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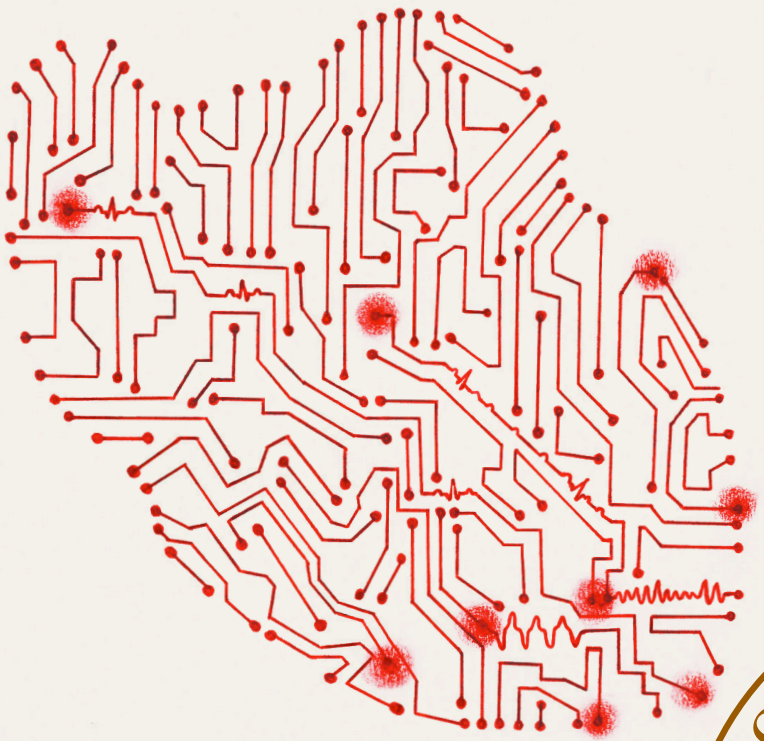
FACULTY OF MEDICINE | LUND UNIVERSITY



Uzma Chaudhry is currently working as a consultant Cardiologist at the department of Cardiology, Arrhythmia clinic at Skåne University Hospital in Lund. She completed her medical degree in 2006 from University of Newcastle upon Tyne (UK) and did her initial specialist training in London.

Her doctoral thesis comprises four studies examining the predictive value of ECG indices for ventricular arrhythmias and mortality, in cohorts with ICD therapy; myocardial scar quantification with Selvester score, vectorcardiography indices and lastly a review of survivors of idiopathic ventricular fibrillation.

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LUND
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Non-invasive prediction of malignant ventricular arrhythmias and mortality in patients with implantable cardioverter-defibrillator

Abstract
Sudden cardiac death (SCD) is a major disease burden often triggered by ventricular arrhythmias in patients with underlying cardiac disease. Globally SCD has been estimated to account for 6 million deaths per year. To date the only efficient primary and secondary prevention treatment of SCD is the insertion of an implantable cardioverter-defibrillator device (ICD). There is, however, a grey zone regarding which patient cohorts are expected to benefit the most from ICD therapy. Risk stratification of SCD and prediction of ventricular arrhythmias is paramount in an ICD cohort. Furthermore, it is essential to correctly identify patients who are expected to benefit the most from the ICD therapy and are at the highest risk for developing complications associated with therapy. ECG remains the most easily available inexpensive non-invasive diagnostic modality. Quantification of myocardial scar burden has emerged as an important clinical parameter. ECG based scar quantification with Selvester score is routinely done manually. Recently, a semiautomated computer algorithm for Selvester QRS scoring has been developed to evaluate scar burden in patients with left bundle branch block (LBBB) as per Strauss criteria, the QuAReSS software. Moreover vectorcardiography (VCG) is gaining more attention. This thesis sought to evaluate the predictive value of ECG indices for ventricular arrhythmias and mortality, in cohorts with ICD therapy.

In *study I* it was shown that QuAReSS software provides valid automatic measurements of the Selvester score in patients with strict LBBB as per Strauss criteria. Thus, potentially, the QuAReSS could deliver broad application of the Selvester score. In *study II* we showed that there is a modest correlation between late gadolinium enhancement cardiovascular magnetic resonance (LGE-CMR) and Selvester score verified myocardial scar in cohorts with ischemic cardiomyopathy (ICMP) and non-ischemic dilated cardiomyopathy (NICMP). LGE-CMR based scar burden was correlated to clinical outcome, but Selvester score quantified scar burden was not. The Selvester scoring algorithm needs further refinement in order to be clinically relevant and reliable for detailed scar evaluation in patients with strict LBBB. In *study III* we showed that the spatial QRS-T angle, QRS vector magnitude and T-wave vector magnitude are VCG indices associated with mortality in patients with reduced left ventricular ejection fraction due to ICMP or NICMP. The VCG variables can be automatically computed from standard 12-lead ECG and could potentially be utilised in risk prediction models. In *study IV* we followed a cohort with idiopathic ventricular fibrillation (IVF). IVF is a rare diagnosis with a 3.1% risk of recurrent ventricular arrhythmia per year. Reported mortality was 4% during follow-up, none due to cardiovascular cause. Thus IVF has a good prognosis provided ICD therapy is initiated. Routine clinical follow-up is recommended due to potential late emerging cardiac pathology, which may also have implications for relatives. ECG changes were common, but had no prognostic value in determining the risk of ventricular arrhythmias recurrence. Screening for genetic diseases was low, and this calls for improvement, especially since cheaper and more comprehensive genetic panels are now readily available.

Key words Implantable cardioverter-defibrillator, late gadolinium enhancement cardiovascular magnetic resonance, ischemic cardiomyopathy, non-ischemic dilated cardiomyopathy, Selvester score, QuAReSS, spatial QRS-T angle, QRS vector magnitude, T-wave vector magnitude, idiopathic ventricular fibrillation

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List of Publications

This thesis is based on the following publications and are referred to in the text by their Roman numerals:

I. Selvester scoring in patients with strict LBBB using the QUARESS software

Xia X, **Chaudhry U**, Wieslander B, Borgquist R, Wagner GS, Strauss DG, Platonov P, Ugander M, Couderc JP

Journal of Electrocardiology. 2015 Sep-Oct;48(5):763-8

II. Evaluation of the ECG based Selvester scoring method to estimate myocardial scar burden and predict clinical outcome in patients with left bundle branch block, with comparison to late gadolinium enhancement CMR imaging

Chaudhry U, Platonov PG, Jablonowski R, Couderc JP, Engblom H, Xia X, Wieslander B, Atwater BD, Strauss DG, Van der Pals J, Ugander M, Carlsson M, Borgquist R

Annals of Noninvasive Electrocardiology. 2017 Sep;22(5)

III. Vectorcardiography findings are associated with recurrent ventricular arrhythmias and mortality in patients with heart failure treated with implantable cardioverter-defibrillator device

Chaudhry U, Cortez D, Platonov PG, Carlson J, Borgquist R

Submitted

IV. Idiopathic ventricular fibrillation – long term prognosis in relation to clinical findings and ECG patterns in a Swedish cohort

Chaudhry U, Platonov PG, Rubulis A, Bergfeldt L, Jensen SM, Lundin C, Borgquist R

Journal of Electrocardiology. 2019 Sep-Oct;56:46-51

Populärvetenskaplig sammanfattning

Årligen drabbas cirka 10 000 människor i Sverige av plötsligt hjärtstopp utanför sjukhus[1]. Oftast till följd av kammararytmier, störningar i hjärtats elektriska system. Det kan vara kammartakykardier eller kammarflimmer, som gör att hjärtat inte förmår pumpa runt blodet. Endast cirka 6% (600st) beräknas överleva den akuta fasen och blir utskrivna från sjukhuset i livet efter hjärtstopp årligen[1]. Det stora flertalet som drabbas är antingen medelålders eller äldre patienter med känd bakomliggande hjärtsjukdom, såsom hjärtinfarkt eller hjärtsvikt. Det finns även en ansenlig subgrupp bestående av unga människor utan känd hjärtsjukdom, där insjuknandet får dramatiska konsekvenser både för själva patienten, men även för deras närstående. Således får alla patienter enligt gängse rutiner en hjärtstartare inopererad, en så kallad implanterbar defibrillator (ICD) i förebyggande syfte. Även patienter med känd hjärtsjukdom, som aldrig haft en livshotande kammararytmi, är potentiella kandidater till att erhålla en ICD, eftersom deras hjärtsjukdom medför en extra hög risk att drabbas av allvarliga kammararytmier. En ICD kan avbryta snabba livshotande kammararytmier, bland annat genom att avge en elektrisk chock över hjärtat eller med snabba pulsar köra över kammartakykardin (ATP). Patienter som behandlas med ICD har ett gott skydd mot livshotande kammararytmier, men behandlingen innebär ibland återkommande elchocker, vilka kan upplevas som oerhört smärtsamma. De kan vara så pass påtagliga, att en individs livskvalitet påverkas negativt. Det föreligger även risk för infektioner (cirka 1,3%) i samband med batteribyte eller uppgradering av ett befintligt ICD-system. Vid infektion måste hela ICD-systemet avlägsnas. Det i sig är riskabelt. Det finns även patientgrupper som aldrig får uppleva en ICD-behandling och därmed kan man ifrågasätta nyttan med en ICD framförallt då det är en kostsam behandling och inte helt riskfri. Risken att drabbas av återkommande allvarliga kammararytmier, vilka behandlas med elchockbehandling skattats till mellan 1,1 – 3,8% per år. Därför är det av stor vikt att tidigt identifiera, vilka patienter som har hög risk att drabbas av återkommande kammararytmier men även kunna identifiera vilka som har en låg risk att drabbas av kammararytmier. Det finns därmed ett behov av att förfina urvalskriterierna för en ICD och därigenom förbättra risk-nytta-kvoten vid ICD behandling.

EKG är numera en vanlig hjärtundersökning, som mäter hjärtats elektriska aktivitet. EKG-kurvan förändras i samband med underliggande hjärtsjukdom. Den senaste tiden har EKG fått allt större betydelse, då olika EKG-markörer kan lätt erhållas. Syftet med avhandlingen var att utvärdera ifall olika EKG-markörer kan förutspå risken för allvarliga kammararytmier och dödlighet hos patienter med ICD-behandling.

Ärrvävnad i hjärtmuskeln bildas oftast till följd av hjärtinfarkt och hjärtsvikt, och har i studier förknippats med ökad risk för allvarliga kammararytmier. Undersökningen för bedömning av ärrvävnad med magnetröntgen (MR) av hjärtat

är både kostsam och tidskrävande. Dessutom varierar tillgängligheten från sjukhus till sjukhus. Selvester-score är en EKG-variabel som kan bedöma andelen ärrvävnad med vanlig EKG-analys. Dock är manuell analys tidskrävande, samt förutsätter vidgade EKG-kunskaper, eftersom 46 kriterier bedöms. QuAReSS är ett nytt datorprogram som kan automatiskt bedöma Selvester-score, förutsatt att patienten uppföljer ett EKG-kriterium, dvs vänstergrenblockering enligt nya kriterier. Då det sker automatiskt, kan det tillföra mycket klinisk nytta. Programmet ger även användaren möjlighet att korrigera och validera varje analyserad kriterium. Tredimensionell EKG avbildning, så kallat vektorkardiogram (VKG) är ett EKG-koncept som numera kan inhämtas automatiskt och har visat sig vara överlägset ett vanligt EKG, för att bekräfta hjärtsjukdom. I studie I-II har Selvester-score bedömts i en kohort med ICD-behandlad hjärtsvikt, med MR-hjärta som referensmetod, för att bestämma graden av ärrvävnad. I studie III har VKG-markörer (QRS-T angle, QRS vector magnitude och T-wave vector magnitude) bedömts i en patient kohort med ICD behandlad hjärtsvikt, samt även i relation till ärrbedömning med MR-hjärta. Utöver detta är studie IV ett unikt projekt, då det är den första större deskriptiva studien med en svensk kohort av patienter som överlevt hjärtstillestånd pga. kammarflimmer, men som inte har haft någon påvisbar hjärtsjukdom vid insjuknandet (idiopatisk kammarflimmer, Idiopathic Ventricular Fibrillation (IVF)). Det är en relativt liten grupp av patienter, men de har vid ung ålder drabbats av allvarlig sjukdom, som även kan påverka deras familjemedlemmar. Osäkerheten för patient och närstående är betydlig om man inte har en säker diagnos, och om man inte vet huruvida risken för hjärtstillestånd är ärftlig. Genom att studera dessa patienter kan vi få ny kunskap om långtidsprognosen samt utvärdera EKG-faktorer som kan förutspå återinsjuknande i allvarlig hjärtarytmi. Slutligen kan vi utvärdera ifall en konklusiv diagnos kan fastställas med uppföljande kontroller med bilddiagnostik (ultraljud hjärta) samt med dagens utvidgade genetiska kunskap, och därmed underlätta genetisk rådgivning och screening av förstagradssläktingar till den som överlevt hjärtstopp.

Denna avhandling bygger på retrospektiva registerbaserade observationsstudier. Två studiepopulationer har studerats. Studie I-III; patienter med hjärtsvikt som genomgick MR-hjärta innan inopererad ICD vid Skånes universitetssjukhus i Lund mellan 2002 och 2013. Studie IV: patienter med IVF från Skånes universitetssjukhus i Lund, Sahlgrenska universitetssjukhuset samt Norrlands universitetssjukhus mellan 1988 och 2016. Medicinska upplysningar har inhämtas via den elektroniska journalen Melior, via pappersjournalhandlingar, via digitalt lagrade undersökningsresultat (EKG från Regions Skånes EKG databas) och via Socialstyrelsen.

I studie I (67 patienter) påvisades att QuAReSS är ett användarvänligt program, som ger tillförlitliga mätningar av Selvester-score hos patienter med känt vänstergrenblock enligt nya kriterier.

I studie II (60 patienter) bedömdes ärrbedömning med Selvester-score enligt QuAReSS program med MR-hjärta som referensmetod. Vi såg en blygsam korrelation mellan båda undersökningarna. Selvester-score hade en tendens att antingen överskatta eller underskatta andelen ärrvävnad. Under uppföljningstiden på närmare 3 år var MR-verifierad ärrvävnad förknippat med ICD behandlad kammararytmier samt dödlighet. Samma analys kunde inte genomföras med Selvester-score, eftersom alla hade ärrvävnad enligt den beräkningen, även då MR-hjärta påvisade frånvaro. Selvester-score måste förfinas ytterligare, för att kunna tillföra en klinisk nytta med tillförlitliga mätningar av ärrvävnad. Utöver detta rekommenderas modifiering av QuAReSS program så att alla EKG typer kan analyseras. Möjligen har Selvester-score en framtida roll ifall den används i riskbedömningar med andra kliniska faktorer och undersökningar.

I studie III (178 patienter) visade vi att tre EKG-markörer, ökad QRS-T angle, lägre QRS vector magnitude och lägre T-wave vector magnitude är förknippade med högre dödlighet i patientgrupper med ICD-behandlad hjärtsvikt. En ökad QRS-T angle var primärt förknippat med hjärtsviktsdöd. Utöver det var lägre QRS vector magnitude och lägre T-wave vector magnitude förknippade med ärrvävnad. Därmed kan beräkning av dessa EKG-markörer ha nytta i riskvärderingsbedömningar tillsammans med andra kliniska faktorer och undersökningar. Resultaten måste dock valideras i större studier.

I studie IV följde vi 50 patienter med IVF, under en median-tid på 13,8 år. Under denna period avled 2 patienter (4%), men den bakomliggande orsaken var inte hjärt- och kärlsjukdom. Hela 32% fick under ICD uppföljningstiden (median 12,3 år) återfall av behandlingskrävande kammararytmi. Dock var risken att få ny kammararytmi relativt låg per patient år. Den årliga risken för kammararytmi beräknades till 3,1%. Således är prognosen överlag mycket god, förutsatt välfungerande ICD. Sju patienter (14%) fick en kardiologisk slutdiagnos förknippad med ökad risk för kammararytmier och utav dessa var åtminstone 3 (6%) förknippat med det ursprungliga hjärtstoppet. EKG-förändringar noterades i samband med hjärtstoppet och vid uppföljning, men inget som kunde förutspå kammararytmier. En låg andel genomgick genetiska analyser vid insjuknande och vid uppföljning, 18% respektive 24%. Av de som genomgick genetisk analys påfanns en genetisk avvikelse associerad med en hjärtsjukdom som förklaring till hjärtstopp hos 23,1%. Regelbundna rutinläkarkontroller rekommenderas pga. potentiellt senkommande hjärtsjukdomar som förklaring till hjärtstopp. Vi måste även bli bättre på att undersöka denna extraordinära grupp för genetiska avvikelser, framförallt då det numera dels är billigare jämfört med tidigare och dels att mer omfattande genetiska paneler numera är lättillgängliga.

Abbreviations

ACE-i	Angiotensin converting enzyme inhibitor
ACMG	American College of Medical Genetics and Genomics
ARB	Angiotensin II receptor blocker
ARVC	Arrhythmogenic right ventricular cardiomyopathy
ATP	Antitachycardia pacing
CHF	Congestive heart failure
CMR	Cardiovascular magnetic resonance
CPVT	Catecholaminergic polymorphic ventricular tachycardia
CRT	Cardiac resynchronization therapy
CRT-D	Cardiac resynchronization therapy with defibrillator
ECG	Electrocardiogram
EPS	Electrophysiology studies
ER	Early repolarization
ERP	Early repolarization pattern
ERS	Early repolarization syndrome
ESC	European Society of Cardiology
EU	European Union
ICD	Implantable cardioverter-defibrillator
ICMP	Ischemic cardiomyopathy
IVF	Idiopathic ventricular fibrillation
LBBB	Left bundle branch block
LGE	Late gadolinium enhancement
LV	Left ventricle
LV-EF	Left ventricular ejection fraction
MI	Myocardial infarction
NICMP	Non-ischemic dilated cardiomyopathy
NYHA	New York Heart Association functional classification

PRD	Periodic Repolarization Dynamics
QRSd	QRS dispersion
QRSvm	QRS vector magnitude
QuAReSS	QUantitative and Automatic REport of Selvester Score
ROC	Receiver operating characteristics
SCD	Sudden cardiac death
Twvm	T-wave vector magnitude
VA	Ventricular arrhythmia
VCG	Vectorcardiography
VF	Ventricular fibrillation
VT	Ventricular tachycardia

Introduction

Sudden cardiac death

The earliest suggested reference to sudden cardiac death (SCD) dates back to 5th century BC to the teachings of Hippocrates[2];

> *"Those who are subject to frequent and severe fainting attacks without obvious cause die suddenly"*

Sudden death is defined as unexpected death that occurs within 1 hour from onset of symptom in witnessed cases and in unwitnessed cases, within 24 hours of last being seen alive[3, 4]. Sudden death is widely accepted as a reference to an unexpected death secondary to cardiac arrhythmia. The mechanism proposed behind sudden death from cardiac arrhythmia is a cascade of arrhythmias, with onset of ventricular tachycardia (VT) degenerating to ventricular fibrillation (VF) and later to asystole[5]. Bradyarrhythmia alone, especially in patients with advanced heart disease has also been reported[5]. In a case series from 1989 with SCD during ambulatory Holter registration, the arrhythmia behind fatality was VT degenerating to VF in 62.4%, followed by bradycardia 16.5%, torsades de pointes 12.7% and primary VF 8.3%[6].

