoidance of radiation exposure during fluoroscopy, which is required for transvenous ICD implantation. In CHAPTER 9 we describe for the first time in the world the initial performance of the S-ICD with a minimum of 1-year follow-up in the first 118 patients who were treated with this novel technology in the Netherlands. All induced tachyarrhythmias during defibrillation threshold testing were successfully converted. After 18 months of follow-up 98% of the spontaneous ventricular tachycardia/fibrillation events were successfully converted into sinus rhythm, while 1 episode ended spontaneously. Inappropriate shocks were observed in 13% of the patients. Other ICD-related complications in occurred in 14% of the patients, including a relatively high infection rate of 5.9%. Both inappropriate shocks and device-related complications seemed to be related to a learning curve of both the device and the physician, since more inappropriate shocks and complications occurred in the first 15 implanted patients per center. Hence, this study demonstrates that the S-ICD is a viable alternative to conventional transvenous ICD systems in selected patients.

Suitability and patient selection for the S-ICD is based on three variables: (1) no indication for bradycardia or antitachycardia pacing; (2) no ventricular tachycardias <170 bpm in medical history; and (3) appropriate QRS-T morphology assessed with a preimplantation T-wave morphology screenings ECG (TMS-ECG). CHAPTER 10 tests the suitability for S-ICD implantation in a large cohort of current ICD carriers who could have been potential S-ICD candidates according to the TMS-ECG. Due to the subcutaneous position of the S-ICD, the sensing algorithm is morphology based, which is fundamentally different compared to transvenous ICDs. It compares the monitored QRS- and T-wave morphology to a QRS- and T-wave morphology template registered and stored by the S-ICD immediately after implantation in order to differentiate between supraventricular and ventricular arrhythmias. We found that only 7.4% of patients, who were all males, failed the TMS. These patients are therefore not suitable for S-ICD implantation. Independent clinical predictors of TMS failure were hypertrophic cardiomyopathy, a heavy weight, a prolonged QRS duration, and a R:T ratio <3 in the lead with the largest T-wave on a standard 12-lead surface ECG. These data might alert physicians that selection of patients for a S-ICD should be considered with special caution in certain patient groups because they may not satisfy ECG criteria for adequate sensing. Adequate sensing is mandatory since inappropriate sensing can or lead to inappropriate shocks or impede appropriate shocks. To further optimize appropriate selection of patients suitable for an S-ICD and to gain more insight into the sensing algorithm, TMS should additionally be analyzed in patients with abnormal QRS/T-wave morphology, such as patients hyperkalemia, or conditions with changing QRS/T-wave morphology over time, such as acute myocardial infarction and Brugada syndrome. Moreover, QRS/T-wave morphology analysis using the actual S-ICD sensing algorithm should be developed in the future to screen S-ICD suitability more accurately.

Except for appropriate patient selection to minimize the number of patients with inappropriate sensing, we furthermore aimed to identify patients with an S-ICD implanted who
experienced inappropriate shocks. **CHAPTER 11** describes the incidence and predictors of inappropriate shocks in a large S-ICD registry. Of 581 patients, 48 patients (8.4%) received a total of 101 inappropriate shocks. Cardiac signal oversensing was the most common mechanism for inappropriate shock (73%), followed by supraventricular tachycardias (18%). Patients with hypertrophic cardiomyopathy or patients with a history of atrial fibrillation had an increased risk of receiving inappropriate shocks. Patients with other inherited arrhythmia syndromes seemed also at risk for inappropriate shocks, although this was not significant. Programming of the primary sensing vector, one of the three sensing vectors which the S-ICD can use for morphology analysis, was independently associated with a reduced risk of inappropriate shocks. Identification of patients at risk of inappropriate shocks might provide strategies to anticipate on the occurrence of inappropriate sensing. Treadmill testing has been proposed to analyse inappropriate sensing during exercise, since inappropriate shocks mainly occur during increased heart rate. Consequently, during exercise inappropriate sensing can be managed adequately with optimization of the sensing vector and/or the therapy zones and using a template acquired during exercise.

