Invasive therapy for inherited cardiac arrhythmias: towards a better benefit-risk equilibrium

Olde Nordkamp, L.R.A.

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1 Introduction, aim and outline
Sudden cardiac death (SCD) is defined by abrupt and unexpected death due to a cardiac cause, often attributed to sustained ventricular arrhythmias.\(^1,2\) It is the most common single cause of death in developed countries and has an overall incidence of 0.6 to >1.4 per 1000 individuals per year with 300,000 to 350,000 deaths annually in the United States\(^3\) and similar incidence rates in Europe.\(^4,5\) The incidence of SCD varies with age, gender and presence of a history of cardiovascular diseases. The majority of lethal arrhythmias occur in older individuals with coronary heart disease which develops over a prolonged period and is influenced by environmental factors, such as lifestyle.\(^6\)

In young individuals (aged <35 years), in whom the incidence of SCD (estimated incidence of 0.005-0.2 per 1000 individuals per year) is lower than in the general adult population, genetic factors causing congenital structural heart disease and inherited cardiac arrhythmia syndromes have a prominent role (Figure 1).\(^7\) SCD is especially devastating when it occurs in these young individuals in the prime of life who were previously thought to be in good health. These deaths are a tremendous loss not only for families and health care providers, but also for entire communities, as evidenced by the often high profile media attention. Consequently the request for prevention of SCD is frequently posed and much research is done to identify patients at risk and to find treatment strategies for SCD prevention. This thesis

Figure 1: Relative contribution of genetic factors to the pathogenesis of sudden cardiac death (from Marsman et al.\(^7\), with permission)
contributes to the development of effective risk stratification and optimization of treatment in patients with a genetic predisposition for SCD.

**INHERITED CARDIAC ARRHYTHMIA SYNDROMES**

Inherited cardiac arrhythmia syndromes may predispose individuals to SCD as a consequence of an inherited genetic abnormality affecting the function of key proteins in the cardiomyocyte. Traditionally, these genetic disorders are categorized in inherited cardiomyopathies, which are associated with structural heart disease, and inherited primary electrical disease, which is associated with abnormal electrical characteristics and a structurally normal heart.

Hypertrophic cardiomyopathy (HCM), genetic dilated cardiomyopathy (DCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC) are classified as inherited cardiomyopathies. HCM is the most common inherited arrhythmia syndrome occurring in at least 1 of 500 individuals. It is characterized by unexplained hypertrophy, that is thickening of the heart wall, of the left ventricle (and sometimes of the right ventricle), myocyte disarray and fibrosis, which is a substrate for ventricular arrhythmias. HCM is commonly associated with mutations in genes encoding for proteins in the contractile apparatus.

DCM is characterized by enlargement of the left ventricle or both ventricles of the heart, accompanied by diminished myocardial contraction, in the absence of hypertension, valve disease, coronary artery disease or other abnormal loading conditions. Mutations in more than 50 genes encoding the cytoskeletal proteins, nuclear membrane proteins, or proteins involved in calcium homeostasis have been related to DCM. ARVC is characterized by right ventricular and/or left ventricular dysfunction and fibrofatty replacement of cardiomyocytes, resulting in a substrate for ventricular arrhythmias.