History of sudden death and ventricular arrhythmias

During the 18th century, studies confirmed a link between sudden death and coronary artery disease[7]. John Hunter was the first to describe extensive coronary artery disease in patients with sudden death and history of angina[7]. The first suggested reference to ventricular arrhythmia (VA) was by John Erichsen in 1840 who during experimental studies on dogs observed ceased ventricular activity when a coronary artery was ligated[7]. Further studies elaborated on these findings and also confirmed onset of reperfusion VAs[7]. Translation of these findings to clinical relevance however was weak. John A. MacWilliam established its importance and accurately described VF in 1887, a description which still holds today[8];

> *"…sudden syncope from plugging or obstructing some portion of the coronary system (in patients) is very probably determined or ensured by the*

occurrence of fibrillar contractions in the ventricles. The cardiac pump is thrown out of gear, and the last of its vital energy is dissipated in a violent and prolonged turmoil of fruitless activity in the ventricular walls''

In medical terms, VF is characterised by rapid and grossly irregular ventricular activity with loss of cardiac output and cardiac arrest[9]. Though a recognised phenomenon, it didn't gain attention due to rarity, lack of supported arrhythmia documentation and fatal outcome[7]. In 1912, August Hoffman recorded the first human tracing of VF[10]. By the 1960s, in parallel to advances in electrocardiographic recordings with introduction of bedside and ambulatory electrocardiographic monitoring, the clinical significance of VA was recognised and has remained so ever since[7].

Electrocardiography and Vectorcardiography

The introduction of the electrocardiogram (ECG) has revolutionised cardiac medicine and has become a gold standard non-invasive investigative tool. The principle of the ECG was developed by Willem Einthoven and earned him the Nobel Prize in Physiology or Medicine in 1924[11]. Furthermore, work by Peter Macfarlane has enabled the digitalisation of ECG recording and automated ECG interpretation[12].

The ECG measures the action potential spread (see figure 1) across the cardiac myocytes i.e. the resultant electrical current generated dependent of myocardial mass measured on the skin surface[13]. The ECG is a measure of atrial and ventricular activity, a linear function of depolarisation and repolarisation waves over time, but not the cardiac conduction system alone[13]. The 12-lead ECG represents 12 different 'electrical' views of the heart i.e. 12 different angles in both horizontal and vertical planes[13].

Vectorcardiography (VCG), first described by Mann in 1920 and initially termed monocardiogram, with subsequent developments by Frank in the 1950s, is an important complement to standard 12-lead electrocardiography[14, 15]. The vectorcardiogram is a measure of the magnitude and direction of cardiac activity through the conduction system (see figure 2) in three orthogonal planes; vertical, transversal, and sagittal (orthogonal Frank-leads)[16] as shown in figure 3. A three-dimensional representation of the cardiac vector loop is formed which enables various measurements of depolarisation and repolarisation pathologies, in contrast to the linear time-dependent one-dimensional ECG[16]. The VCG has been reported to be a more superior measure than the ECG in diagnosis of cardiac disease[15, 17, 18]. Measurement of VCG requires additional skin electrodes and is therefore not routinely used in clinical practice[19]. But with digitalisation of the ECG and

application of the software 'Glasgow algorithm', computerised transformation of digital 12-lead ECGs to VCG by Kors' regression related method is possible[12, 19, 20].

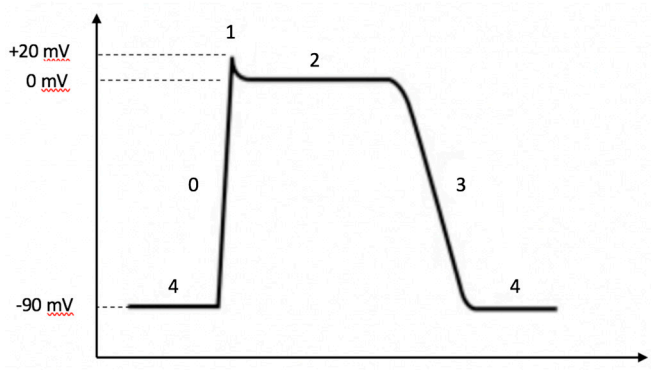

Figure 1. Cardiac action potential

The action potential has four phases[13];

Resting (4): The recovery time before initiation of action potential. The resting membrane potential of the cell is negative (-90mV).

Depolarisation (0): The sodium channels open and there is a fast influx of sodium ions. There is a shift of charge to positive, from -90 mV to +20 - 30 mV.

Peak (1): The cell is at its peak positive charge, thus negative chloride ions enters the cell and slows the influx of sodium.

Plateau (2): The cell membranes permeability is reduced as sodium channels close. There is an efflux of potassium and influx of calcium, which triggers contraction. The potential stabilises around 0 mV during a short period, prolonging the action potential.

Repolarisation (3): Potassium channels open to repolarise the cell and there is an efflux of sodium, thus the original resting potential of -90 mV is restored.

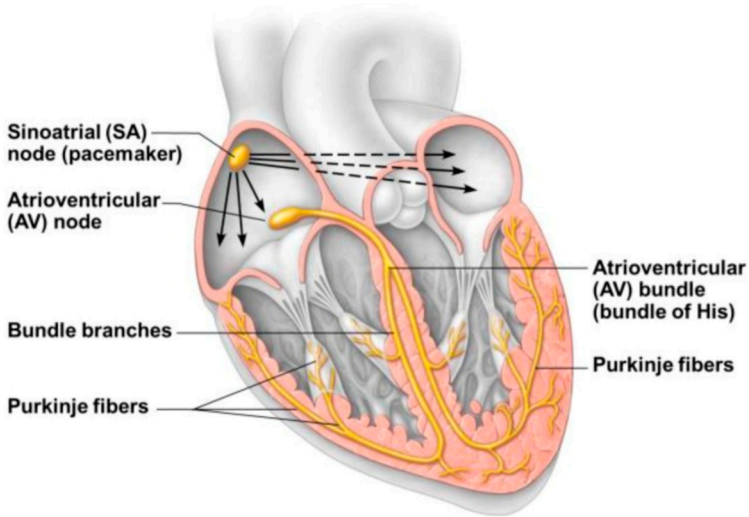

Figure 2. The cardiac conduction pathway.

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The electrical stimulation arise in the sinoatrial node, the hearts intrinsic pacemaker which discharge at regular intervals stimulating the atria to contract[13]. The electrical conduction is independent of the autonomic nervous system, however the rate of electrical discharge can be increased and decreased by the sympathetic and parasympathetic tone, respectively[13]. The electrical signal then travels to the atrioventricular node and following a delay which allows for atrial contraction, divides and conducts through the left and right bundle of His to the Purkinje fibres, triggering ventricular contraction[13].

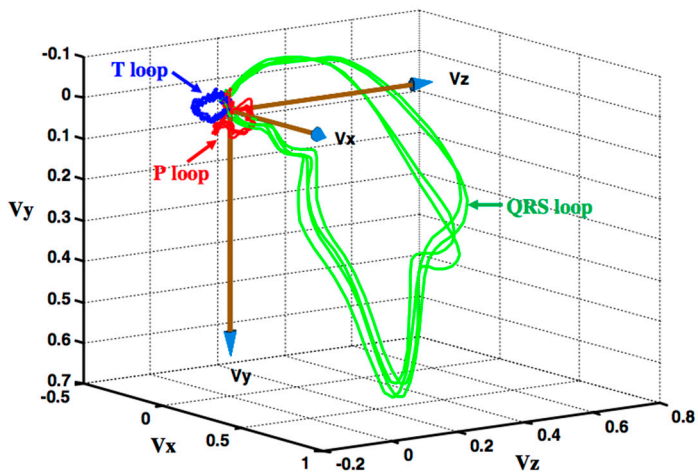

Figure 3. Vectorcardiography loop

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Electrocardiography in relation to cardiac action potential

With each heartbeat, all of the cardiac myocytes are activated in a specific sequence as the cells are depolarised and repolarised. The deflections seen on an ECG tracing represent the different activation phases in the atrium and ventricle. Figure 4.

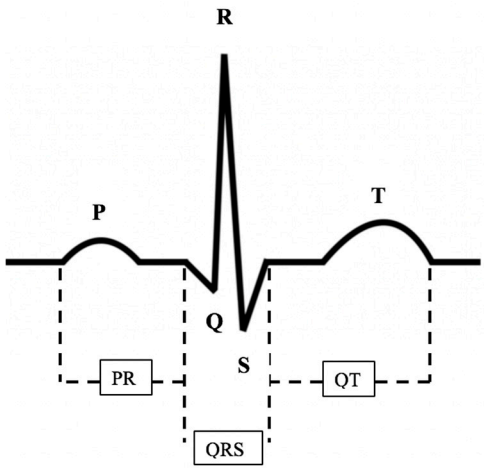


Figure 4. ECG tracing

P-wave: Atrial depolarisation. Atrial repolarisation is not visible on ECG as it coincides with the larger ventricular depolarisation force.

QRS-complex: Ventricular depolarisation.

T-wave: Ventricular repolarisation.

PR-interval: Reflects sinoatrial node activation with subsequent activation of the conduction pathway and delay at AV-node till the impulse passes the Purkinje fibres.

During the depolarisation phase, the myocardial cells are in an absolute refractory state i.e. the cells do not respond to an external stimuli like ventricular extrasystole[13]. In contrast, the repolarisation phase also known as the vulnerable phase, is relative refractory[13]. Repolarisation coincides with the apex of the T-wave and a ventricular extrasystole can therefore initiate an action potential, R- on T-phenomenon, with possible resultant VF[22]. This is however more commonly observed in patients with electrical instability such as in acute myocardial ischemia or channelopathies[22].

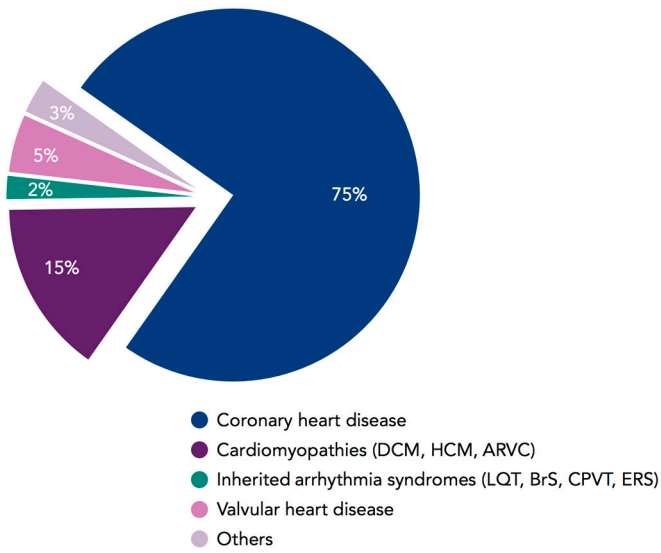
Aetiology of ventricular arrhythmias

Globally, the leading underlying cause of VA is coronary artery disease[3, 9, 23]. Other imperative causes of VA include non-ischemic dilated cardiomyopathy (NICMP), valvular heart disease, myocarditis, hypertrophic cardiomyopathy, arrhythmogenic

right ventricular cardiomyopathy (ARVC) and infiltrative diseases such as sarcoidosis[4]. Since the 1990s the attention has also been shifted to predisposing genetic substrates for SCD[24, 25] (see table 1), the channelopathies e.g. long QT syndrome, short QT syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT)[4, 24], the latter group being more commonly observed in younger patients (< 35 years of age)[4, 24, 25]. In absence of structural heart disease, channelopathies, metabolic, toxic and respiratory causes i.e. unexplained sudden cardiac arrest, idiopathic ventricular fibrillation (IVF) is diagnosed[25]. It is estimated that IVF accounts for 5 - 10% of all patients who survive an out-of-hospital cardiac arrest[26].

Table 1. Cardiac disease and associated genetic mutation

	Genetic mutation
Long QT	*KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2*
Short QT	*KCNH2, KCNQ1, KCNJ2*
Brugada	*SCN5A*
CPVT	*RyR2, CASQ2, KCNJ2*



ARVC = arrhythmogenic right ventricular cardiomyopathy; BrS = Brugada syndrome; CPVT = catecholaminergic polymorphic ventricular tachycardia; DCM = dilated cardiomyopathy; ERS = early repolarisation syndrome; HCM = hypertrophic cardiomyopathy; LQTS = long QT syndrome.

Figure 5. Causes of sudden cardiac death

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Epidemiology

Management of cardiac diseases have improved over the preceding decades. This is primarily due to better understanding and awareness, but also due to implementation of primary and secondary preventive measures, pharmacological optimisation, coronary revascularisation and the use of implantable cardioverter-defibrillator/cardiac resynchronization therapy (ICD/CRT) as appropriate[27-31]. As a result, over the past 20 years a decline in cardiovascular mortality has been observed[4]. However, despite this, cardiovascular disease remains a global health problem with reported 17 million deaths annually[4]. An estimated 15-20% of all deaths in Western world are due to SCD[23]. About 40-50% of cardiovascular deaths are by SCD, the majority of which (~80%) are due to acute VAs[3, 5, 32]. According to Rahul Mehra, based on above figures, about 6 million SCDs due to VAs occur annually worldwide [32].

Mechanisms behind ventricular arrhythmias

Several mechanisms behind VAs have been established. With abnormal *automaticity*, injury currents formed between healthy ventricular myocardium and infarcted or ischemic ventricular myocardial tissue due to increased extracellular potassium, may spontaneously initiate depolarisation[9]. With *triggered* activity, there are alterations in the different phases of the action potential[9]. The action potential can thus induce afterdepolarisations i.e. depolarisation occurring either during repolarisation (early afterdepolarisation) or after repolarisation (delayed afterdepolarisation)[9] as shown in figure 6. Such afterdepolarisations can result in a cascade of action potentials and thus trigger ventricular extrasystole[9]. However, to trigger a VA, *re-entry* mechanism is required[9]. In re-entry there is a closed loop of pathways (unidirectional block) with different speeds of depolarisation and repolarisation; one fast and one slow. Once a trigger, ventricular extrasystole enters the loop, there is an endless circuit and due to changes in myocardial tissue either at cellular level or due to fibrosis as seen in structural heart disease, there is an excitable substrate to sustain a VA[9].

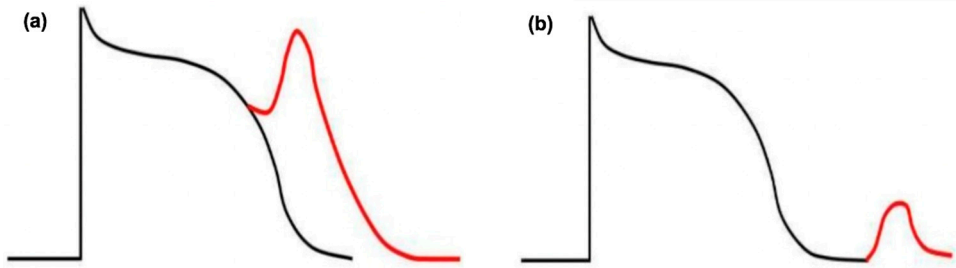

Figure 6. Illustration of afterdepolarisations
A. Early afterdepolarisation (bradycardia, long QT syndrome, hypokalemia, heart failure)[9]
B. Delayed afterdepolarisation (digoxin toxicity, CPVT)[9]

Management of ventricular arrhythmias

The cornerstone in VA management is treatment of the underlying cardiac aetiology[4]. Coronary revascularisation is fundamental in coronary artery disease in addition to primary and secondary prevention measures[27, 29, 30]. Adjunctive pharmacological approach in congestive heart failure (CHF) include treatment optimisation with beta-receptor blockers, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers (ACE-i/ARB) and mineralocorticoid receptor antagonists as appropriate[31]. Their efficacy in reducing morbidity and mortality are well established in clinical trials[31, 33-43]. Sacubitril/valsartan, a combination drug with neprilysin inhibitor sacubitril and ARB valsartan, is a new heart failure drug which was commercialised in 2015[44]. Recently, it has been suggested that sacubitril/valsartan may also have antiarrhythmic properties[45]. In the PARADIGM-HF study, sudden death was reduced in patients with sacubitril/valsartan treatment[46]. Furthermore, one study observed reduced VA burden and appropriate ICD shocks in a small cohort with sacubitril/valsartan treated heart failure (mean LV-EF 35%) and ICD therapy compared to control arm with ACE-i/ARB and ICD therapy (mean LV-EF 30%)[47].

Quinidine was the first antiarrhythmic drug introduced by Scott in 1922 for the management of VT and it remained mainstay treatment up until 1950s when procainamide became available[48, 49]. This was followed by several antiarrhythmic drugs in the 1960s, namely, lidocaine, disopyramide, beta-receptor blockers, mexiletine and amiodarone[48, 49]. Beta-receptor blocker is the only known drug that has been shown to reduce the risk of SCD[4, 9, 50]. Though antiarrhythmic drugs may reduce arrhythmia burden, their effectiveness in primary and secondary prevention of SCD have not been confirmed in randomised clinical trials[4, 9, 50, 51].

The hallmark of VA management has been the discovery of defibrillation therapy. Experimental studies and clinical evidence laid the platform for its feasibility during the 19th century[7]. By the 1960s, external cardiac defibrillation was standard therapy provided in coronary care units[7].

The ICD was developed by Michel Mirowski in the 1970s[52, 53]. In 1975, ICD was first implanted in dogs. Following notable success in experimental studies, the first implant in humans was done in 1980 at John Hopkins Hospital, USA[52]. In Sweden, the first ICD implant was performed at Sahlgrenska University Hospital in 1984[54]. Initially ICD was reserved for patients who had survived at least two cardiac arrests[55]. A number of pivotal primary and secondary prevention ICD trials followed, which laid the foundation for international device guidelines. A modern ICD has the ability to provide pacing, antitachycardia pacing (ATP) and shock as appropriate.

Randomised clinical trials

The Antiarrhythmics Versus Implantable Defibrillators Trial (AVID[56], 1999), which may be controversial today, randomised survivors of cardiac arrest to either antiarrhythmic drug therapy (amiodarone or sotalol) or ICD therapy. At three years follow-up, a significant reduction was seen in all-cause mortality for patients treated with an ICD compared to patients treated with an antiarrhythmic drug. CASH[57] and CIDS[58] trials also evaluated ICD therapy versus antiarrhythmic drug therapy in survivors of cardiac arrest, and though findings were promising, they were not statistically significant.

