Henri Terho

ELECTROCARDIOGRAPHIC RISK MARKERS FOR CARDIAC EVENTS IN MIDDLE-AGED POPULATION
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Academic dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium 3 of Oulu University Hospital, on 15 November 2019, at 12 noon

UNIVERSITY OF OULU, OULU 2019
Cardiovascular diseases are the leading cause of death in developed countries. Approximately 50% of these events are due to sudden cardiac death (SCD) and often without preceding diagnosis of cardiac disease. Many risk factors for cardiac events have been identified and prevention strategies have improved markedly.

The aim of this thesis was to evaluate the usability of the 12-lead electrocardiogram (ECG) to predict cardiac events. The study population consisted of 10,904 middle-aged general population subjects with ECG recordings between the years 1966–1972 with a long follow-up (30±11 years).

The first part of the thesis (I) focused on the prevalence and prognostic significance of fragmented QRS complex (fQRS). The prevalence of fQRS was 19.7%. Fragmented QRS complex did not predict mortality in subjects with no history of cardiac disease. Among subjects with underlying cardiac disease and lateral fQRS, the risk of cardiac death was 2.5-fold (P=0.001) and the risk of SCD was almost 3-fold (P<0.004).

Other major electrocardiographic abnormalities were assessed in subjects without known cardiac disease for the risk of cardiac death, SCD and hospitalization due to coronary artery disease (II, III). Abnormal ECG was moderately associated with cardiac death after 10 and 30 years of follow-up (hazard ratio 1.7, P=0.009; hazard ratio 1.3, P>0.001, respectively) (II). The risk of hospitalization was not associated with abnormal ECG findings. Abnormal ECG moderately predicted SCD during 10 and 30 years of follow-up (hazard ratio 1.6, P=0.052; hazard ratio 1.3, P=0.007) (III). The risk of SCD was 3-fold when ≥2 ECG abnormalities were present.

In conclusion, lateral fQRS in middle-aged subjects with underlying cardiac disease was associated with increased risk of death. Certain abnormal ECG findings associated with the risk of non-arrhythmic cardiac mortality and arrhythmic death. The risk of arrhythmic mortality was substantially elevated when multiple ECG abnormalities were present in middle-aged population.

Keywords: cardiac death, electrocardiography, follow-up studies, fragmented QRS-complex, risk prediction, sudden cardiac death
Tiivistelmä
Sydänsairaudet ovat yleisin kuolinsyy kehittyneissä maissa. Noin 50 % näistä kuolemista aiheutuu äkillisestä sydänpyyhdyksestä, suuri osa ilman aiempaa tietoa sairaudesta. Useita sydänsairauksien riskitekijöitä on tunnistettu ja ennaltaehkäisy on kehitetty merkittävästi.


Ensimmäisessä osajulkaisussa (I) tutkimme QRS-kompleksin fragmentointia sydänperäisissä sydänsairauksissa. Fragmentointeen QRS-kompleksin esiintyvyys oli 19.7 %. Fragmentointutut QRS-kompleksi ei lisännyt koalauksen riskiä henkilöillä, joilla ei ollut sydänsairauksia. Henkilöillä, joilla oli todettu QRS-fragmentointi, lisääntyi sydänperäisen kuolemaa 2.5-kertaiseksi (P=0.001) ja rytmihäiriöperäisen kuolemaa 3-kertaiseksi (P=0.004).

Tutkimme muiden poikkeavien EKG-lyööntien ennustavuutta vallitsevasta ja sairaalahoidon tarpeesta seppelvalmistokokouksen vuoksi (II, III). Poikkeavien EKG-muutosten esiintymisen liittyvän sydänperäisen koalauksen riski sekä 10- vuoden (riskitiheyysuhde 1.7, P=0.009) että 30- vuoden seurannassa (riskitiheyysuhde 1.3, P<0.001) (II). Poikkeavat EKG-muutokset eivät ennustaneet sairaalahoidon tarpeisuutta. Poikkeava EKG ennusti sydänperäisen koalauksen riskiä sekä 10- vuoden (riskitiheyysuhde 1.6, P=0.052) että 30- vuoden seurannassa (riskitiheyysuhde 1.3, P=0.007) (III). Äkkikuoleman riski oli 3-kertainen henkilöillä, joilla todettiin ≥ 2 EKG-poikkeavuutta.