Long QT syndrome (LQTS), short QT syndrome (SQTS), Brugada syndrome (BrS) and catecholaminergic polymorphic ventricular tachycardia (CPVT) are classified as inherited primary electrical disease, in which often specific electrocardiographic (ECG) abnormalities are present either at baseline or during particular circumstances. The diagnosis of congenital LQTS is mainly based on the presence of a prolonged QTc interval on the ECG in combination with clinical features such as aborted cardiac arrest or arrhythmic syncope or the presence of a LQTS-causing mutation. Different LQTS subtypes are classified by their underlying genetic substrate, such as LQTS type 1 (loss of \( I_{ks} \) function), type 2 (loss of \( I_{kr} \) function) and type 3 (gain of \( I_{Na} \) function), which together constitute 92% of the genotyped LQTS patients. These subtypes have specific clinical features such as the presence of arrhythmias during exercise (specifically swimming) in LQTS type 1, arrhythmias during unexpected auditory stimuli and emotional stress in LQTS type 2, and bradycardia-dependent arrhythmias in LQTS type 3. SQTS is a rare autosomal dominant disorder characterized by markedly accelerated cardiac repolarisation and manifested by a shortened QTc (a cutoff of ≤330 ms is often used), atrial...
<table>
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<th>Disease hallmark</th>
<th>Commonly involved genes</th>
<th>Prevalence</th>
<th>Risk factors for SCD</th>
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| **HCM**          | MYBPC3, MYH7, TNNT2, TNNI3 | 1:500      | 1. History of ventricular arrhythmias  
2. Unexplained syncope, family history of SCD, NSVT at Holter monitoring, septum thickness ≥30mm; no rise in blood pressure during exercise  
3. Presence of myocardial fibrosis on CMR and atrial fibrillation to be determined  
4. Compound heterozygosity |
| **DCM**          | >50 genes described: e.g. DES, LMNA, MYBPC3, MYH7, PKP2, PLN, SCN5a, TNNT2, TTN | 1:2500     | 1. History of ventricular arrhythmias  
2. LVEF <35%  
3. In the presence of a LMNA mutation in combination with conduction disorders, presence of NSVT, LVEF <45%, male sex or non-missence mutations |
| **ARVC**         | DSC2, DSG2, DSP, JUP, PKP2, TNMEM43 | 1:5000     | 1. History of ventricular arrhythmias  
2. Unexplained syncope  
3. NSVT in combination with a probable or definite diagnosis according to the modified Task Force criteria  
4. Compound heterozygosity |
| **LQTS**         | KCNQ1, KCNH2, SCN5a | 1:2000     | 1. History of ventricular arrhythmias  
2. Unexplained syncope  
3. QTc >500ms  
4. Deafness (JLNS)  
5. Compound heterozygosity |
| **SQTS**         | KCNH2, KCNQ1, KCNJ2 | 1:10,000,000 | 1. History of ventricular arrhythmias  
2. Unexplained syncope  
3. Family history of SCD |
| **BrS**          | SCN5a | 1:4000 | 1. History of ventricular arrhythmias  
2. Unexplained syncope  
3. Spontaneous type 1 BrS-ECG |
| **CPVT**         | RyR2, CASQ2 | 1:10,000 | 1. History of ventricular arrhythmias  
2. Unexplained syncope |

ARVC, arrhythmogenic right ventricular cardiomyopathy; BrS, Brugada syndrome; CMR, cardiac magnetic resonance imaging; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; JLNS, Jervell-Lange-Nielsen syndrome; NSVT, non-sustained VT; LMNA, lamin A/C mutation; LVEF, left ventricular ejection fraction; SCD, sudden cardiac death; SQTS, short QT syndrome
and ventricular arrhythmias, and sudden cardiac death. BrS is characterized by a signature ST segment elevation in right precordial ECG leads (type 1 BrS-ECG) which often fluctuates over time, but is particularly present in situations with an augmented vagal tone (e.g. during sleep). The estimated prevalence is approximately 1:4000 in Europe and the United States. CPVT is characterized by bidirectional or polymorphic ventricular arrhythmias under conditions of increased sympathetic activity, such as exercise. Table 1 summarizes clinical characteristics of the different inherited cardiac arrhythmia syndromes.

**Risk stratification**

After diagnosing an inherited arrhythmia syndrome, risk stratification for future ventricular arrhythmias is mandatory. The prognosis and optimal risk stratification among the various inherited arrhythmia syndromes are, however, debated. Generally, inherited cardiac arrhythmia syndromes show marked phenotypic variability, even within families carrying the same mutation. Risk for future ventricular arrhythmias is generally accepted to be high in patients who are known to have already experienced life-threatening ventricular arrhythmias, that is, patients with a history of aborted sudden cardiac death. In patients without previous ventricular arrhythmias, it is more difficult to establish risk factors associated with SCD. Risk factors vary substantially among these diseases. However, in general, numerous demographic variables, such as age and gender, electrocardiographic features, echocardiographic features, abnormalities on MRI, and genetic risk markers, such as mutation type, mutation location and single nucleotide polymorphisms in mRNAs have been proposed and evaluated in an attempt to better identify patients at risk for ventricular arrhythmias. Only a history of syncope, i.e. transient loss-of-consciousness due to cerebral hypoperfusion, has systematically been associated with an increased risk of ventricular arrhythmias. Yet, syncope as a symptom constitutes a diagnostic dilemma. Although syncope in patients with inherited arrhythmia syndromes is often ascribed, by default, to cardiac arrhythmias in this setting, syncope may also stem from other causes. In the general population, reflex syncope is by far the most frequent cause of syncope, especially in the young, with a life-time cumulative incidence of ≥1 syncopal episode in teenagers up to 40% by the age of 21 years. Hence, syncope represents a complex symptom with a multifactorial etiology and the assumption that all syncopal events in patients with inherited arrhythmia syndromes are dangerous may be erroneous. Adequate risk stratification is therefore necessary to distinguish arrhythmic from non-arrhythmic syncope. Misclassification of the origin of syncope can result in wrongful commencement of – invasive – treatment, with a significant chance of side effects as a consequence.
THERAPEUTIC MANAGEMENT