In the Multicenter Unsustained Tachycardia Trial (MUSTT[59], 1999), patients with ICMP (ischemic cardiomyopathy) (LV-EF $\leq$ 40%) and non-sustained VT underwent electrophysiology studies (EPS). In patients in whom sustained VAs were induced, randomisation to either antiarrhythmic therapy (drugs or ICD) or no antiarrhythmic therapy was done. Reduced mortality was observed in the antiarrhythmic therapy group, but subanalysis confirmed that the net benefit was driven by ICD therapy and not antiarrhythmic drugs.

The Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II[60], 2002) paved the way for ICD implantation in primary prevention in patients with history of myocardial infarction (MI) and reduced LV-EF ($\leq$ 30%) as the ICD group had 31% reduced risk of mortality compared to control group on conventional medical therapy.

In the DEFIbrillators in Non-Ischemic cardiomyopathy Treatment trial (DEFINITE[61], 2004) with NICMP patients (LV-EF < 36%), fewer deaths were reported in patients with ICD therapy and standard medical therapy compared to

group with standard medical therapy alone, but this did not reach statistical significance (p = 0.08). Subanalysis however, showed a significant reduced risk of mortality due to arrhythmia in the ICD group patients in NYHA class III, thus concluding that high risk patients also benefit from ICD therapy in addition to standard medical therapy. A year prior to DEFINITE trial, results from AMIOVART[62] were released which randomised patients with NICMP (LV-EF ≤ 35%) to either amiodarone or ICD. In this study, no difference in mortality was observed between ICD and amiodarone arm, thus casting a shadow on the benefit of ICD in NICMP. However, results should be interpreted with caution due to small sample size (103 versus 458 in DEFINITE).

From The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT[63], 2004) it has been established that the optimal time frame to wait with ICD therapy in patients following acute MI and reduced LV-EF (≤ 35%) is 40 days. In the trial, early ICD implantation was associated with reduced arrhythmia mortality (-58%), but was offset by an increase in nonarrhythmic deaths.

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT[51], 2005) was a landmark study which randomised patients with CHF (LV-EF < 35%) due to ICMP or NICMP to either amiodarone, placebo or ICD therapy. No difference in mortality was observed in amiodarone and placebo group, however, the ICD group had reduced overall mortality of 23%. Thus, a net benefit of ICD in primary prevention was evident in both ICMP and NICMP. Of note, 79% with NICMP and 64% with ICMP did not have any appropriate ICD therapy during a 5-year follow-up.

An ongoing study is the The EUropean Comparative Effectiveness Research to Assess the Use of Primary ProphylacTic Implantable Cardioverter Defibrillators (EU-CERT-ICD[64]). Primary endpoint is to characterise all-cause mortality in a prospective cohort with ICMP or NICMP, who as per European Society of Cardiology (ESC) guidelines receive a newly implanted primary preventive ICD, and compare with a non-randomised no-ICD control cohort (against ESC guidelines). The decision to implant an ICD or opt for a conservative approach is not determined by the study design, but rather based on the decision of the treating physician and the patient, and influenced by regional and national health policy practices. Furthermore, ECG and Holter ECG analysis will be used for risk stratification. During the annual ESC conference 2019, interim data was presented[65]. A total of 2247 patients were enrolled with 1516 in the ICD arm and 731 in the control arm, a ratio of 2:1. Age was near similar in both groups with mean 62 and 63. A male predominance in both cohorts (82%) was observed with LV-EF 28 - 29%. The cohorts were dominated by ICMP, with 69% in ICD arm and 57% in the control arm. During a mean follow-up of 2.7 years in the ICD arm and 1.7 years in the control arm, the reported mortality was 5.5% per year and 9.2% per year, respectively. One hundred and seven patients (7.0%) had appropriate shock therapy,

which translated to 2.8% per year. Further survival analysis (adjusted for mortality predictors) showed that the incidence of all-cause mortality was 27% lower in the ICD arm ($p = 0.0140$). Subanalysis for SCD showed a near 6-fold increased risk in the control arm ($p < 0.0001$). No conclusive results were obtained for ICMP versus NICMP analysis. The authors conclude that both ICMP and NICMP patients treated with an ICD in primary prevention as per ESC guideline recommendations derive mortality benefit, but should be used with caution in subgroups with advanced age or diabetes. Randomised ICD studies are called for.

Lastly, another ongoing trial is the Programmed Ventricular Stimulation to Risk Stratify for Early Cardioverter-Defibrillator (ICD) Implantation to Prevent Tachyarrhythmias Following Acute Myocardial Infarction (PROTECT-ICD[66]), with proposed study completion date in 2023. No interim data has been released at the time of thesis publication. The PROTECT-ICD trial is a complement to DINAMIT[63] and MUSTT[59] trials and aims to determine the role of EPS guided ICD implantation in patients with recent revascularised STEMI (LV-EF ≤ 40%). Patients are randomised to either conventional treatment as per guidelines or undergo EPS within 40 days of MI. If VAs are induced with EPS, an ICD is implanted. Parallel, a proportion in both arms will undergo cardiovascular magnetic resonance (CMR) imaging to primarily correlate with VA at EPS, and SCD and non-fatal arrhythmia at follow-up.

ICD guidelines

The mentioned ICD trials have had a fundamental role in guiding ICD treatment, both in primary and secondary prevention. Furthermore, both prospective and retrospective observational studies have guided ICD utilisation[67-70]. The ESC guideline recommendations for ICD in CHF are shown in table 2[31]. There is little debate regarding the choice of treatment options for those who have survived cardiac arrest[4, 25]. ICD indication in secondary prevention is a Class Ia recommendation, provided recovery from VA and expected survival of more than a year[31]. For primary prevention in CHF patients, ICD is recommended if NYHA class II-III and LV-EF (≤ 35%) despite more than 3 months optimised medical therapy and expected survival of more than a year[31]. The ESC guidelines also differentiate on the level of recommendation for ICD depending on aetiology of cardiomyopathy, with ICMP receiving a Class 1a recommendation and NICMP Class Ib recommendation, confirming that evidence for primary preventive ICD in heart failure is stronger in ICMP compared to NICMP, the latter which are largely based on subanalysis[31, 51, 61, 71, 72]. After MI, ICD implantation in primary prevention is discouraged within 40 days[31].

Proper patient selection for primary ICD implantation especially in asymptomatic patients with certain genetically determined cardiomyopathies e.g. ARVC and channelopathies or acquired cardiomyopathies e.g. cardiac sarcoidosis, requires risk stratification, despite which there may be a grey zone[9, 25, 73].

Table 2. ESC ICD recommendations in patients with heart failure

Recommendations	Class [a]	Level [b]
Secondary prevention An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing haemodynamic instability, and who are expected to survive for >1 year with good functional status.	I	A
Primary prevention An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA Class II–III), and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than one year with good functional status, and they have:		
• IHD (unless they have had an MI in the prior 40 days – see below).	I	A
• DCM.	I	B
ICD implantation is not recommended within 40 days of an MI as implantation at this time does not improve prognosis.	III	A
ICD therapy is not recommended in patients in NYHA Class IV with severe symptoms refractory to pharmacological therapy unless they are candidates for CRT, a ventricular assist device, or cardiac transplantation.	III	C
Patients should be carefully evaluated by an experienced cardiologist before generator replacement, because management goals and the patient's needs and clinical status may have changed.	IIa	B
A wearable ICD may be considered for patients with HF who are at risk of sudden cardiac death for a limited period or as a bridge to an implanted device.	IIb	C

Cardiac resynchronization therapy

The CRT was first introduced in 1993 by Patricia Bakker and has since become an established treatment option for patients with CHF on a background of impaired LV-EF (≤ 35%) and wide QRS[31, 74]. There is an increased susceptibility to VAs and SCD with advanced CHF[4, 31]. The implantation of defibrillator with CRT is therefore recommended, provided criteria for both ICD and CRT are met[31].The criteria for CRT implantation are largely the same as for ICD, but with additional requirement of wide QRS and consideration of CRT-P in patients in ambulatory NYHA class IV[31, 75, 76]. See table 3.

Table 3. ESC CRT recommendations

Recommendations	Class [a]	Level [b]
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	I	A
CRT should be considered for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIa	B
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	I	B
CRT may be considered for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIb	B
CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class who have an indication for ventricular pacing and high degree AV block in order to reduce morbidity. This includes patients with AF (see Section 10.1).	I	A
CRT should be considered for patients with LVEF ≤35% in NYHA Class III–IV[d] despite OMT in order to improve symptoms and reduce morbidity and mortality, if they are in AF and have a QRS duration ≥130 msec provided a strategy to ensure bi-ventricular capture is in place or the patient is expected to return to sinus rhythm.	IIa	B
Patients with HFrEF who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite OMT and who have a high proportion of RV pacing may be considered for upgrade to CRT. This does not apply to patients with stable HF.	IIb	B
CRT is contra-indicated in patients with a QRS duration < 130 msec.	III	A

Successful CRT treatment results in cardiac reverse remodelling of the left ventricle (LV); improved ejection fraction, less mitral regurgitation and lower end diastolic filling pressure in the LV[77]. These beneficial effects are likely to reduce the risk of developing VAs, but on the offset of potential increased risk of arrhythmias if the left ventricular lead is pacing in an area with myocardial scar[76, 78, 79]. The CARE-HF[80] trial confirmed reduced risk of SCD in the CRT-P arm compared to optimal medical therapy arm.

There is no clear consensus definition of CRT response[75]. However, commonly used variables include echocardiographic evidence of reverse structural remodelling (reduced left ventricular end-systolic volume by 15% and improved LV-EF) in addition to improved clinical status (NYHA, Quality of life questionnaire)[75, 81]. The CRT response rate varies due to different criteria analysed to label response. Nevertheless, studies suggest CRT response rate of 60 to 65%[82].

In the COMPANION[83] trial, the CRT-D arm had significantly lower mortality compared to groups with either optimal medical therapy or CRT-P. The trial however was not powered to compare the CRT arms against each other, but in general, mortality benefit with CRT treatment was observed. The MIRACLE-ICD[84] trial didn't show reduced mortality or heart failure hospitalisation in patients in NYHA class III-IV with defibrillator therapy in addition to active or deactivated CRT treatment. Subjective benefits of CRT were noted, but could not be verified with echocardiographic data or 6-minute walk test. The ICD function however, was not compromised by CRT. The MADIT-CRT[85] trial on the other hand, did confirm additive benefit of CRT in a heart failure cohort in NYHA class I-II. Reduced heart failure events were observed, but similar mortality rate in both arms. Both trials

confirm the importance of selective CRT implantation, bearing in mind the clinical severity of underlying heart failure.

Studies have confirmed a greater net CRT benefit for patients with QRS > 150 ms[28]. The LESSER-EARTH[86] trial, which was terminated early, confirmed the adverse effects of CRT in patients with QRS < 120 ms. The EchoCRT[87] trial set to determine the efficacy of CRT in patients with QRS < 130 ms, but with echocardiographic evidence of mechanical dyssynchrony. All patients were implanted with a CRT-D (mean QRS 105 ms), but were later randomised to have the CRT function activated or deactivated. The study was terminated early as an increased mortality was observed in the CRT arm, almost double, primarily driven by cardiovascular deaths. It was suggested that proarrhythmia may have contributed to adverse outcome, with both appropriate and inappropriate ICD therapy contributing to mortality. The rate of appropriate shock was equal in both arms, but inappropriate ICD shock was more abundant in the CRT arm. The EchoCRT trial has clarified guidelines and highlighted the importance of assessing QRS duration. However, the EchoCRT trial also questions the significance and potential harm of mechanical dyssynchrony, as suggested in the substudy[88].

To date, there is only one randomised clinical trial that has compared CRT-D to CRT-P treatment. In the Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure trial (DANISH[89], 2016), patients with NICMP (LV-EF ≤ 35%) on standard heart failure treatment including CRT when applicable, were randomised to receive ICD therapy[76]. At follow-up, all-cause mortality was not reduced in both arms (p = 0.28). Subanalysis however showed that ICD therapy was associated with a 3% absolute risk reduction in cardiac death, but on the offset of 1.5% absolute increase in device infection. Furthermore, patients under the age of 59 and patients with 'less severe' heart failure as guided by NT-proBNP level, derived mortality benefit from ICD therapy. Notably the noncardiovascular mortality rate was 31%, thus undermining the effect of ICD therapy. The trial confirms that ICD therapy should be individualised, with special consideration to age, comorbidities and frailty. These conclusions were also supported by the CeRtiTuDe[79] prospective cohort study published a year before. The outcomes of the DANISH trial have not been translated into guidelines, but in a survey study conducted at 48 device implanting centres in 17 countries in Europe, 46% confirmed that they had been influenced by the findings from the DANISH trial and as such, restricted implantation of primary preventive ICD in patients with NICMP[90].

The role of primary prophylactic ICD with CRT is a hot topic, heightened especially following the DANISH trial. In a propensity adjusted retrospective observational study, the added benefit of defibrillator to CRT was noted in ICMP, but not for NICMP[70]. Meta-analyses however have delivered diverging outcomes, with some favouring defibrillator use with CRT, even in NICMP cohorts while others have

failed to show the superiority of CRT-D over CRT-P[72, 91-94]. Results however must be interpreted with caution as many of the randomised clinical trials were not homogenous and were carried out several years ago, following which pharmacological treatment of heart failure has greatly improved. Consensus is that ICD implantation decision is at physician discretion, with patients' best interest and clinical status in mind.

Device statistics, costs and complications

Since the introduction of ICD, implantation rates have increased exponentially. EHRA statistical data from 2013 confirm regional variation, with mean implants per million inhabitants 176 in 28 EU member countries and 137 in Sweden[95, 96]. Historical ICD implantation rates in Sweden are shown in figure 7. For CRT, numbers are less compared to ICD, with mean 106 in 28 EU member countries and 100 in Sweden[95]. Subanalysis show CRT-D and CRT-P implants per million inhabitants of 44 and 17, respectively, a ratio of 2.6[95]. Data from The National Swedish Pacemaker and Implantable Cardioverter-Defibrillator (ICD) Registry further shows that in 2017, ~1,400 ICDs (inclusive of CRT-D) were implanted in Sweden of which 66% were in primary prevention[96]. In total during 2017, ~1,200 CRTs were implanted (54% CRT-D and 46% CRT-P)[96].

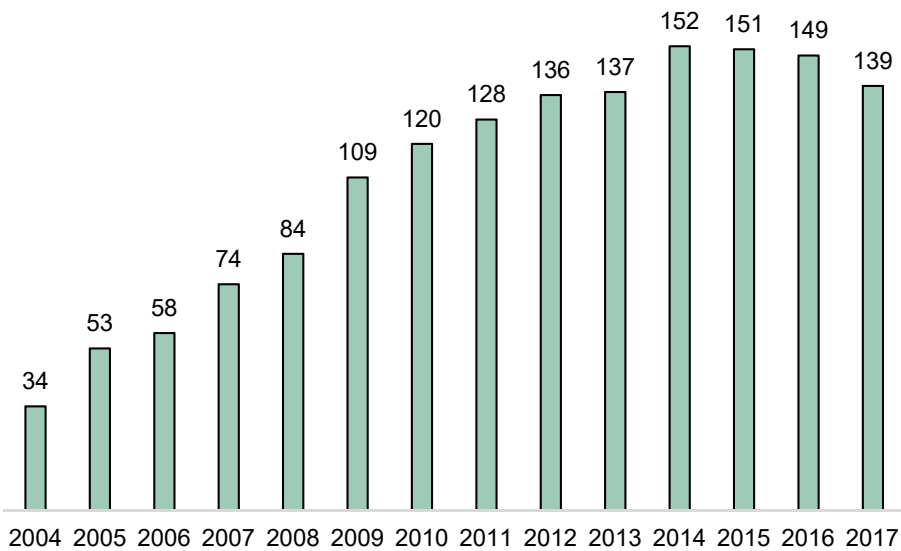

Figure 7. Historical ICD implantation rates per million in Sweden
Adapted from the Annual Statistical Report 2017[96].

The evidence for ICD and CRT treatment efficacy in appropriately selected patients is strong and as such favours widespread utilisation[4, 25, 31, 76]. This is however offset by associated high upfront device costs, though which have reduced over the last decade, with generator costs for ICD ~31,000 SEK, CRT-D ~31,000 SEK and CRT-P ~13,500 SEK. An ICD shock electrode costs ~10,500 SEK. Based on these figures, excluding perioperative and other lead costs, ICD and CRT-D device costs with shock electrode amounts to ~58 million SEK annually.

A large proportion may never experience any appropriate ICD therapy (ATP or shock), thus the net benefit of ICD is questioned. In a prospective ICD registry study, the annual risk of appropriate ICD shock therapy or appropriate ICD therapy in primary prevention cohort was 1.1% and 3.9%, respectively; and 3.8% and 8.4% in the secondary prevention cohort[97]. In another prospective ICD registry with focus on ICMP patients with primary preventive ICD, the annual risk of appropriate ICD shock therapy was 4.1% and 7.1% for appropriate ICD therapy[98].

There are also potential adverse effects of ICD implantation, which include a 3% perioperative risk of pneumothorax, perforation of the right ventricular wall, bleeding and CHF decompensation and procedure-related mortality (which does not however exceed 1%)[96, 99, 100]. Data from the Swedish pacemaker registry compared to the DANISH trial are shown in table 4, and highlights a probable under-reporting of complications in the Swedish registry. In the prospective trial, cumulative rate of serious complications were 9.8% in the ICD arm. After implantation, care must be taken in order to program the ICD to avoid ventricular pacing that can aggravate underlying CHF[101]. Inappropriate shocks due to sinus tachycardia, atrial fibrillation, non-sustained VT, lead malfunction or oversensing occur at a yearly rate of 3.8% leading to a life-time risk of inappropriate shocks approaching 1/3 in ICD recipients despite programming optimisation[102, 103]. ICD shocks reduce quality of life and have been associated with increased mortality, possibly related to adverse effects of high voltage shock itself[104]. ICD-related infection is another complication feared, with ~1.3% risk during upgrade or generator replaement[105, 106]. Once ICD-related infection is diagnosed, ICD and lead extraction are mandatory, which itself is associated with 0.28% mortality[107].

Table 4. ICD complications in Sweden for new implants and replacements compared to DANISH trial[89] (%)

Complication	2016	2017
Discontinued surgery due to hemodynamic reasons	0.1	0.0
Electrical dysfunction	1.8	1.5
Local bleeding	0.5	0.2
Perforation/tamponade	0.4	0.3
Pneumothorax	0.7	0.3
Infection/perforation	1.0	1.0
Electrode displacement	2.8	2.5
Other	0.6	0.5
Subclavian or other related thrombosis	0.2	0.0
Death	0.0	0.0
Pericardial fluid	0.0	0.1
Stroke	0.0	0.0
Total	**8.1**	**6.4**

	DANISH trial	
	ICD group	*Control group*
Device infection	4.9	3.6
Serious device infection	2.7	2.3
Bleeding requiring intervention	0.2	0
Pneumothorax	2.0	1.1
Total	**9.8**	**7.0**

Adapted from the Annual Statistical Report 2017[96] and DANISH trial[89].