At present, the S-ICD has demonstrated to be a viable alternative to TV-ICD therapy. However until now it is unclear whether the positive aspects of the S-ICD outweigh its disadvantages compared to conventional ICDs. In **CHAPTER 12** we report the rationale and design of the PRAETORIAN trial. This trial is an investigator-initiated, randomized, controlled, multicenter, prospective 2-arm trial that compares the relative safety and effectiveness of subcutaneous and TV-ICDs. The primary objective is to study non-inferiority of the S-ICD compared with the TV-ICD with respect to inappropriate shocks and major ICD-related complications in patients with a class I or IIa indication for ICD therapy without an indication for pacing. The PRAETORIAN trial aims to define the role of the S-ICD as an adjunctive or primary therapy in patients at risk for SCD.

**FUTURE PERSPECTIVES**

Despite undisputed beneficial effects of invasive therapies in selected patients with inherited cardiac arrhythmia syndromes, a substantial part of these patients experience treatment-related harm.

Enhancing syncope risk stratification and thereby refining treatment indications can decrease treatment harm. This thesis demonstrated that non-arrhythmic syncope, mostly reflex syncope, frequently occurs in patients and their family members. However, distinguishing arrhythmic syncope from non-arrhythmic syncope remains a challenge, especially in this specific patient population with a high pre-test likelihood of non-arrhythmic syncope because of age, and high pre-test likelihood of arrhythmias because of underlying disease. Although we demonstrated that the current ESC guidelines can be used reliably to diagnose
non-arrhythmic syncope in Brugada syndrome, this needs to be confirmed in LQTS and other inherited arrhythmia syndromes, preferably using a prospective approach and long-term follow-up.

The need for an improved patient-tailored risk stratification is highlighted by the results on the efficacy and safety of ICD therapy in patients with inherited arrhythmia syndromes described in this thesis. Next to improving syncope risk stratification, the assembly of larger cohorts from multiple centers with detailed clinical, genetic and lifestyle information may identify additional and more sensitive or specific risk factors and can maximize overall ICD benefit. Both patients who are currently eligible for ICD implantation, but who have no benefit from the device during follow-up, and patients at risk for SCD who currently not have an indication for ICD therapy should be studied. Additionally, a more sophisticated understanding of the links between the molecular pathophysiology and outcome is necessary to promote the development of more relevant and targeted treatment strategies. On the other side of the benefit-harm equilibrium, ICD-related adverse events need to be further assessed by studies focusing on an in-depth analysis, such as analyzing the rates of in-hospital vs. post-discharge events separately and studies searching for predictors of ICD harm to identify patients who are at highest risk for ICD harm.

Reducing ICD harm with the entirely subcutaneous ICD might optimize the benefit-harm equilibrium further. However, this thesis demonstrated that inappropriate shocks and complications are still present, but probably related to a physician- and device-related learning curve. To optimize S-ICD therapy further, the exact role of treadmill testing after or even prior to S-ICD implantation to reduce the occurrence of inappropriate shocks should be defined in future studies. Moreover, a new S-ICD sensing algorithm has been developed with promising pre-clinical results of reducing the number of inappropriate sensing episodes. After implementation in clinical practice, this algorithm needs to be evaluated in S-ICD patients prospectively. In the near future, next generation S-ICD systems will be reduced in volume possibly reducing complications related to the size of the generator, and facilitate implantation in thinner or pediatric patients. Also, in next generation S-ICD systems, wireless communication will facilitate remote follow-up. The deployment of leadless electrodes for pacing (Nanostim) might potentially extend the indication for S-ICD to incorporate patients requiring pacing. At last, the possible use of the S-ICD as a first-line strategy or as an alternative approach for specific population will require the results of the PRAETORIAN trial, which are expected in 2018.

**Final Remarks**

We pursue the best therapies, establish the highest standards of care, strive for a proper cost-effectiveness, diligently measure clinical outcomes, and attempt to improve quality of life
and survival of our patients because we believe that every life counts. However, patients with inherited cardiac arrhythmia syndromes can pose a serious challenge to physicians regarding both risk stratification and choosing the right therapy whilst balancing the effectiveness and side effects. Nonetheless, risk taking is essential to success in any goal where the stakes are high. The results from the studies presented in this thesis may help physicians to improve their management for a better benefit-harm equilibrium for patients with inherited cardiac arrhythmia syndromes.
REFERENCE LIST