Lifestyle modifications, such as avoidance of (strenuous) exercise in HCM, ARVC, LQTS and CPVT patients, reduction in exposure to abrupt loud noises (alarm clock, phone ringing etc.) in LQTS2 patients and avoidance of drugs that prolong QT interval or provoke a type 1 BrS-ECG in LQTS and BrS respectively, are the cornerstone of therapeutic management in patients with inherited arrhythmia syndromes.

Medical treatment with beta-blockers is indicated in all symptomatic LQTS and CPVT patients, unless there is a contraindication such as active asthma.28 Also in asymptomatic LQTS patients with a QTc >470ms, beta-blockers are recommended. Additional flecainide has proven to be an effective therapy in patients with CPVT29 and quinidine is known to suppress arrhythmias in BrS patients.30 Patients with ARVC, HCM or DCM cardiomyopathy who have heart failure symptoms should receive adequate heart failure medication.

Invasive therapies such as left cardiac sympathetic denervation (LCSD) and implantable cardioverter defibrillators (ICD) are recommended in a selection of patients who are at high risk of ventricular arrhythmias despite lifestyle modifications and optimal medical treatment.1

LEFT CARDIAC SYMPATHETIC DENERVATION

LCSD, first described in 197131, has been a safe procedure to reduce fatal arrhythmias and prevent cardiac death. The surgical technique has undergone several modifications, with variations in strategy among different centers. Nowadays, a thoracoscopic approach is often used for the transection of the upper part of the left sympathetic neural chain.32 LCSD prevents norepinephrine release in the heart, therefore raising the threshold for ventricular fibrillation without reducing the heart rate or impairing myocardial contractility.33 In the last decade LCSD has received renewed attention as a viable alternative treatment for therapy-resistant LQTS and CPVT patients. A significant protective effect of LCSD was demonstrated in both symptomatic and asymptomatic LQTS and CPVT patients.34,35

IMPLANTABLE CARDIOVERTER DEFIBRILLATOR

The use of ICDs is an established therapy for the prevention of death from ventricular arrhythmias. ICDs are programmed to detect cardiac arrhythmias and correct these by delivering a high voltage shock to the myocardium. Multiple trials, such as AVID36 and CIDS37, demonstrated a significant reduction in mortality in survivors of ventricular arrhythmias causing hemodynamic compromise. Moreover, other large randomized trials, such as MADIT-I38 and II39 and SCD-HeFT40 patients, demonstrated that ICD therapy also reduced mortality
in selected patients with ischemic and non-ischemic cardiomyopathy, prior to cardiac arrest or sustained VT.

In contrast to the ischemic and non-ischemic cardiomyopathy ICD population, appropriate selection criteria for ICD implantation in patients with inherited arrhythmia syndromes rely on non-randomized studies including registries and consensus statements. ICD therapy is undebated in survivors of ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) because of the presumed risk of recurrence (i.e. secondary prevention). Indications for prophylactic device implantation in patients without spontaneous VT/VF (i.e. primary prevention) are uncertain, but there might be over-utilization despite risk stratification in certain disease categories, since many patients do not receive appropriate shocks.\(^{41, 42}\) Appropriate shock rates are generally between 10-30% over 8 years in inherited arrhythmia syndrome patients implanted with an ICD for primary prevention, opposed to 40-65% in patients implanted for secondary prevention (Figure 2).\(^{41, 43, 44}\) Moreover, the use of ICD therapies as an endpoint may overestimate the incidence of life-threatening arrhythmias by 2-fold, because appropriate ICD shocks occur more frequently than SCD.\(^{45}\) This rate might be even higher in LQTS, in which many ventricular arrhythmias are self-limiting and might be treated with shocks prematurely. Therefore, enhanced risk stratification for better selection of patients with inherited arrhythmia syndromes who are likely to experience appropriate ICD therapy, and therefore benefit, seems currently underdeveloped.