Risk prediction

Proper patient selection is the key to minimisation of ICD adverse effects, improvement of risk:benefit ratio of ICD therapy and optimisation of resource utilisation. In 2001, Huikuri et al described various factors' predictive value for sudden arrhythmic deaths, see table 5.

Table 5. Indicators of an increased risk of sudden death from arrhythmia

Variable	Measure	Predictive Power
Conventional coronary risk factors High cholesterol High blood pressure Smoking Diabetes	Risk of underlying disease	Low power to discriminate the individual person at risk for sudden death from arrhythmia
Clinical markers NYHA functional class Ejection fraction	Extent of structural disease	High power to predict death from cardiac causes; relatively low specificity as predictors of death from arrhythmia
Ambient ventricular arrhythmia Frequency of premature ventricular depolarizations Nonsustained VT Sustained VT	Presence of transient triggers	Low overall power if not combined with other variables
Electrocardiographic variables ***Standard ECG*** Left ventricular hypertrophy Width of QRS complex QT dispersion	Presence of electrical abnormalities	Low power to predict death from arrhythmia
Electrocardiographic variables ***Standard ECG*** ***Specific abnormalities*** - Prolonged QT interval - Right bundle branch block plus ST segment elevation in lead V_1 (Brugada syndrome) - ST-segment and T-wave abnormalities in leads V_1 and V_2 (right ventricular dysplasia) - Delta waves (Wolf-Parkinson-White syndrome)	Presence of electrical abnormalities	High degree of accuracy in identifying specific electrical abnormalities
Electrocardiographic variables ***High resolution ECG*** Late potentials on signal-averaged electrocardiography T-wave alternans	Presence of electrical abnormalities	High negative predictive value but low positive predictive value Primary predictive value unknown
Markers of autonomic nervous function Heart-rate variability Baroflex sensitivity	Presence of conditioning factors	Exact predictive value unknown
Electrophysiological testing Inducibility of sustained tachyarrhythmia by programmed electrical stimulation	Presence of permanent substrate for ventricular arrhythmia	High degree of accuracy in specific high risk subgroups

Adapted with permission from New England Journal of Medicine, 345 (20), Huikuri HV, Castellanos A, Myerburg RJ., Sudden death due to cardiac arrhythmias, 2001[5]. © Massachusetts Medical Society.

Furthermore, Myerburg et al illustrated the relationship between incidence of SCD and the actual event rate in overall adult population[108], as shown in figure 8. In the general population there is low individual risk, but overall a large number of events as there are many individuals in this category. Subsequently in other groups, there is a progressively higher individual risk (highest with previous MI, low LV-EF and VT), but the overall number of events is less as the size of the groups becomes smaller and smaller. Thus, there is an inverse relationship in subset populations between incidence and actual events. This illustrates the difficulties in identifying the vast majority of SCDs with established risk factors as most events occur in the general population without known risk factors. In reference to numbers needed to treat (NNT), it is prudent to invest in the high-risk group, but offset by the fewer total number of preventable events. It is therefore of equal importance to identify risk markers applicable to the general population and not only to specific subgroups.

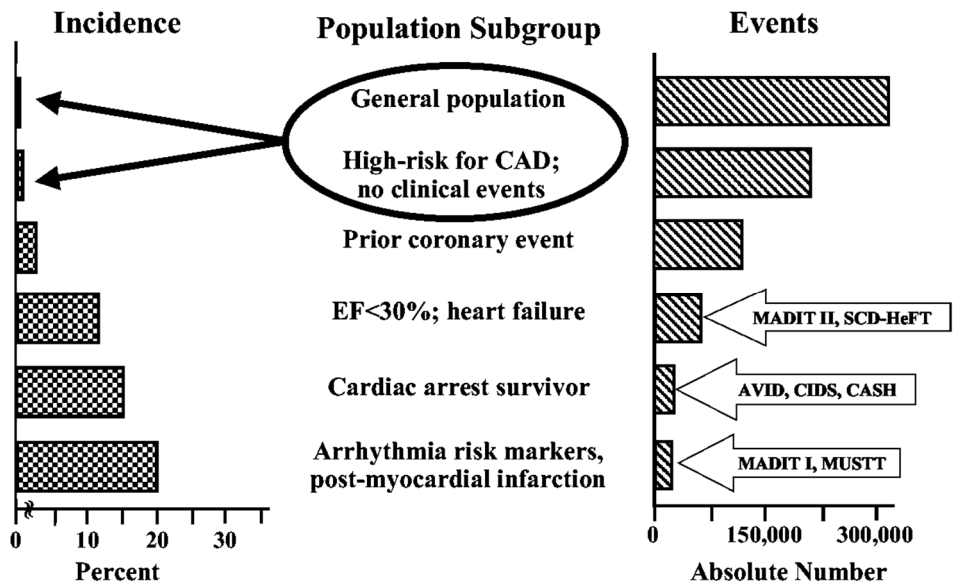

Figure 8. Sudden cardiac death; Incidence vs. occurrence over 1 year

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Earlier attempts to identify risk factors which may help pinpointing patient subgroups expected to gain the most benefit from ICD therapy were based on retrospective analyses of the large-scale trials that around 15 years ago lead to the development of current guideline recommendations. Post hoc analyses of patients enrolled in the MADIT-II trial showed that age >70 years, history of atrial fibrillation, renal failure, QRS >120 ms and NYHA class ≥ II, were significantly

associated with prognosis in a U-shaped pattern[109]. Absence of risk factors and patients with very high risk derived no ICD therapy benefit, while medium-score patients demonstrated a 49% reduction in the risk of death[109]. These findings were reproduced in a single–site register study that showed that ICD treated patients with only one risk factor had 3.4% annual mortality compared with 33% in those with 3 and more risk factors[110]. Patients without any risk factors did not demonstrate any notable mortality benefit from ICD therapy during follow-up[110]. Other studies have included diabetes mellitus, chronic obstructive pulmonary disease and peripheral arterial disease as surrogate risk markers associated with sudden death/appropriate ICD therapy in patients with primary preventive ICD, with similar conclusions drawn as from previous studies[111, 112].

Cardiac magnetic resonance imaging

In search for further VA predictors to identify patients likely to benefit from ICD intervention, studies have focused on evaluation of myocardial scar burden by CMR imaging, i.e. substrates (re-entry circuits and arrhythmogenic triggers) for recurrent VAs. In large, almost all ICMP patients exhibit fibrosis, whereas in NICMP, ~30 - 40% do[113]. Patients with late gadolinium enhancement (LGE) detected fibrosis had a significantly higher risk of adverse outcome, suggesting that evaluation of myocardial scar might serve as a predictor for better risk stratification[113-116]. Scar seems to confer a higher risk of VAs and worse prognosis both in ICMP and NICMP, but especially in ICMP patients, a detailed evaluation of the scar areas and heterogeneity of the scar may be able to further stratify the risk of VAs[113, 117-119]. LGE-CMR imaging is considered a gold standard investigative tool with high clinical yield, but this technique is fairly time consuming and expensive with variable centre specific availability, thus not utilised as a screening tool.

Periodic repolarization dynamics

The predefined substudy to EU-CERT-ICD as described on page 10 assessed Periodic Repolarization Dynamics (PRD) as a marker of mortality[120, 121]. PRD is a novel ECG-based risk marker that quantifies low-frequency oscillations of cardiac repolarisation instability. These oscillations can be extracted through mathematical algorithms from multipolar surface ECGs and are most likely caused by phasic sympathetic activation of the LV. In previous studies, increased PRD was strongly linked with arrhythmic complications, including VAs, appropriate ICD shocks and SCD[122-124]. It was therefore hypothesised that PRD may be a suitable tool in predicting ICD treatment effect on total mortality in contemporarily treated patients with ICMP and NICMP with LV-EF $\leq$ 35%. At enrolment, all patients in sinus rhythm underwent high-resolution 12-lead 24h Holter recording. The ICD derived

mortality benefit was strongly influenced by the PRD value, with low values conferring to low ICD benefit and higher levels associated with ICD benefits. With no known optimal cut-off level, it was observed that a level of 7.5 degrees enabled the best separation between responders and non-responders to ICD therapy. A PRD value of ≥ 7.5 was associated with a 75% risk reduction by ICD treatment. Furthermore, the number needed to treat, NNT, was 3.1 for PRD ≥ 7.5 and 18.3 for < 7.5. PRD was an independent predictor of appropriate ICD shock. The trial confirms that PRD predicts the mortality benefit with primary prophylactic ICD therapy and therefore may be a new novel tool to guide prophylactic ICD-implantation in patients with ICMP and NICMP. However, validating studies are called for.

QRS-T angle

ECG indices are emerging for risk prediction, particularly VCG derived. Electrical instability correlates to repolarisation changes and ventricular structural abnormalities to depolarisation changes, both of which can be measured by spatial QRS-T angle[125]. The spatial QRS-T angle is the three-dimensional angle between the mean spatial QRS-vector and the mean spatial T-vector i.e. the angle between ventricular depolarisation and repolarisation vectors[126]. In a normal myocardium, the QRS- and T-vector loops point in the same spatial direction, but with changes in ventricular depolarisation and repolarization, the vectors point in opposite spatial directions[125, 126]. A widened spatial QRS-T angle has been associated with cardiac mortality and VAs[126-129]. It is suggested that a widened QRS-T angle generates an electrical instability, which predisposes to VAs[126, 127].

The threshold value to separate normal QRS-T angle from abnormal is not universally defined. In a post hoc analysis of the DEFINITE[61] trial (described on page 9), the planar QRS-T angle (absolute difference between the QRS axis and T axis) as opposed to the three-dimensional spatial QRS-T angle, showed that an angle > 90° was independently associated with composite primary endpoint of death, appropriate ICD shock or resuscitated cardiac arrest in 25.4% of patients (adjusted HR 1.64, 95% CI 1.02–2.65, p = 0.039)[130]. Total mortality however was not significantly reduced. In an ICMP cohort with primary preventive ICD therapy, both planar and spatial QRS-T angles were assessed, > 90° and >100°, respectively[129]. The adjusted hazard ratios for appropriate ICD device therapy was 2.4 for planar QRS-T angle and 7.3 for spatial QRS-T angle, confirming the importance of measuring the QRS-T angle, but also the superiority of spatial QRS-T angle. Further analysis showed that a spatial QRS-T angle ≤ 100° could also predict appropriate therapy-free follow-up (positive predictive value 98% and negative predictive value 15%). In a prospective general population-based study (n=6,134), spatial QRS-T angles were categorised as normal 0 – 105°, borderline 105 – 135° and abnormal

135 - 180°[127]. During 6.7 years of follow-up, borderline or abnormal spatial QRS-T angles were associated with cardiac mortality, with adjusted hazard ratios of 1.7 and 3.7, respectively[127]. In another population based study (n=46,573), spatial QRS-T angles were categorised as normal 0 – 50°, borderline 50 – 100° and abnormal 100 - 180°[128]. During mean follow-up of 6 years, both borderline and abnormal spatial QRS-T angle conferred to a higher risk of cardiovascular death, with increasing divergence in angle associated with adverse outcome (> 107° HR 3.9 [CI 3.5– 4.4, $p < 0.0001$])[128].

QRS dispersion and QRS vector magnitude

QRS dispersion (QRSd) is the difference between the widest and narrowest QRS interval, as measured on 12-lead ECG, and is a marker of ventricular depolarisation[131-134]. An increased QRSd correlates to inhomogenous ventricular depolarisation, reflecting underlying ventricular pathology[131-134]. A widened QRSd has been linked to predict cardiovascular events and mortality in an asymptomatic population, cardiac mortality in CHF cohort, a near 3-fold risk of appropriate ICD therapy in cardiomyopathy cohorts with underlying bundle branch block, in addition to being an independent predictor of sudden death in ARVC patients[131-135]. In a small prospective case series with LBBB (left bundle branch block), a widened QRSd was associated with left ventricular systolic impairment[136]. There are however no standardised reference values, with values above 25 - 46 ms associated with adverse outcome[131-135]. The QRS vector magnitude (QRSvm) is a VCG derived measure of depolarisation voltage dispersion (sum of QRS amplitude peaks or troughs), a complement to QRSd. The QRSvm has in selected cohorts with Tetralogy of Fallot and Brugada syndrome shown to predict VAs[137-139]. The studies hypothesise that the dispersion of depolarisation due to ventricular pathology results in a decrease in unidirectional forces, thereby yielding a lower QRS peak magnitude[137].

T-wave vector magnitude

T-wave amplitude is measured form standard 12-lead ECGs and is a measure of ventricular repolarisation[133]. A reduced T-wave amplitude, suggestive of ventricular repolarisation heterogeneity, has been shown to predict a near 4-fold risk of appropriate ICD therapy in cardiomyopathy cohorts without bundle branch block and appropriate ICD therapy in a hypertrophic cardiomyopathy cohort[133, 140]. The T-wave vector magnitude (Twvm) is VCG derived, thus avoids potential underestimation or bias due to rotation of the main vector. It is an emerging ECG index and possibly a superior measure of T-wave amplitude. The Twvm utility has been assessed in selected cohorts[141, 142]. Twvm is a marker of hypertensive ventricular repolarisation changes (< 0.24 mV, no clinical endpoints assessed)[141]. In

females with long QT syndrome (genotype positive KCNH2 with normal QTc values), a Twvm < 0.30 mV conferred to a threefold increased risk of cardiac events A change in T-wave morphology (repolarisation) occurs secondary to cardiac pacing i.e. cardiac memory and as such, perhaps limits its use to pre-device treatment[143, 144]. However to date, no studies have evaluated the Twvm's prognostic utility in patients with CHF.

Early repolarization pattern

Shipley and Hallaran first described early ST elevation in 1936 and in 1951, Grant termed it early repolarization (ER)[145, 146]. Traditionally, ER pattern (ERP) has been considered a benign phenomenon, a normal variant with a J-wave in the QRS-ST junction[145]. In 2008 following an observational case series on IVF survivors where 31% had ERP compared to 5% in control group ($p < 0.001$), ERP gained renewed interest and even labelled as a marker for SCD[4, 9, 145, 147]. Homogenous ER definition has been lacking over the preceding decades, but lately the consensus is an end-QRS notch or slur ≥ 0.1 mV above baseline on the downslope of a prominent R-wave (J-point), in two or more contiguous inferior leads (II, III and aVF) and/or lateral leads (I, aVL, V_4-V_6) and QRS duration < 120 ms[148]. In the general population, a 13.1% prevalence has been reported with a 2- to 4- fold increased risk of cardiac mortality[149]. A diagnosis of early repolarization syndrome (ERS) is reserved for survivors of idiopathic VF and/or polymorphic VT who have ECG changes consistent with ERP[4]. In ERS and in ICD heart failure cohorts, a further increase in J-point amplitude has been observed immediately before the onset of a VA, suggesting ER is arrhythmogenic[145, 150]. The ESC guideline has taken a cautious approach and decided not to give any management advice, but ERS is recognised[4]. ERP is more commonly observed in younger males and there may be a familiar pattern, but to date, there is no method to accurately differentiate benign ERP from malignant[145].

Selvester score

In the 1960s, computer simulation of the cardiac electrical activation wave gained momentum[151]. Roland Selvester developed the Selvester QRS score in 1972 aiming to localise and quantify myocardial infarct size in the LV by 12-lead ECG recording, building on the concept that changes in ventricular depolarisation are mirrored by QRS morphology changes[151, 152]. In total 57 QRS criteria were established, representing measurements in all leads except aVR and III (10 out of 12 standard leads)[151]. A total of 32 points could be gained, with each point corresponding to 3% scar in the left ventricular myocardium, totalling to 96% of the LV[151]. The manually calculated ECG derived findings were validated with autopsy-measured myocardial

infarct size and subsequent studies verified its prognostic utility[151, 153-156]. However, the Selvester QRS didn't gain widespread clinical utility due to rather tedious manual calculations of all 57 criteria in addition to being limited to ECGs without conduction abnormalities, the latter often being observed in MI[151, 157]. But due to widened interest in establishing risk stratification tools for ICD and CRT therapy, the Selvester score gained renewed attention and even allowed for automated measurements[151, 158-160]. In 2009, together with David Strauss, the Selvester score was refined to include 46 criteria assessed over 8 leads (9 categories), and expanded for application in conduction abnormalities[157]. See figure 9. The new semi-automatic QuAReSS software, 'QUantitative and Automatic REport of Selvester Score', for use in 'strict' LBBB cohorts (see figure 10), requires manual validation of all 46 criteria and at times adjudication, nevertheless has simplified scoring and enabled quick ECG assessments[160, 161]. The QuAReSS software has previously been validated in a cohort from the MADIT-CRT trial (n= 180)[160].

LBBB		
Lead	**Critera**	**Pts**
I	any Q	1
	R/Q ≤ 1	2
	R/S ≤ 1	
	R/Q ≤ 1.5	1
	R/S ≤ 1.5	
II	Q ≥ 40 ms	2
	Q ≥ 30 ms	1
	R/Q ≤ 0.5	1
	R/S ≤ 0.5	
aVL	Q ≥ 50 ms	2
	Q ≥ 40 ms	1
	R/S ≤ 0.5	2
	R/Q ≤ 0.5	
	R/S ≤ 1	1
	R/Q ≤ 1	
aVF	Q ≥ 50 ms	2
	Q ≥ 40 ms	1
	R/Q ≤ 0.5	1
	R/S ≤ 0.5	
V1 Ant.***	NchInit40	1
	R ≥ 0.3 mV	2
	R ≥ 30 ms	
	R ≥ 0.2 mV	1
	R ≥ 20 ms	
V1 Post	S/S' ≥ 2.0	3
	S/S' ≥ 1.5	2
	S/S' ≥ 1.25	1
V2 Ant.***	NchInit40	1
	R ≥ 0.4 mV	2
	R ≥ 30 ms	
	R ≥ 0.3 mV	1
	R ≥ 20 ms	
V2 Post	S/S' ≥ 2.5	3
	S/S' ≥ 2.0	2
	S/S' ≥ 1.5	1
V5	any Q	1
	R/R' ≥ 2	2
	R/R' ≥ 1	1
	R/S ≤ 2	
	R ≤ 0.5 mV	1
V6	Q ≥ 20 ms	1
	R/R' ≥ 2	2
	R/R' ≥ 1	1
	R/S ≤ 2	
	R ≤ 0.6 mV	1
Total	Points	

Figure 9. Selvester scoring

Reprinted with permission from Journal of Electrocardiology, 44(5), Loring Z, Chelliah S, Selvester RH, Wagner G, Strauss DG., A detailed guide for quantification of myocardial scar with the Selvester QRS score in the presence of electrocardiogram confounders, 2011[153]. © Elsevier.