**DRAWBACKS OF ICD THERAPY**

The increasing awareness and diagnosis of patients with a genetic predisposition for SCD can provide timely lifestyle modifications and treatment in disease-carrying individuals from
affected families, thereby preventing SCD. Moreover, it increased the number of young ICD recipients. While the presumed benefit of ICDs is reflected in the indications for ICD implantation in the consensus statement, which is predominantly based on the ICD efficacy, the associated harm receives less attention. Inappropriate shocks may occur because of lead failure, electromagnetic interference, myopotentials, cardiac oversensing and supraventricular tachycardia. In major randomized trials and in the setting outside of clinical trial, the occurrence of inappropriate shocks is well assessed, approximately 13% over 2 years of follow-up. However, higher numbers of inappropriate shocks are reported in patients with a history of atrial fibrillation and, generally younger, patients with inherited or congenital heart diseases. This number of inappropriate shocks can safely and substantially be reduced by contemporary ICD programming. Recent studies, such as MADIT-RIT and ADVANCE III study focussed on reducing inappropriate and unnecessary ICD therapies by setting long detection intervals and high rates cut-offs. Increasing the delay before initiating therapy has been shown to safely permit fast ventricular tachycardia self-termination before therapy delivery. This is of particular importance in LQTS and CPVT, were the majority of arrhythmic episodes are self-terminating. High rate cut-offs allow for therapy for fast symptomatic ventricular arrhythmias only and thereby reducing inappropriate therapies on supraventricular tachycardias such as physiological sinustachycardia. Also this is probably beneficial in particular for the relatively young patients with inherited arrhythmia syndromes. Dual chamber detection enhancements have not been shown to be beneficial to reduce the rate of inappropriate shocks, although they are associated with increased implantation risk, compared to single-chamber devices. The decision to implant a dual-chamber defibrillator in a patient with an inherited arrhythmia syndrome without a pacing indication should therefore be carefully weighted.

Furthermore, even when pursuing maximized patient safety, approximately 10% of ICD patients experience severe implant-related or long-term complications, some with lethal consequences. Relatively young and active patients might even be more likely to encounter device complications over many decades of expected use compared to the general ischemic and dilated cardiomyopathy ICD patients. However, data on complications such as device failure, lead dislodgements, pocket infections, in young ICD recipients have scarcely been assessed. Additionally, considering that young ICD recipients have a higher life-expectancy than those with ischemic- and dilated cardiomyopathy, this might result in multiple lead- and device replacements. Previous studies have demonstrated that surgical re-interventions, such as device replacements, are correlated to an increased occurrence of device infections. Young ICD patients are therefore likely to face a substantial burden of future complications. Another major concern for young ICD patients is lead longevity. Despite decades of lead innovation, failures of lead design, such as with the Sprint Fidelis and Riata lead, remain present and are undoubtedly the Achilles' heel of ICD therapy. This might be particularly pertinent in young patients due to their physically active lifestyle.
Moreover, ICD therapy may lead to a psychological burden. Studies consistently show impairments in health status and quality of life in ICD patients, with an elevated risk for anxiety and depression in up to 30% of the patients. ICDs exacerbate psychological distress and the experience of one or more ICD shocks further negatively affects quality of life.\textsuperscript{64,65}

**SUBCUTANEOUS ICD**

In an attempt to reduce potential ICD harm, an entirely subcutaneous ICD (S-ICD) has been introduced in 2010 (Figure 3).\textsuperscript{66} Currently, ICDs rely on transvenous leads for cardiac sensing and defibrillation. The S-ICD eliminates the need for transvenous lead placement. This might reduce the implant-related complications associated with transvenous lead insertion, most importantly pneumothorax or hematothorax and cardiac perforation. Additionally, there may be less risk of infective endocarditis because of the extravascular position. Also difficulties in achieving venous access, which can prolong the procedure and occasionally results in failed ICD implantation, can be avoided.

On the other hand, an important drawback is the lack of bradycardia pacing and antitachycardia pacing possibilities in the absence of an endocardial lead. Also, the size of the pulse generator of the S-ICD is approximately twice the weight and volume of currently used transvenous ICDs. The current size is in part due to a higher capacity battery, which can achieve the delivery of a high output 80 Joule shock. This higher output is mandatory because of the higher defibrillation threshold in S-ICD systems due to the extra-thoracic position compared to the threshold of intracardiac leads. The larger generator might increase the risk of skin erosion, patient's discomfort, and infection as compared with the conventional ICDs. Until now it is unclear whether the positive aspects of the S-ICD outweigh its disadvantages.

![Figure 3: A schematic drawing of the transvenous ICD and the subcutaneous ICD](source: www.textbookofcardiology.org)
AIM AND OUTLINE OF THIS THESIS

One of the principal precepts of bioethics in medicine and a fundamental principle throughout the world is “Primum non nocere”, which means “First, do no harm”. The current use of invasive treatment in often young patients with inherited arrhythmia syndromes relies on expert opinions and many patients are invasively treated without having treatment benefit. On the other hand treatment related adverse events are frequently present. The aim of this thesis was to optimize the benefit-harm equilibrium in patients with inherited cardiac arrhythmia syndromes who are at risk for SCD.

Part I aims to improve risk stratification of patients experiencing syncope in order to prevent treatment harm. CHAPTER 2 describes the prevalence and causes of syncope in the general population compared to the general practice and emergency unit. Moreover, it aims to gain insight into the selection and referral process of patients with syncope, in particular the proportion from the general population that present to a general practitioner and/or emergency unit in general and by age groups. CHAPTER 3 is a comment on the etiology of syncope events in another study describing the prognostic importance of syncope in patients with LQTS. To determine whether benign non-arrhythmic syncope are also frequent in patients and family members with inherited arrhythmia syndrome we performed the studies described in the following two chapters. In CHAPTER 4 we hypothesize that syncope events in LQTS family members are of vasovagal origin. By analyzing the clinical characteristics of the syncope events, we aim to support this hypothesis. CHAPTER 5 assesses the prevalence of arrhythmic and non-arrhythmic syncope in BrS patients. Additionally, it describes the clinical characteristics of arrhythmic and non-arrhythmic syncope and analyzes the clinical relevance of non-arrhythmic syncope.

Part II describes the benefit and harm in current treatment possibilities in patients with inherited arrhythmia syndromes. CHAPTER 6 describes the ICD indications, efficacy and safety in patients with inherited arrhythmia syndromes in the Academic Medical Center in Amsterdam. It aims to assess whether the potential adverse effects on morbidity outweigh the efficacy in this population. CHAPTER 7 is a systematic review on ICD harm in these relatively young patients of all available literature in order to quantify the risk of ICD therapy. This data is needed to better inform patients and physicians regarding the expected risk of adverse events and therefore to facilitate truly informed consent. As described earlier, another treatment possibility in patients with inherited arrhythmia syndromes is LCSD. CHAPTER 8 describes the indications and outcome of LCSD in LQTS and CPVT patients in the Netherlands.

Part III gives an overview of the performance of the entirely subcutaneous ICD in order to possibly reduce treatment harm. The S-ICD is introduced in Europe in 2008 and approved for
commercial use in 2010. **CHAPTER 9** describes the initial experience regarding the efficacy and safety of the S-ICD in a large Dutch cohort of patients implanted between 2008 and 2011. To further increase our knowledge on the S-ICD, we aimed to investigate several aspects of the morphology based sensing algorithm, which differs substantially from the sensing algorithm of conventional transvenous ICDs. **CHAPTER 10** assesses which patients are not suitable for an S-ICD because of a failed morphology screening. **CHAPTER 11** describes the incidence and predictors of inappropriate shocks in the largest S-ICD registry world-wide to identify patients who are at risk for inappropriate sensing. Moreover, we here evaluate the type and successfulness of therapies on inappropriate shocks. In addition to studies describing the performance of the S-ICD currently, a head-to-head comparison of S-ICD therapy and transvenous ICD therapy is needed to determine whether the positive aspects of the S-ICD outweigh its disadvantages compared to transvenous ICDs. **CHAPTER 12** therefore describes the rationale and design of the currently ongoing PRAETORIAN trial, a prospective randomized trial, comparing the S-ICD with the transvenous ICD with regard to ICD-related harm.

In the last chapter, **CHAPTER 13**, a summary of the studies with recommendations for future research is presented.
REFERENCE LIST


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