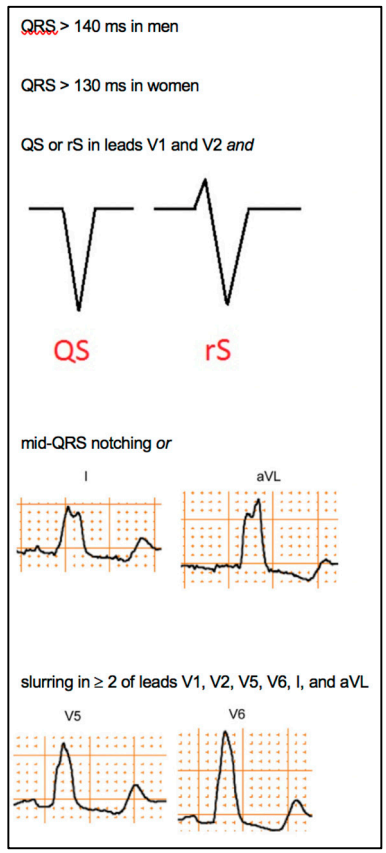


Figure 10. Strict LBBB criteria

Modified with permission from the American Journal of Cardiology, 107, Strauss DG, Selvester RH, Wagner GS., Defining left bundle branch block in the era of cardiac resynchronization therapy, 2011[147]. © Elsevier.

ECG remains the most easily available inexpensive non-invasive diagnostic modality for evaluation of myocardial scar, although with a lesser predictive accuracy than CMR[157, 162, 163]. In a CRT cohort, a higher Selvester score (> 9) i.e. higher myocardial scar burden (>27%) predicted echocardiographic non-responders (reduced reverse LV remodelling), in keeping with previous CMR verified scar data[159, 164]. The Selvester scoring is useful for quantifying transmural left ventricular scar, and has been used in combination with CMR findings in small series of patients with ICD implants for prediction of VAs[151, 157, 158, 163, 165]. In one study, the receiver operating characteristics (ROC) area was 0.91 with r=0.74 and in another ROC 0.66 with r=0.42. [157, 163]. In the latter study with ICMP and ICD therapy, an increasing Selvester score had no predictive value for VAs[163]. However, Selvester score ≥ 6 was associated with all-cause mortality. In a population-based study, Selvester score ≥ 5 assessed together with planar QRS-T angle ≥ 105°, were associated with an annual mortality of 8.8 – 13.9%[125]. The corresponding numbers for low Selvester score and narrow QRS-T angle were 3.8 – 5.5%[125]. In a substudy to SCD-HeFT[51] trial (described on page 10), the Selvester scoring was applied to the majority of the ICD arm[158]. A score ≥ 1 was associated with VAs whereas a score of 0, conferred to a 48% reduced risk of VAs. Furthermore, each 3-point (9%) increase in Selvester score was significantly related to appropriate ICD shock therapy (HR 1.14, p = 0.01)[158].

Other ECG indices

The rSr´ pattern in right precordial leads (QRS < 120 ms) has been observed in up to 7% without known heart disease[166]. It can be a benign sign, but also a marker for underlying pathology like ARVC or Brugada syndrome[166]. Diagnostic work-up algorithms have been proposed, with focus on measurement of the triangle base of the r' wave[166]. Fragmented QRS (fQRS, r' or notching of R or S wave) due to alteration of normal ventricular depolarisation is a possible marker for myocardial fibrosis. fQRS has been shown to be associated with SCD and all-cause mortality in ICMP and NICMP cohorts, with even greater risk in patients with LV-EF > 35% and QRS < 120 ms[162, 167, 168]. In selected cohorts with Brugada syndrome, it is a predictor of VAs[169].

Aims

The general aim of this thesis was to evaluate the predictive value of ECG indices for ventricular arrhythmias and mortality, in cohorts with ICD therapy.

The specific aims of the papers included in this thesis were:

I. To assess the inter-observer variability, usability and validity of the semi-automated Selvester scoring system for ECG based assessment of left ventricular scar burden in patients with left bundle branch block.

II. To evaluate LGE-CMR assessed scar burden with Selvester score derived measurements and to determine whether presence of myocardial scar can predict ventricular arrhythmias and mortality in patients with ICD therapy due to underlying congestive heart failure.

III. To assess vectorcardiography indices' prediction of ventricular arrhythmias and mortality in patients with primary and secondary prophylactic ICD therapy due to underlying congestive heart failure.

IV. To review the long-term prognosis and the predictive value of ECG abnormalities for ventricular arrhythmias in a Swedish cohort of idiopathic ventricular fibrillation survivors.

Methods

Paper I-III are based on the review of patient material from ICD recipients (including CRT-D) at Skåne University Hospital in Lund, Sweden, between 2002 – 2013, who all prior to ICD implantation underwent CMR imaging. The National Swedish Pacemaker and Implantable Cardioverter-Defibrillator (ICD) Registry was screened for ICD recipients and systematically cross-matched with medical records to identify patients with ICMP and NICMP who prior to ICD implantation did a CMR. The project was approved by the local ethics committee in Lund (Dnr 2013/236, 2014/726, 2014/65) and complies with the Declaration of Helsinki. Requirement of informed consent was waived by the ethics committee.

Paper IV is based on the review of patient material from survivors of IVF at three university hospitals in Sweden between 1988 and 2016. The participating hospitals were Skåne University Hospital in Lund (principal investigator), Sahlgrenska University Hospital and University Hospital of Umeå. The National Swedish Pacemaker and Implantable Cardioverter-Defibrillator (ICD) Registry was screened for secondary prophylactic ICD recipients and cross-matched with medical records to identify patients with IVF. The project was approved by the local committee in Lund (Dnr 2015/363) and complies with the Declaration of Helsinki.

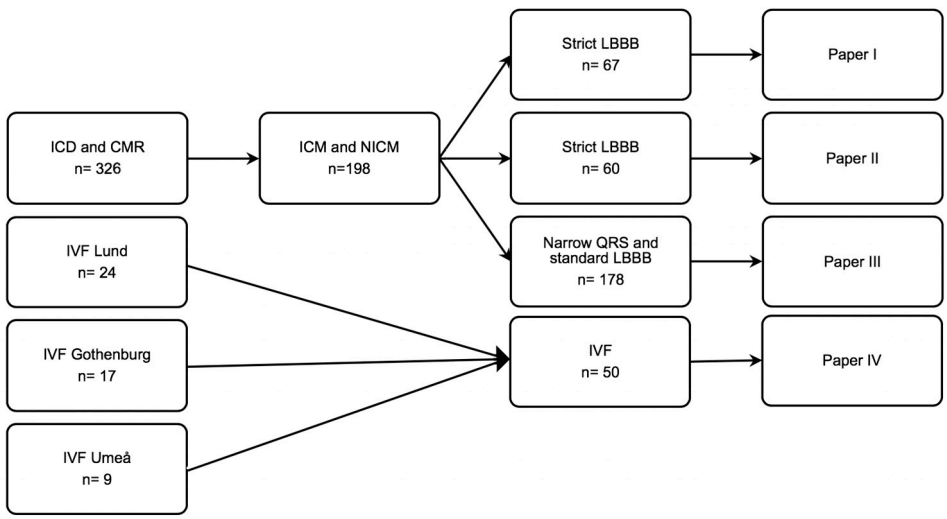


Figure 11. Flowchart of patient cohorts for papers I-IV.

Data sources

Paper II - IV are registry-based retrospective observational studies with at least 1-year follow-up period. Demographic and clinical information was obtained from electronic medical records and the National Swedish Pacemaker and Implantable Cardioverter-Defibrillator (ICD) Registry. ICD data, either from manual interrogation or remotely (Merlin®, CareLink® or Latitude®) were obtained from electronic medical records. Sustained VA was defined as ≥ 30 seconds and appropriate ICD therapy was defined as ATP or shock due to tachyarrhythmia of ventricular origin. Electrical storm was defined as 3 or more sustained episodes of VA or appropriate shocks from an ICD within 24 hours. The cause of death and primary in-hospital diagnosis were obtained from the Swedish National Board of Health and Welfare cause of death register and inpatient register. Three of the studies focus on ICMP, which was defined as (i) history of MI or revascularisation (CABG or PCI), (ii) ≥ 50% stenosis of LM or ≥ 70% proximal LAD or (iii) ≥ 70% stenosis of two or more epicardial vessels[170]. Patients not fulfilling the criteria for ICMP were classified as NICMP. Endpoints were adjudicated by a senior electrophysiologist.

Electrocardiogram

A prerequisite for study I-III was pre-device implantation digital ECG in order to avoid potential effect of cardiac pacing on electrophysiological remodelling i.e. worsening or correction of vector dispersion[143, 144]. Furthermore, patients with existing pacemaker were excluded from analysis in study I-III. In study IV, ECG prior to index event or during hospitalisation in addition to follow-up ECG (> 1 year from index) was essential. Baseline resting 12-lead ECGs were performed at 25 mm/s speed with 10 mm/mV for limb and precordial leads. Digital ECGs were retrieved from the local hospital server, MUSE and MegaCare. Study I-II was a collaborative project with the Heart Research Follow-up Program team at University of Rochester, USA, who developed the semi-automated Selvester scoring software QuAReSS. Only patients with strict LBBB as described on page 25, were eligible for semi-automated Selvester analysis. The strict LBBB ECGs were validated by the ECG core laboratory group at Duke University, USA. The VCG indices in study III were obtained automatically using the Glasgow algorithm to define the QRS and T-wave fiducial points in lead I, II, V_1 to V_6, followed by application of the Kors' regression related method to calculate spatial QRS-T angle, QRSvm and Twvm[20]. In study III, LBBB was defined as a QRS width over 120 ms with broad notched or slurred R wave in leads I, aVL, V_5 and V_6[171, 172].

Cardiovascular magnetic resonance

CMR data were used for papers II and III. CMR imaging was performed on two 1.5T scanners (Philips Achieva, Best, The Netherlands and Siemens Magnetom Vision, Erlangen, Germany). Images were analysed using the validated software Segment v1.9 (http://segment.heiberg.se)[173]. LGE-CMR images were acquired by cine imaging in breath hold, both in short axis and long axis projections collected 10–20 min after injection of 0.2 mmol/kg of a gadolinium based contrast agent. LV-EF, end-diastolic and end-systolic volumes were determined by manual delineation of the endocardium and epicardium in short axis cine images, both in end-systole and end-diastole. Scar was quantified using a semi-automatic algorithm after manual delineation of the endocardium and epicardium[174]. The regional scar distribution and burden was assessed using the American Heart Association 17-segment model[175]. Any LGE-CMR imaging of poor quality or with artefacts excluded the patient from LGE-CMR related analysis.

Statistics

All statistical analyses were performed with IBM SPSS Statistics (v. 22 and 25 IBM Corporation, Armonk, NY, USA). Continuous variables expressed as means (+/- standard deviation, SD) or median (interquartile range, 25th and 75th percentile), as appropriate. Categorical variables presented as frequencies and percentages and compared with the $\chi 2$ test. Kaplan-Meier curves were used for survival analysis, with the log-rank test for significance testing. A p-value < 0.05 was considered statistically significant.

Paper I

The ECGs with strict LBBB were digitally uploaded to the semi-automatic QuAReSS software program for assessment by two groups of cardiologists working independently from each other and blinded to clinical data and LGE-CMR based data; the clinical group and the ECG core laboratory group. The agreement between the Cardiology groups analysed ECGs and between the manual and automatic readings were evaluated by the Heart Research Follow-up Program team. The average agreement was calculated as the percentage of agreed measurements in total measurements for each of nine categories, including R-amplitude, R/R′ ratio, presence of Q wave, S/S′ ratio, R-wave duration, notched R (a notch that begins within the first 40 ms, NchInit40), Q-wave duration, R/S ratio and R/Q ratio. An agreement between readings was considered if the peak/nadir was in the exact

position for the categories R-amplitude, R/R′ ratio, S/S′ ratio, R/S ratio and R/Q ratio. Similarly, if duration of R- and Q-wave were the same and lastly if the presence or absence of Q-wave or notch at initial 40 ms were correctly identified. Following analysis of all results, in case of discrepancy between the Cardiology groups, the final score was determined by consensus.

The average score differences between ECG readings were presented as mean +/- SD. Bland-Altman plots were used to quantify and illustrate the level of consistency between adjudicated and automatic ECG readings and between Cardiology groups.

Paper II

Following ECG analysis and adjudication of results in paper I, the Selvester score results were transferred to paper II to correlate with LGE-CMR scar quantified data.

The correlation between the burden of left ventricular scar (%) by Selvester score and LGE-CMR was assessed using bivariate correlation analysis with Spearman's test. Bland-Altman plots were used to assess and illustrate any potential bias between the two scar quantification methods. Analyses were made for all patients and ICMP and NICMP subgroups. Subanalysis was done on patients with LGE-CMR scar in relation to clinical outcome (mortality or appropriate ICD therapy). ROC analysis was used to select an appropriate cut-off mark for scar burden by Selvester scoring, in relation to clinical outcome (mortality or appropriate ICD therapy).

Errata

After publication of paper II, an error in table 1 was discovered. The reported numbers of CRT-D and ICD were incorrect due to merging of two databases. However, this did not alter main results, other tables and figures. Errata has been published. The error was discovered and corrected before paper III.

Paper III

VCG indices spatial-QRS-T angle, QRSvm and Twvm vector were computed automatically from digital 12-lead ECG as previously described.

Bivariate Spearman correlation test was used to assess the internal correlation between the VCG variables, and correlation between CMR verified scar. A correlation coefficient more than 0.3 was considered significant. Due to high

internal correlation between VCG variables and pre-existing LBBB, the variables were analysed both in the entire cohort and subgroups with and without LBBB in Cox proportional hazards regression univariate analysis when evaluating potential association with primary endpoints (appropriate ICD therapy, mortality or a composite of both). If the p-value was less than 0.10, the variable was entered into a multivariable Cox regression analysis, adjusting for different sets of covariables (age, gender, aetiology of cardiomyopathy, primary or secondary prophylactic ICD, LBBB status, LV-EF, smoker, diabetes and hypertension). Survival analyses were performed using Kaplan-Meier curves for all three ECG variables (dichotomised, using ROC analysis to select an appropriate cut-off mark), with the log-rank test for significance testing and all-cause mortality as outcome.

Paper IV

All patients in the Lund cohort were invited for a follow-up clinical review with lead investigator and screening with ECG, echocardiogram and genetic testing as appropriate. Informed written consent was obtained. 12-lead ECGs at baseline and follow-up were reviewed by two electrophysiologists independently of each other and blinded to clinical outcome. Any discrepancies were adjudicated for consensus. ECGs were screened for ERP, rSr' and S-upstroke time as described on page 23, 26. Any additional repolarisation and depolarisation changes were documented.

EPS at baseline was performed according to local practice at respective sites, and included programmed stimulation from the right ventricular apex and base, with up to three progressively shortened extra stimuli until 200 ms.

Initial genetic evaluation was carried out according to local practice and varied between centres. Follow-up genetic testing in autumn 2018 was performed by XON array (CytoScan XON, Applied Biosystems, Thermo Fisher) of a panel of 115 genes associated with channelopathies and cardiomyopathies. For exome sequencing, libraries were constructed using the SureSelect XT HS Clinical Research Exome V2 (CREv2 kit, Agilent) and sequencing was performed with an Illumina NextSeq 500. Genome version GRCh37/hg19 was used as reference sequence. Genetic changes were classified as pathogenic or likely pathogenic according to the American College of Medical Genetics and Genomics (ACMG) guidelines[176].

Results

Paper I

In the base cohort, 105 had LBBB according to standard definition. Sixty-seven qualified for strict LBBB to which the QuAReSS software was applied. The mean absolute difference of Selvester scores measured by the two independent Cardiology groups, as shown in figure 12 (outliers circled), was 1.4 ± 1.5 score points (4.2 ± 4.5 % LV scar). A 66% score agreement was observed between two independent measurements when the difference of score was within 1 point range, and the agreement improved to 82% within a 2 point difference. Overall the agreement was above 72%, except R-wave duration with 24%, see figure 13. Five ECGs had a score difference of ≥ 4, all of which were rereviewed.

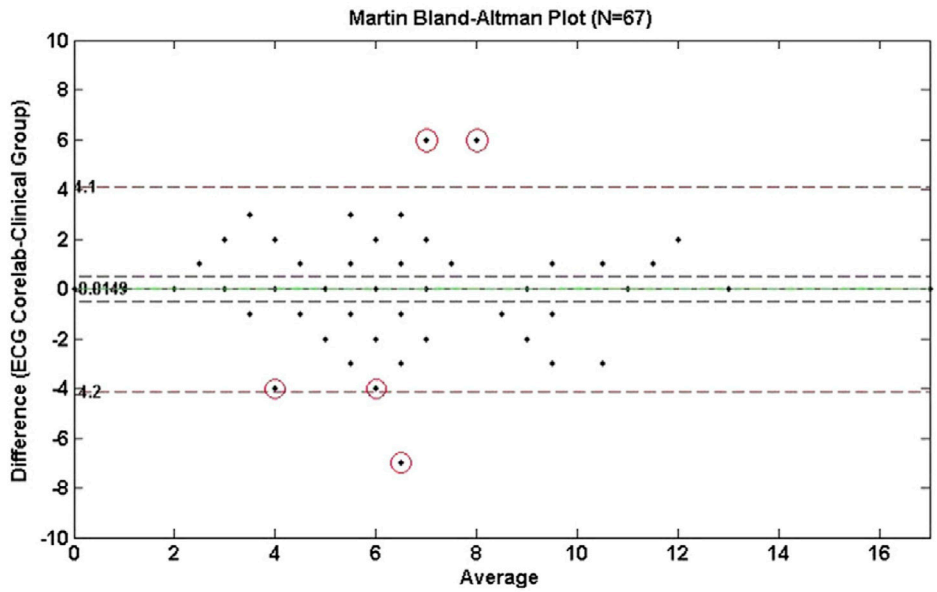


Figure 12. Differences between Selvester scores measured by the two Cardiology groups. Adapted from paper I.

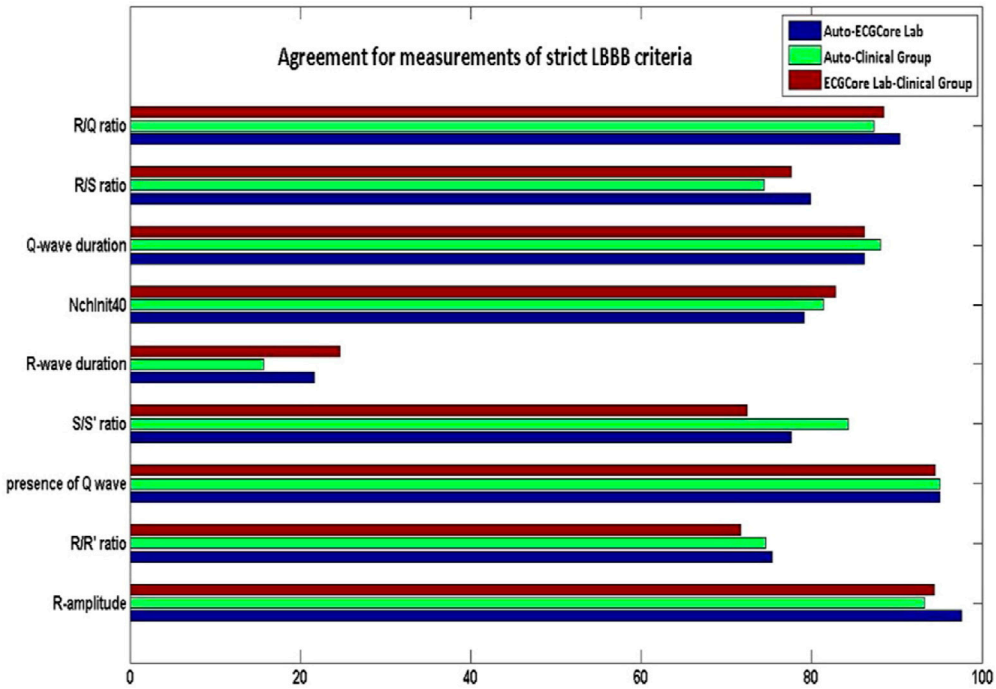


Figure 13. Average agreement on measurements between two Cardiology groups and automatic and-semiaitomatic readinggs. Adapted from paper I.

Further comparison between the automatic and two semi-automatic readings by the Cardiology groups (see figure 14) showed a mean absolute difference of Selvester scores of 1.2 ± 1.2 (3.6 ± 3.6%) and 1.3 ± 1.2 (3.9 ± 3.6%). The level of agreement was 67 - 69% with a score difference within 1 point range and 84 - 90% within a 2 point difference. Overall the agreement was above 74 – 75%, with lowest agreement for R-wave duration, 16 – 22%, see figure 13.

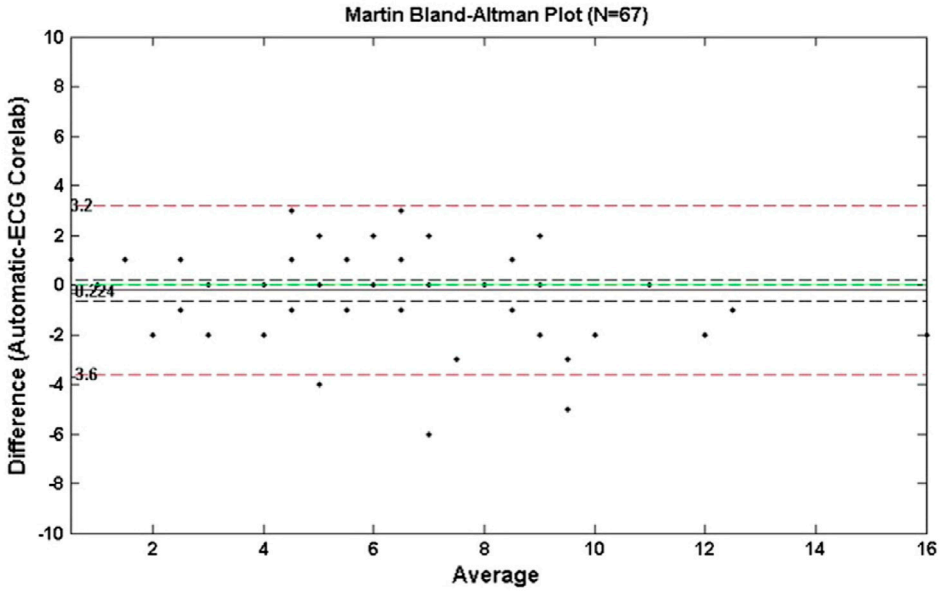


Figure 14. Differences between Selvester scores by automatic and semi-automatic readings. Adapted from paper I.

Paper II

Sixty-seven patients with Selvester scoring results from paper I were transferred to paper II. Seven patients were excluded. Baseline characteristics are shown in table 6.

Table 6. Patient characteristics. Adapted from Corrigendum paper II.

Patients (n= 60)	
Age (y), mean ± SD	65.1 ± 9.0
Men, n (%)	40 (67)
LV-EF by CMR, mean ± SD	27.6 ± 11.7
Non-ischemic dilated CMP, n (%)	34 (57)
Ischemic CMP, n (%)	26 (43)
Diabetes mellitus, n (%)	10 (17)
Smokers, n (%)	18 (30)
Hypertension, n (%)	34 (58)
NYHA class pre-ICD implant, n (%) Missing data (n=2)	
I	3 (5.2)
II	16 (27.6)
II-III	4 (6.9)
III	35 (60.3)
IV	0
Time to CMR (m), mean ± SD	7.7 ± 15.2
CRT-D, n (%)	54 (90)
ICD, n (%)	6 (10)
* CMP = Cardiomyopathy	

Patients were followed for a mean 34.6 ± 23.0 months. All patients had evidence of scar by Selvester scoring (score > 0) and 62% by LGE-CMR (n=37). The Spearman correlation coefficient for LGE-CMR and Selvester score derived scar was r=0.35 (p = 0.007). Similarly, in patients with LGE-CMR verified scar and corresponding Selvester scoring, the Spearman correlation coefficient was r=0.37 (p = 0.024). In subgroup analysis for ICMP and NICMP, the Spearman correlation coefficient was 0.39 (p = 0.047) and 0.29 (p = 0.09), respectively.

There was an overestimation of scar burden by Selvester scoring, including in absence of scar by LGE-CMR. The mean difference between LGE-CMR score and Selvester score was −13.3% ± 10.1% SD. In patients with LGE-CMR verified scar and corresponding Selvester scoring, the mean difference between LGE-CMR score and Selvester score was −11.7% ± 11.0% SD.

In ICMP, Selvester score underestimated scar burden. Selvester score based scar between 9% – 51% (median 21%) corresponded to a 11% – 33% LV scar by LGE-CMR. Conversely in NICMP, there was a tendency for overestimation of scar burden by Selvester scoring.

Fourteen patients (23%) had an event during the follow-up period; 11 (18%) deaths, and 6 (10%) adequate ICD therapies. Using the LGE-CMR based scar calculation, there was a significant trend indicating that presence of scar increased the risk of combined clinical endpoints of death or adequate ICD therapy ($p = 0.045$; Figure 15). A similar analysis could not be performed for Selvester scoring since all patients had evidence of scar by this method. Nevertheless, a 5.5 point cut-off level was obtained through ROC curve analysis, although with low diagnostic accuracy (sensitivity 57% and specificity 48%, AUC 0.60). Further survival analyses with Kaplan–Meier for this Selvester scar level cut-off confirmed the low predictive value and did not show a significant correlation with clinical outcome ($p = 0.33$).

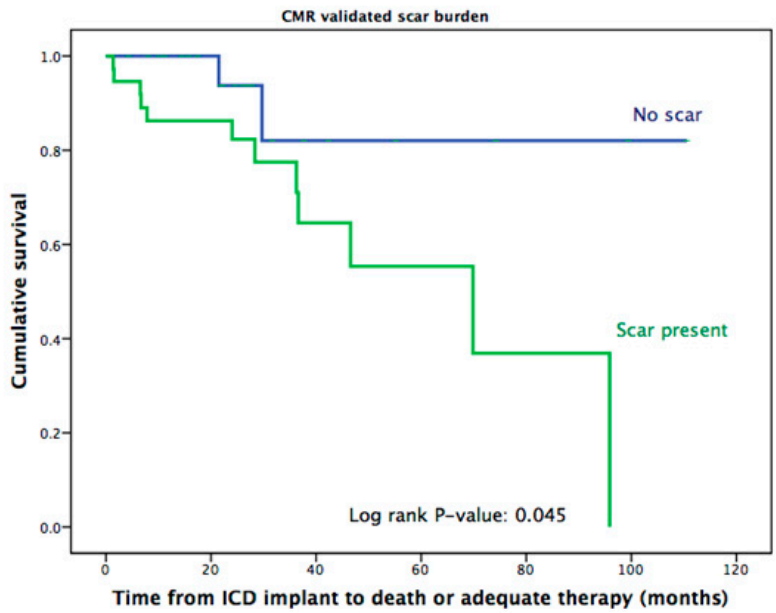


Figure 15. Kaplan–Meir survival curve for CMR patients with and without scar. Adapted from paper II.

Paper III

One hundred and seventy-eight patients were included in the study, with complete LGE-CMR scar data available for analysis in 153 patients. Baseline characteristics are shown in table 7.

Table 7. Patient snd ECG characteristics. Adapted from paper III.

Mean (SD), n (%) or median (IQ values)	All cohort n= 178	LBBB n=103	Narrow QRS n=75
Age (y)	60.5 ± 13.6	63.7 ± 11.0	56.2 ± 15.7
Men	141 (79.2)	79 (76.7)	62 (82.7)
LV-EF by CMR	27.4 ± 10.9	26.2 ± 10.4	28.9 ± 11.4
Non-ischemic dilated CMP	83 (46.6)	51 (49.5)	32 (42.7)
Ischemic CMP	95 (53.4)	52 (50.5)	43 (57.3)
Secondary prophylactic ICD	55 (30.9)	24 (23.3)	31 (41.3)
Diabetes mellitus	35 (19.6)	17 (16.5)	18 (24)
Smoker	40 (22.5)	28 (27.2)	12 (16.0)
Hypertension	95 (53.4)	58 (56.3)	37 (49.3)
NYHA class pre-ICD implant			
I	30 (16.9)	7 (6.8)	23 (30.7)
II	45 (25.3)	25 (24.3)	20 (26.7)
III	91 (51.1)	65 (63.1)	26 (34.7)
IV	3 (1.7)	0	3 (4.0)
CRT-D	83 (46.6)	82 (79.6)	1 (1.3)
ICD	95 (53.4)	21 (20.4)	74 (98.7)
Follow-up (months)	89 (70 – 119)	82 (67 – 111)	93 (79 – 126)
Sinus rhythm	142 (79.8)	84 (81.6)	58 (77.3)
Heart rate (bpm)	71.0 (61 – 87)	72 ± 17	77 ± 18
PR interval (ms)	177 (149 – 205)	178 (156 – 216)	177 ± 39
QRS duration (ms)	120 (100 – 156)	156 (130 – 168)	100 (92 – 114)
QTc duration (ms)	451 ± 34.4	462 (441 – 487)	437 (415 – 468)
LBBB	103 (57.9)	103 (100)	-
Spatial QRS-T angle	151 (110 – 165)	161 (148 – 167)	111 (69 – 145)
QRSvm	1.60 (1.23 – 2.07)	1.73 (1.39 – 2.22)	1.47 (1.04 – 1.75)
Twvm	0.39 (0.25 – 0.56)	0.49 (0.38 – 0.68)	0.27 (0.20 – 0.38)
* CMP = Cardiomyopathy			

The patients were followed for a median of 89 (IQR 70 – 119) months post ICD implant, with no patients lost to follow-up. Forty patients (23%) died during the follow-up time. Twenty-eight (16%) died due to cardiovascular causes, of which 17 (61%) were due to congestive heart failure. Fifty-five patients (31%) had adequate ICD therapy for ventricular tachycardia or ventricular fibrillation.

A larger QRS-T angle was associated with increased mortality both in univariate and multivariate analyses (adjusted for LBBB); HR per 10° 1.10, 95% CI 1.00 to 1.20, p = 0.04; HR 1.16, 95% CI 1.04 to 1.30, p = 0.01. In subanalyses in narrow QRS subgroup, QRS-T-angle was independently associated with an increased risk for composite endpoint of death and adequate ICD therapy; HR of 1.16 per 10° angle increase (95% CI 1.05 to 1.27, p = 0.004). Similar analyses for LBBB cohort were not significant.

A decreasing QRSvm was associated with increased mortality in univariate analyses; HR of 0.96 per 0.1 mV increase (95% CI 0.91 to 1.01, p = 0.09). However, this did not reach statistical significance in multivariate analysis. Subanalyses in narrow QRS- and LBBB subgroups were not statistically significant.

A decreasing Twvm was associated with increased mortality in univariate analysis; HR of 0.99 per 0.01 mV increase (95% CI 0.97 to 1.00, p = 0.06), but no statistical significance was reached in multivariate analysis. It was however evident from univariate analyses that significance in 'all cohort' for death outcome analysis was primarily due to results within the narrow QRS subgroup. In subanalysis for narrow QRS subgroup, a decreasing Twvm was associated with increased mortality and composite endpoint in univariate analysis. Twvm was also independently associated with both death and the composite endpoint of death or adequate ICD therapy in multivariate analysis; HR of 0.95 per 0.01 mV increase (95% CI 0.90 to 1.00, p = 0.04) and HR of 0.97 per 0.01 mV increase (95% CI 0.94 to 1.00, p = 0.03), respectively (see supplement table 1). In subanalyses in the LBBB subgroup, no significant values were obtained.

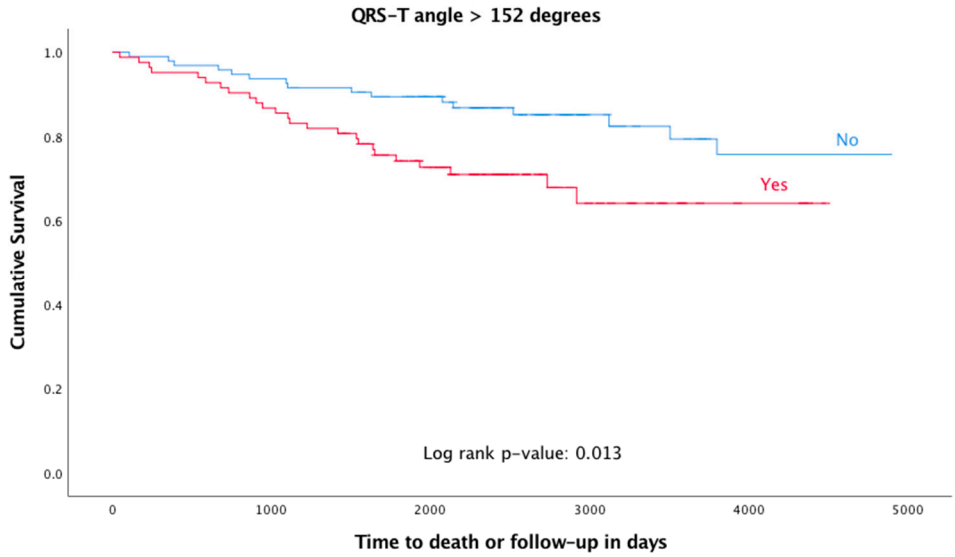
Table 8. Optimal cut-ff levels using ROC curve analysis. Adapted from paper III.

	Cut-off	Sensitivity	Specificity	AUC
QRS-T angle (°)	152	61	58	0.58
QRS vector magnitude (mV)	1.54	61	58	0.60
T-wave vector magnitude (mV) All cohort	0.38	68	59	0.63
T-wave vector magnitude (mV) Narrow QRS subgroup	0.24	59	67	0.70

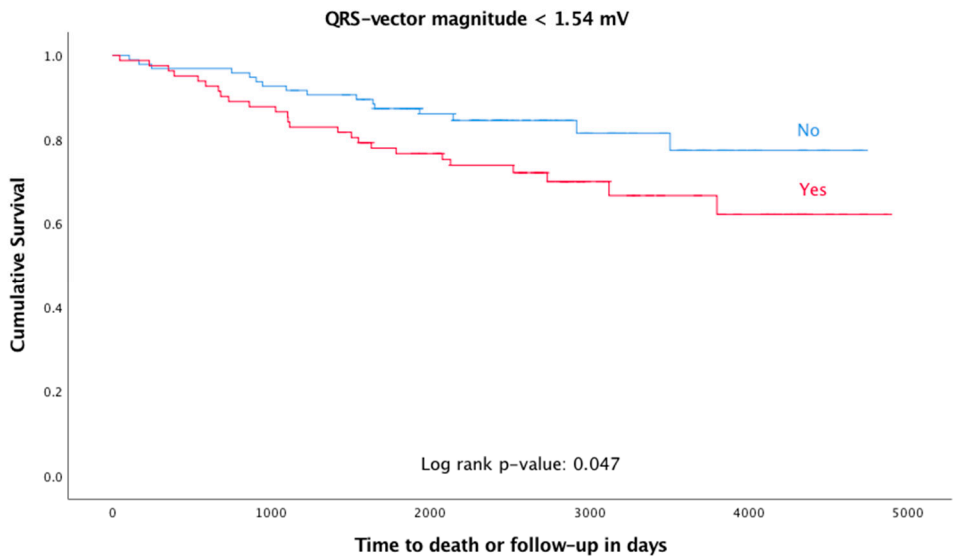
Survival analyses with Kaplan–Meier curves showed that an QRS-T angle *above* cut-off was associated with increased mortality, which was primarily driven by heart failure deaths (p = 0.017). Twvm and QRSvm *below* cut-off were associated with increased mortality. See figure 16a-c.

A combined score was constructed using all three VCG variables with ROC curve cut-off marks. A higher score (≥ 2) was significantly correlated to higher mortality, p < 0.001 (Figure 16d).

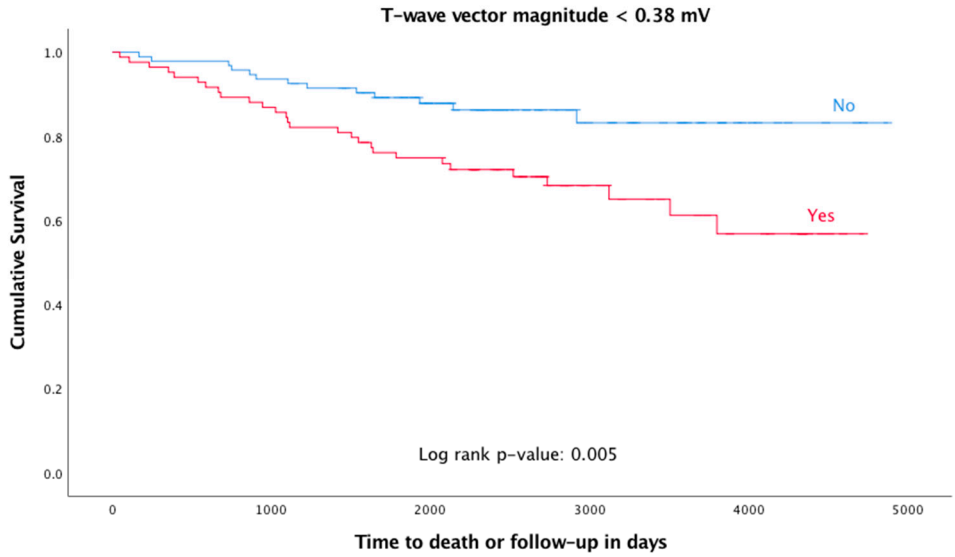
(a)


QRS-T angle > 152 degrees
Cumulative Survival
1.0
0.8
0.6
0.4
0.2
0.0
No
Yes
Log rank p-value: 0.013
0
1000
2000
3000
4000
5000
Time to death or follow-up in days

(b)


QRS-vector magnitude < 1.54 mV
Cumulative Survival
1.0
0.8
0.6
0.4
0.2
0.0
No
Yes
Log rank p-value: 0.047
0
1000
2000
3000
4000
5000
Time to death or follow-up in days

(c)



(d)

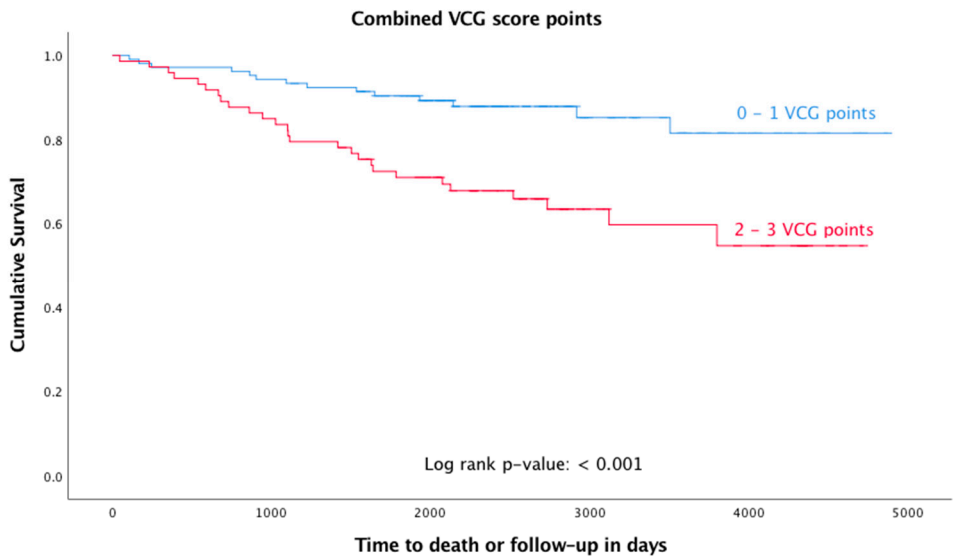


Figure 16. Kaplan–Meir survival curve for the VCG indices and combined VCG score points. Adapted from paper III.

One hundred and nine patients had LGE-CMR verified scar. QRS-T angle had no correlation to scar including in subanalysis for ICMP. However, with QRSvm and Twvm, there was a significant negative correlation between more scar, r=- 0.40 ($p < 0.001$) and r=- 0.36 ($p < 0.001$), respectively.

Paper IV

Fifty patients, followed for a median of 13.8 (QR 9.0 – 20.2) years, were included in the study. Baseline characteristics at the time of index event and investigations performed are presented in table 9.

Table 9. Baseline patient characteristics and investigations performed. Adapted from paper IV.

	Mean (± SD) or N (%)	**Normal finding n (%)**	**Abnormal finding - comment**
Age (years)	34.3 ± 13.3		
Men	28 (56)		
Hypertension	4 (8)		
Diabetes mellitus	2 (4)		
Echocardiography	50 (100)	48 (96)	2 bicuspid aortic valves
Coronary angiogram	38 (76)	34 (68)	4 subtle nonobstructive atherosclerosis
Coronary computed tomography angiography	2 (4)	2 (100)	
Cardiovascular magnetic resonance imaging	27 (54)	27 (100)	
Ajmaline test	9 (18)	9 (100)	
Signal-averaged ECG	22 (44)	22 (100)	
Endomyocardial biopsy	3 (6)	3 (100)	
Exercise tolerance test	30 (60)	30 (100) *	
Holter monitoring	12 (24)	12 (100) *	Short PQ-interval, but not seen on 12-lead ECG.
Electrophysiology studies	17 (34)	13 (76.5)	4 sustained polymorph VT or VF induced
* No sustained ventricular arrhythmia			

Seven patients (14%) received a cardiac diagnosis during follow-up, as shown in table 10. Two deaths occurred during follow-up, one from malignancy and one from acute kidney failure, but there was no reported cardiovascular mortality.

Table 10. Cardiac diagnosis during follow-up. Adapted from paper IV.

Diagnosis	Time after index event, years	Other
Restrictive cardiomyopathy	23.4	
Severe left ventricular dysfunction with EF 25%, global hypokinesia	18.4	No reported admissions for heart failure, but 3 episodes with ventricular arrhythmia, the first one after 16.1 years.
Hypertrophic cardiomyopathy	7.2	
Long QT syndrome type 2	6.9	KCNH2 mutation Baseline ECG QTc 488ms
ARVC	6.5	PKP2 mutation
Congestive heart failure	5.4	No echocardiographic data available for adjudication
Lamin AC gene positive	3.3	

Forty-seven baseline ECGs and 46 follow-up ECGs of sufficient quality recorded more than 1 year after the index event, median 10.5 (QR 6.5–18.2) years after VF date) were available for review. ECG developments during follow-up are shown in figure 17.

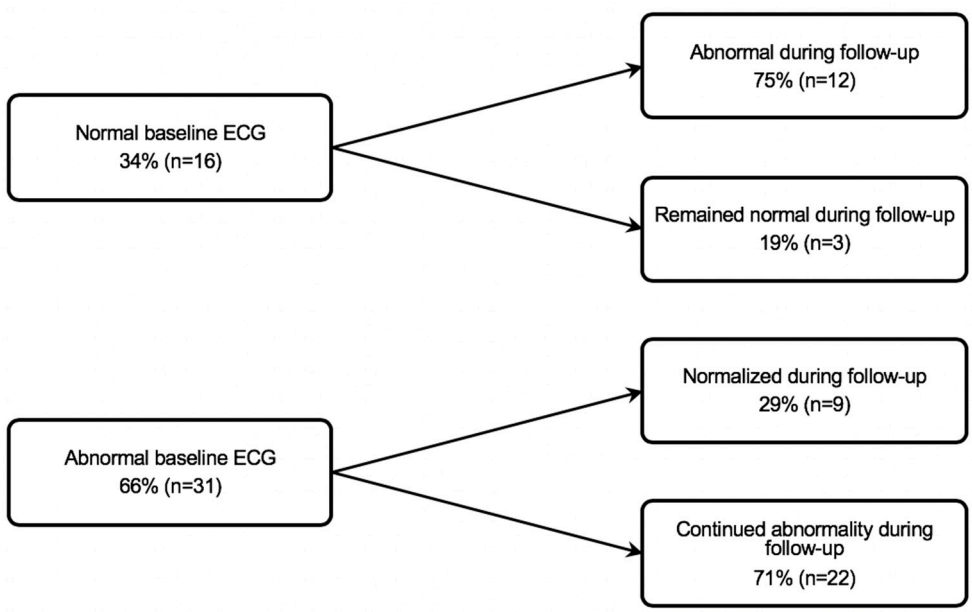


Figure 17. ECG development during follow-up. Adapted from paper IV.

Echocardiography was done in 80% (n=40) of patients during follow-up, with the latest examination at a median time of 7.9 years from index date. In all cases but

one, the ejection fraction was ≥ 50%. Targeted genetic testing at baseline or in the immediate follow-up period was done in 18% (n=9) of patients, with negative yield. During follow-up, 6.9 years after index event, one patient was diagnosed with long QT syndrome type 2 after a positive genetic yield (KCNH2 mutation). Follow-up genetic testing with a broad panel for channelopathies and cardiomyopathies were done in 12 subjects (24%). Eight of them underwent first time genetic screening and 4 had had genetic testing at baseline, but for targeted genes. Two out of 12 patients (16.7%) had pathogenic mutations diagnostic for underlying cardiac pathology as probable cause of VF; ARVC with PKP2 gene positive and LMNA gene positive. The genetic yield for disease causing mutation during follow-up was 23.1% (n=3). Variants of uncertain significance in potential disease related genes were found in 8 cases (66.7%), but according to ACMG guidelines these were not considered pathogenic (class III).

Patients were followed by device interrogations for arrhythmias for median of 12.3 (QR 8.1–19.8) years, during which 32% (n=16) of patients had recurrence of VF or sustained VT requiring ICD therapy at a median time of 1.9 years (range 0.1-20.3) from the index event; 3.1% per year. Abnormal ECG at baseline did not predict ECG-pathology at follow-up (p = 0.98), nor did it predict appropriate ICD therapy (p = 0.56). See table 11.

Table 11. ECG characteristics at baseline and follow-up in relation to subsequent adequate ICD therapy. Adapted from paper IV.

ECG characteristics at baseline	% of total cohort (n) n=47	No ICD therapy n=33	With ICD therapy n=15	ECG characteristics at follow-up n=46	% (n)	No ICD therapy n=34	With ICD therapy n=13
Normal ECG	34 (16)	10	6		28.3 (13)	7	6
ER inferior	6.4 (3)	3	0		15.2 (7)	7	0
ER lateral	6.4 (3)	2	1		8.7 (4)	3	1
Notched S upslope in V1	17 (8)	6	2		26.1 (12)	10	2
Left or right axis deviation	13.7 (6)	4	2		8.7 (4)	3	1
LBBB/RBBB	4.3 (2)	2	0		4.3 (2)	2	0
T-negative in other than V1 or III	27.7 (13)	11	2		28.3 (13)	8	5
RSR' pattern	8.5 (4)	3	1		17.4 (8)	6	2

Four patients had their ICD explanted without re-implantation of a new system. During the follow-up period pre- and post ICD extraction, no syncopal or arrhythmic events were reported requiring hospital admission. Cause for explantation was patient preference due to absence of arrhythmic events after index VF (n=2), device endocarditis (n=1) and device-related complications (n=1, further details unavailable).

Discussion

The four studies included in this thesis have ECG as a common denominator, with view of prediction of VA in ICD cohorts. Studies I-II evaluated semi-automated Selvester scoring in ICMP and NICMP cohorts with ICD treatment. The QuAReSS software is user friendly and provides valid measurements of the Selvester score in patients with strict LBBB. However, there was only a modest correlation between LGE-CMR verified scar and the semi-automated measurements by QuAReSS. Thus in its present form, it has limited clinical utility. Study III showed that the VCG indices spatial QRS-T angle, QRSvm and Twvm are independently associated with mortality in patients with reduced LV-EF due to ICMP and NICMP. Thus, the clinical applicability has a potential future in patient management. Lastly, study IV followed a cohort with IVF, a rare diagnosis. ECG changes were common, but had no prognostic value in determining the risk of VA recurrence, which was 3.1% per year. Provided ICD therapy is initiated, the prognosis is good, and applies to the vast majority of patients today.

Selvester scoring with QuAReSS software

In the preceding decades, the potential of Selvester score has been recognised and validated, despite which it has been underutilised, primarily due to practical limitations inherent to time and training associated with manual assessments of the many quantitative ECG waveform variables. In study I we have shown that semi-automatic Selvester scoring with QuAReSS is a promising new software to identify, localise and quantify presence of scar in cohorts with LBBB as per Strauss criteria. Application of the QuAReSS software requires user review and validation or adjustment when applicable of the automated criteria measurements (illustrated in figure 18), which include; positioning of the start and end of QRS complex, characterisation of the QRS morphology, localisation of the wave peak and interval, detection of notches in the first 40 ms of the QRS and lastly detection of mid-QRS notch and slur patterns. Thus, electrocardiographic experience and knowledge is mandatory. However despite the expertise, there may be diverging opinions as evident in our study, particularly for assessment of R-wave duration (overall agreement 24%). Selvester et al highlighted the importance of ECG training and further even stated that additional ECG assessments should be performed until the

level of inter-observer agreement is ≥ 90%[152]. Nevertheless, the QuAReSS is user friendly and allows for quick ECG assessments (~2 minutes per ECG analysed) with minimum manual adjustment, provided the user has preselected ECGs with LBBB as per strict criteria and has an understanding about the different QRS patterns evaluated. As a comparison, for the trained observer, manual Selvester scoring takes less than 5 minutes per ECG[157, 177]. However, to increase the clinical utility by incorporating the algorithm to commercially available ECG diagnostic programs used in standard digital ECG machines and considering the bulk of ECGs in potential screening programs, automatisation is the best option.

The QuAReSS is limited to analysis of strict LBBB only. The drawback of the software is that it cannot automatically detect strict LBBB i.e. to be used as a pre-screening test for strict LBBB. Nevertheless, with modifications, its utility may be broaden to all ECG types.

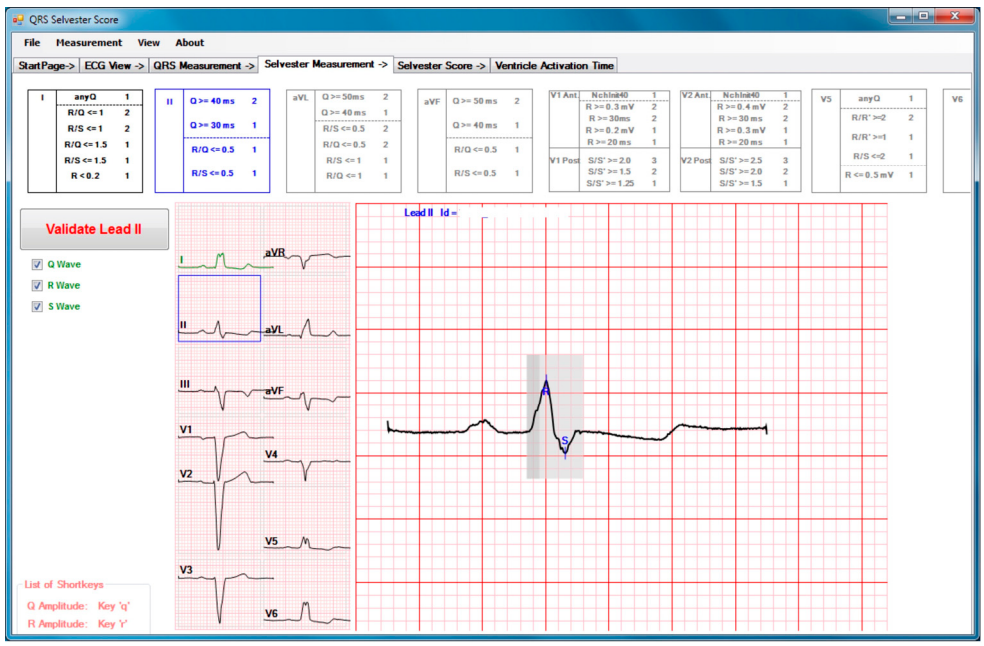


Figure 18. A screenshot from the scoring process in QuAReSS. The user is asked to validate the automated identification of the Q, R and S waves of the QRS complex in lead II (in this particular lead, there is no Q wave). User validation is required for all leads mesured, with possibility to adjust if required (blue tick marks on the curve). Following validation of all leads, a report is generated with details which criteria are met and the total Selvester score obtained. The individual criteria of the Selvester score are visible to the user, as seen on the top panel of this screenshot.

Validation of QuAReSS

Prior to study I, the QuAReSS was validated in a set of ECGs from the MADIT-CRT trial, following which the software was refined[160]. In MADIT-CRT ECGs, the inter-observer variability was not assessed, however the mean of absolute differences between automatic and adjudicated Selvester scoring was 1.2 ± 1.5 points (3.6 ± 4.5%), comparable to the results in our study[160]. The QuAReSS can potentially facilitate the clinical use of the Selvester scoring system, broaden its application for risk assessment and prognostic purposes in selected cohorts due to the advantage of being easily accessible, non-invasive and inexpensive. However, the 2009 refined Selvester criteria have been met with critique due to the low specificity for the 46 criteria assessed, compared to corresponding LGE-CMR reference data with absence of myocardial scar[178]. Thus, casting a shadow on the potential of QuAReSS[178]. The QuAReSS, though unique for strict LBBB, is not the first attempt on automatisation of the Selvester score. In 1988, Pope et al showed a high correlation between automated and manual scoring (r=0.94) in a 54-criteria/32-point Selvester scoring system[177]. The mean difference between methods was -0.2 ± 1.2 points, with identical ECG matched scores in 54%[177]. The goal was to incorporate the algorithm into clinically-used ECG systems, but perhaps due to difficulties with precise and reproducible measurements, compounded by lack of validation, the automatisation concept dissolved. Similarly, the automated Selvester scores by Haisty et al (1992), Horacek et al (2006) and Bono et al (2014) didn't gain any momentum[179-181]. Nevertheless, the QuAReSS is different as it is a one-step model and requires only one software, which enables manual adjustment and validation by the user i.e. semi-automated measures.

New LBBB criteria – the implications

In study I-II, strict LBBB criteria was applied, but we decided against this in study III as the proposed criteria have not achieved widespread recognition nor have guidelines been updated[182]. The conventional LBBB criteria have for many decades been a QRS width over 120 ms with broad notched or slurred R wave in leads I, aVL, V_5 and V_6[171, 172]. The importance of LBBB, a sign of electrical dyssynchrony, has been heightened following introduction of CRT therapy. The CRT ECG eligibility criteria as per guidelines are straightforward with reference to both QRS duration and LBBB QRS morphology, but doesn't elaborate on the latter[28, 31]. The new strict LBBB evolved on the notion to identify myocardial scar and thus improve CRT responders. Our study cohort was however mixed, with both ICD and CRT-D, with no outcome measures specifically for CRT therapy arm. Previous studies have suggested that about 1/3 of patients diagnosed with conventional LBBB may not

have true LBBB, but likely have a combination of left ventricular hypertrophy and left anterior fascicular block[161]. The QRS width redefined for men and women, were extrapolated from subanalysis of CRT responders in the MADIT-CRT trial[161]. The gender threshold difference is attributed to that men have larger hearts which take longer to depolarise[161]. In study I, 105 patients were identified with standard LBBB, however after application of the new strict LBBB criteria, 67 eligible patients were identified. Thus, about 1/3 were excluded (36%). Largely patients were eliminated on basis of QRS duration.

Selvester score vs. LGE-CMR

The original Selvester score was recognised because of its strong correlation with histopathological verified myocardial infarct size (r=0.72 – 0.80, n=72)[154-156]. Subsequent CMR studies in small cohorts with ischemic heart disease (absence of conduction defect) have tried to mirror these findings with variable results (r=0.33 – 0.79)[165, 183-188]. In our study, a modest correlation between LGE-CMR verified scar and the semi-automated measurements by QuAReSS was observed (r=0.35). Selvester score had low correlation with LGE-CMR findings in patients with absence of scar or with very high burden of scar. The latter is less of a problem since a distinction between 30% and 50% scar is not as pivotal as compared to distinction between presence or absence of scar, a surrogate marker for arrhythmic substrate. The Selvester score was more robust for scoring in ICMP (n=26, r=0.39), with comparable data to a study by Carlsen et al from 2012 (r=0.41, n=55)[189]. Our findings however were not in keeping with another similar study with a mixed ICMP and NICMP cohort (n=162), some with ECG confounders; correlation between new 2009 Selvester criteria and LGE-CMR was 0.74[157]. However, subanalysis showed that, similar to our data, in the NICMP subgroup, the Selvester score correctly identified absence of scar in only 51%[157]. This was a limiting factor, but the correlation was still significant at 0.60, compared to our non-significant level of 0.29[157]. In the strict LBBB arm, the correlation was strong, r=0.80 (n=32)[157]. It is difficult to speculate on such diverging results, however, limiting factors may be differences in standards for measuring the infarct size by LGE-CMR and Selvester score.

Over- and underestimation of scar

Our results confirmed an overestimation of scar by Selvester scar in NICMP, even in absence of scar by LGE-CMR. Particularly ECG changes in leads V_1, V_2, and V_5 were responsible for 39% of all scar points in patients with positive Selvester score but no scar on CMR. Small R-waves in leads V_1 and V_2 often exceeded threshold values for positive scoring, even when there was no scar tissue, as did the R/R′ ratio over 1 in lead V_5. Our findings are in keeping with Åkerlund et al who investigated

the new Selvester scoring manually against LGE-CMR data with absence of myocardial scar[178]. In 27 of the 46 criteria, the specificity met ≥ 95%[178]. Thus, further refinement or perhaps even elimination of some of the non-specific criteria is necessary[178]. Notably in the original Selvester scoring, all criteria were modified until at least 95% specificity was achieved[152]. It is however plausible that other pathophysiological mechanisms like electrical instability not detected by CMR affects the Selvester score[157]. Moreover, the distribution of scar is different in NICMP (patchy, subepicardial or midmyocardial), which may further affect the Selvester score[164].

Although the correlation for Selvester score and LGE-CMR was significant in our ICMP subgroup, there was a tendency for underestimation of scar by Selvester score, which was also observed by Strauss et al[157]. In our study, patients were classified as ICMP without any further subanalysis to determine regional MI distribution. Strauss et al however showed that the Selvester score was more robust for detecting single-territory infarcts (88%) compared to two distinct MI areas (60%)[157]. If both large and small infarcts were present, the Selvester score only detected the larger[157]. This further shows that Selvester score is limited and perhaps better suited for segmental single coronary artery territory analysis, similar to the histopathological validated findings from the 1980s[154-156].

Other studies evaluating Selvester score in single reperfused coronary artery territory infarct area have shown both over- and underestimation of myocardial scar by Selvester score[165, 184, 185, 189-191]. The overestimation of MI size by Selvester score may partly be due to advent of reperfusion treatment. The original Selvester score measured the MI size in acute and chronic non-reperfused MI[152]. Since then, early reperfusion therapy has become mainstay. Knippenberg et al re-evaluated the quantitative relationship between Selvester score and reperfused MI[191]. In the study, Selvester score measured reperfused MI size was significantly correlated with a conversion factor of 2% for each point for small to moderate sized infarcts (undefined), and 3% for large infarcts (undefined) [151, 191]. Thus, suggesting that Selvester score may not be linearly related to MI size as previously thought[191].

ECG indices and scar

At present, there are no standardised reference levels to separate normal from abnormal, or low risk from high risk for the ECG indices assessed in study II and III. Therefore cut-off levels were obtained using ROC curve analysis.

In study II, a major limiting factor was the positive Selvester scar quantification despite absence of scar by the gold standard LGE-CMR. We obtained a cut-off level of 5.5 points corresponding to 16.5% LV scar, albeit with low sensitivity and

specificity i.e. not optimal. In an ideal setting, in absence of scar, a marker with higher specificity balanced with an optimal sensitivity is warranted. Nevertheless, at the 5.5 cut-off level, no correlation to clinical outcome was observed. Previous studies with Selvester score however have shown that values ≥ 5 (in combination with planar QRS-T angle ≥ 105º) correlates to mortality in the general population. Interestingly, in a risk population with ICMP and ICD therapy, a similar score, ≥ 6 was also associated with adverse outcome[163]. Our results did confirm the adverse effects of LGE-CMR verified scar. The Kaplan–Meier curves separated early (within the first year) and then continued to stay separate. This highlights the importance of myocardial scar screening, especially in risk patient groups

In study III there was no correlation between widened QRS-T angle and scar burden (including a subanalysis for ICMP), despite it being a marker for both structural and ion channel changes. This was in contrast to a study by Shi et al, where scar of ischemic aetiology was associated with wider QRS-T angle[192]. On the other hand, a negative but significant correlation was observed with both lower QRSvm and Twvm and scar burden. As there are no previous studies that have evaluated the association between the latter two VCG indices with scar, one can only hypothesise. Myocardial scar is likely to influence ventricular depolarisation due to shift and dispersion of QRS vectors during depolarisation of viable myocardium around the scar[91]. Furthermore, increased scar burden may be associated with myocyte loss (reduced myocardium to depolarise) and hence smaller vectors. In acute MI patients undergoing treatment with thrombolysis, an increased T-wave amplitude was associated with lower 30-day (5.2% versus 8.6%, p = 0.001) and 1-year mortality, suggesting that T-wave amplitude and perhaps even Twvm is influenced by scar size[193].

Predictive value of ECG indices and ECG changes

Univariate results for the LBBB cohort were not statistically significant. Potentially the existent depolarisation abnormality with bundle branch block and resultant vector changes, may have negatively affected further calculations for depolarisation and repolarisation ECG indices. A decreasing Twvm was independently associated with death and the composite endpoint of death or adequate ICD therapy, including in subanalysis for narrow QRS subgroup. The cut-off levels obtained were with moderate sensitivity and specificity at 0.38 mV and 0.24 mV, respectively. The latter being similar to threshold obtained in a cohort with hypertension and narrow QRS, though which did not assess any clinical endpoints[141]. A decreasing Twvm was associated with increased mortality (figure 16c, p = 0.005). For QRSvm, a cut-off level of 1.54 mV was obtained with low to moderate sensitivity and specificity. In two unique cohorts, Brugada syndrome and Tetralogy of Fallot, cut-off levels of

1.55 mV and 1.31 mV, respectively, were reported[137, 139]. Our data showed that a level < 1.54 mV was associated with increased mortality. However, the association of QRSvm to mortality was not significant in multivariate analysis. Lower QRSvm value did not confer to increased risk of adequate ICD therapy, which has been previously reported in a cohort with Brugada syndrome[139]. There is until now no published data on patients with CHF, but in a cohort of patients with Tetralogy of Fallot, lower QRSvm was associated with inducibility of VAs[138], and with perioperative atrial tachycardias[137].

In comparison to Twvm and QRSvm, there are more studies that have evaluated QRS-T angle, both planar and spatial. The difficulties that arise are the different thresholds for abnormality. In our cohort a level of 152° was identified with low to moderate sensitivity and specificity. Values above cut-off were however significantly correlated to mortality. In our study, every 10º increase in QRS-T angle was associated with a 16% raised risk of adverse outcome ($p = 0.01$), in keeping with previous reported data[194]. Furthermore, widened QRS-T angles have been shown to (independent of conventional cardiovascular risk factors) predict a 5-fold increased risk of cardiac death[127]. Our results did not show an association between widened QRS-T angle and adequate ICD therapy, in contrast to Borleffs et al who found a 7-fold increased risk of adequate ICD therapy, adjusted for covariates in a cohort with ICMP and spatial QRS-T angle > 100° (n=412)[129].

Combining all VCG scores i.e. one point for each value above or below ROC curve cut-off marks as appropriate (total 3 points), confirmed the additive benefit of the VCG indices. Score points ≥ 2 was significantly correlated to higher mortality, $p < 0.001$.

IVF cohort outcome

In study IV we followed a Swedish cohort with IVF, a diagnosis which may pose therapeutic and prognostic challenges[195]. During the follow-up period of 14 years, mortality rate was 4%, none of which were due to a cardiovascular cause. The clinical outcome however, remains uncertain as studies have reported VA recurrence rates of 11–45%[196]. In our cohort, the recurrence rate was 32% over a median of 12.3 years, which translates to an annual risk of recurrent VA to 3.1%, near-similar to findings from a meta-analysis (5%)[26]. A cardiac diagnosis with known association to increased risk of VAs was confirmed in 14% during follow-up. In patients with established long QT syndrome, ARVC and LMNA, the initial VF event was most likely a manifestation of the subsequent underlying cardiac diagnosis. In ARVC patients, there is a phase of arrhythmia risk without manifest cardiac structural changes[197]. Cardiac arrest may have been the first manifestation of disease in patients who subsequently developed dilated or hypertrophic

cardiomyopathy, but this is speculative as all had normal LV function and morphology at discharge after the index event. Two patients were found to have non-obstructive bicuspid aorta. There is little data correlating the presence of a bicuspid aortic valve with VAs and cardiac arrest, but a possible association cannot be ruled out.

Depolarisation and repolarisation changes were observed, both at baseline and at follow-up, but neither had predictive value for future ventricular arrhythmic episodes nor for subsequent cardiac diagnosis. ERP was seen in 12.8% of cases at baseline, similar to data from an epidemiological study where 13.1% was reported[149]. At follow-up, nearly 1/4 had ERP. But both baseline and follow-up ERP were not significantly associated with VAs or ICD therapy. This is in keeping with other IVF studies[145, 198]. Therefore, in view of our results we are hesitant to label the IVF survivors in our cohort with ERP with ERS, although, according to ESC guidelines, they should be[4]. Similarly, rSr´ pattern observed had no predictive value, including in patient diagnosed with ARVC.

Extensive cardiac investigations were performed at all three centres at baseline, a necessity to diagnose IVF[4, 25]. However, the amount of investigations performed at baseline and during follow-up varied significantly and this calls for standardisation. Considering the relatively young IVF population (mean age 34), a hereditary cause for VF could be the primary diagnosis in a significant proportion of cases. In our cohort, a low proportion underwent genetic testing; 18% at baseline and 24% at follow-up despite rapid developments in the area. There are presently more known disease-causing mutations and lower costs for genetic testing compared to when screening initially emerged. This has potential implications for the patients and their relatives as there is an uncertainty, a grey zone encompassing IVF diagnosis. Though a small proportion underwent genetic screening during follow-up, our results show a modest diagnostic yield for common known genetic variations for channelopathies and cardiomyopathies (23.1%) in keeping with a recent study by Broendberg et al, where the diagnostic yield for disease causing mutation was 24% (n=19/80)[24]. Variants of uncertain significance (class III) in arrhythmogenic disease associated genes, is a common finding, including in our cohort. Potentially they could be associated with diseases that may unmask an underlying cardiac disease causing cardiac arrest.

ECG timing

The 12-lead ECG, though a good screening tool is a measurement of depolarisation and repolarisation at a single point of time i.e. representative of the disease stage at a single point of time. Cardiac disease processes including substrates however evolve with time and are dynamic and as such, ECG changes are variable. This is

highlighted in study IV were pathological ECG findings subsequently normalised and vice versa. This can be translated to that the risk of suffering from VAs is dynamic, requiring both a trigger and a substrate. Although the ECG changes observed in study IV had no predictive value, they confirm the importance of repeat ECG measurements as single point measurements are not sufficient to cover the whole spectrum of dynamic evolvement over the years. Moreover, the timing of ECG acquisition is also of importance, both in VCG indices (QRS-T angle, QRSvm and Twvm) and in Selvester scoring. Infarct related QRS and T-wave morphology changes takes time to evolve in phase with myocardial remodelling and therefore ECG evaluation peri-infarct may not be representative of vector dispersion and scar burden[183, 186]. The optimal timing for ECG is however unknown, but repeat ECG assessments are necessary, both for re-evaluation and in risk stratification models, especially in cohorts not equipped with ICD. For example, subjects with unexplained syncope but without structural heart disease who do not meet the criteria to qualify for ICD implantation but have de facto aborted SCD as the cause of syncope.

Limitations

In this thesis four studies are included, all of which are retrospective observational registry based. Study I-III are single centre and due to pre-defined ECG inclusion criteria, the original base cohort was narrowed down, thus perhaps underpowering the study. We analysed a subset of patients with ICM and NICMP and thus cannot make a generalised statement for Selvester score and VCG in other patient cohorts, which have to be validated in future studies.

The ECGs analysed were pre-device implantation i.e. VCG values obtained were before ICD implantation. Therefore it is unknown if the VCG indices change in relation to pacing or resynchronization therapy. Thus our findings may not be applicable to existing ICD cohorts if the patients are paced. The Selvester score however is inapplicable on paced ECGs due to changed QRS morphology. The ECGs used in the study were representative of the disease stage at the time, however one needs to bear in mind that both ECG changes and cardiac disease processes are dynamic. Furthermore, optimal ECG timing and assessment, especially in reperfused MI patients is unknown, but highlights the importance of serial ECG measurements.

The Selvester scoring is easily utilised, but the semiautomatic computerised scoring program (QuAReSS software) is limited in its applicability due to the prerequisite of a strict LBBB inclusion criterion. Modifications are called for in order to include all ECG morphologies.

For the VCG indices, univariate results for the LBBB cohort were not statistically significant and reasons for this are only speculative. Ideally the VCG indices should be further assessed in a larger ICD study population, comparing subjects with narrow QRS and LBBB in order to determine the impact of LBBB on QRS- and T-wave vector dispersion. Thus, perhaps establish whether the VCG indices are applicable to narrow QRS cohorts only or has wider utilisation. Furthermore, the reference values for the VCG indices are not known and warrant further validation.

Study IV is a multi-centre study, despite which the sample size was small. Most likely this is a reflection of the rarity of the disease. Some patients were lost to follow-up. Data from the Swedish National Board of Health and Welfare hospital discharge registry were used for adjudication. But potential ICD therapies could theoretically have been missed if the patient was not hospitalised for arrhythmia as

coded diagnoses from out-patient are difficult to interpret without clinic notes to hand for adjudication. Some, but not all baseline ECGs were acquired early after the cardiac arrest and therefore the impact of drugs and post resuscitation therapy on abnormal ECGs changes are unknown. The proportion of patients undergoing genetic testing was low, in part due to that clinical diagnostic follow-up was only done in 24% of patients. However, it should be noted that in the 1990s, routine genetic investigation was not initiated in this patient cohort. Not all patients were offered, or accepted invitation to, comprehensive clinical follow-up visits (apart from ICD interrogation follow-up, which was 100%). Non-participation in clinical follow-up may reflect that patients have accepted their IVF diagnosis and simply want to continue to live as normally as possibly without further reminders of their underlying cardiac disease.

Conclusions

- The QuAReSS software provides valid automatic measurements of the Selvester score in patients with strict LBBB as per Strauss criteria. Thus, potentially, the QuAReSS could deliver broad application of the Selvester score.
- There is a modest correlation between LGE-CMR and Selvester score verified myocardial scar. LGE-CMR based scar burden is correlated to clinical outcome, but Selvester score quantified scar burden is not. The Selvester scoring algorithm needs to be further refined in order to be clinically relevant and reliable for detailed scar evaluation in patients with strict LBBB.
- The spatial QRS-T angle, QRSvm and Twvm magnitude are relatively new VCG indices which are independently associated with mortality in patients with reduced LV-EF due to ICMP and NICMP. The VCG variables can be automatically computed from standard 12-lead ECG and could potentially be utilised in risk prediction models.
- IVF is a rare diagnosis with a 3.1% risk of recurrent VA per year. The mortality was 4% during follow-up, none due to cardiovascular cause. Thus IVF has a good prognosis provided ICD therapy is initiated. IVF survivors are recommended to undergo routine clinical follow-ups e.g. with genetic screening and echocardiography due to potential late emerging cardiac diagnosis associated with initial cardiac arrest, which also has implications for first degree relatives. ECG changes are common, but have no prognostic value in determining the risk of VAs recurrence. Screening for genetic diseases has previously been low, and this calls for improvement, especially since cheaper and more comprehensive genetic panels are now readily available.

Future perspectives

We have shown that computer-assisted semiautomatic Selvester scoring is an emerging screening tool for detection of scar without performing LGE-CMR, and potentially could become an accessible and inexpensive tool. It allows quantification, but in relation to clinical outcome compared to LGE-CMR, the latter provides more clinical and diagnostic information. The additive information from LGE-CMR- and Selvester QRS scoring in context with measurement of left ventricular function and assessment of functional class may provide more accurate prognostic information and allow for better selection of patient groups that may benefit from ICD therapy. In view of our results, it is evident that in order for the software to be reliably and extensively used as a clinical alternative to CMR imaging for ECG based scar prediction, the Selvester scoring needs higher specificity and perhaps also an increased sensitivity for those with high scar burden. At present a set of 46 criteria is used to characterise the myocardial scar tissue. It is possible that a more accurate score could be obtained if some of the less specific criteria of the score were modified or omitted. Moreover, the Selvester score should be modified to include semiautomatic ECG interpretation of both conventional LBBB (QRS ≥ 120 ms) and non-LBBB ECG morphologies.

With the advent of digitalisation of ECG and new sophisticated algorithms, the potential scope of ECG diagnostic utility has expanded. The QRS-T angle, QRSvm and Twvm are relatively new quantitative ECG measures which could potentially easily be automatically computed from clinically-used ECG systems without necessary manual user validation, thus increasing the clinical utility. We have shown that the VCG indices are associated with adverse outcome in a mixed cohort with ICMP and NICMP treated with ICD therapy. Furthermore, in combination with myocardial scar evaluation, total VCG score points and other clinical risk factors, they may provide additive prognostic information. In addition, the patient needs to be able to balance the advantages and disadvantages of ICD therapy. Thus evaluation of ECG risk markers in combination with other clinical risk factors may guide patient decision. Though our results are promising, external validation in larger prospective studies is warranted.

In study IV we followed a Swedish cohort of IVF survivors. We have shown the importance of clinical re-evaluations as some patients received a cardiac diagnosis with a plausible link to initial VF arrest, despite extensive investigations at baseline.

Genetic screening is essential as highlighted by the established disease causing mutations behind cardiac arrest in our study. Although the IVF survivors are unequivocally treated with an ICD, an established diagnosis further guides patient management and may also have implications for screening of first degree relatives. A proportion of genetic test results were consistent with variants of uncertain significance (class III) i.e. unknown clinical significance. Potentially they could be associated with diseases that may unmask an underlying cardiac disease associated with cardiac arrest. Nevertheless, continued liberty with genetic screening in cardiac arrest survivors with IVF is recommended, both for diagnostic purposes but also to determine the future prospect of pathogenicity or not for patients with class III genetic mutations. Moreover, standardised care for IVF survivors is called for, both at baseline and at clinical re-evaluations.

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