Asiasanat: fragmentointunut QRS-kompleksi, riskiarvio, seurantatutkimus, sydänperäinen kuoltisuus, sydänsähkökäyrä, äkkikuolema
To Enni, Eemeli and Aapeli
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8.9.2019 
Henri Terho
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AP</td>
<td>angina pectoris</td>
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<tr>
<td>ARVC</td>
<td>arrhythmogenic right ventricular cardiomyopathy</td>
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<tr>
<td>AV node</td>
<td>atrioventricular node</td>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>BrS</td>
<td>Brugada syndrome</td>
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<tr>
<td>CAD</td>
<td>coronary artery disease</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CMR</td>
<td>cardiac magnetic resonance</td>
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<td>CVD</td>
<td>cardiovascular disease</td>
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<td>DM</td>
<td>diabetes mellitus</td>
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<tr>
<td>ECG</td>
<td>electrocardiography</td>
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<tr>
<td>ER</td>
<td>early repolarization</td>
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<td>ERS</td>
<td>early repolarization syndrome</td>
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<tr>
<td>fQRS</td>
<td>fragmented QRS complex</td>
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<td>GWA</td>
<td>genome-wide association (study)</td>
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<tr>
<td>HCM</td>
<td>hypertrophic cardiomyopathy</td>
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<tr>
<td>HDL</td>
<td>high-density lipoprotein</td>
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<tr>
<td>HF</td>
<td>heart failure</td>
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<tr>
<td>HR</td>
<td>hazard ratio</td>
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<tr>
<td>ICD</td>
<td>implantable cardioverter/defibrillator</td>
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<tr>
<td>IDI</td>
<td>Integrated Discrimination Increment</td>
</tr>
<tr>
<td>IHD</td>
<td>ischemic heart disease</td>
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<tr>
<td>IVCD</td>
<td>intraventricular conduction disturbance</td>
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<tr>
<td>LBBB</td>
<td>left bundle branch block</td>
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<tr>
<td>LDL</td>
<td>low-density lipoprotein</td>
</tr>
<tr>
<td>LQTS</td>
<td>long QT syndrome</td>
</tr>
<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
</tr>
<tr>
<td>LVH</td>
<td>left ventricular hypertrophy</td>
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<tr>
<td>MI</td>
<td>myocardial infarction</td>
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<tr>
<td>NSTEMI</td>
<td>non-ST segment elevation myocardial infarction</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>QTc</td>
<td>heart rate-corrected QT interval</td>
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<tr>
<td>RBBB</td>
<td>right bundle branch block</td>
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<tr>
<td>RR</td>
<td>relative risk</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>SA node</td>
<td>sinoatrial node</td>
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<tr>
<td>SCA</td>
<td>sudden cardiac arrest</td>
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<tr>
<td>SCD</td>
<td>sudden cardiac death</td>
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<tr>
<td>SPECT</td>
<td>single photon emission tomography</td>
</tr>
<tr>
<td>SQTS</td>
<td>short QT-syndrome</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST-elevation myocardial infarction</td>
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<tr>
<td>TWI</td>
<td>T-wave inversion</td>
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<tr>
<td>VF</td>
<td>ventricular fibrillation</td>
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<tr>
<td>VT</td>
<td>ventricular tachycardia</td>
</tr>
<tr>
<td>WPW</td>
<td>Wolff-Parkinson-White disease</td>
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List of original articles

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:


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1 Introduction

Cardiovascular diseases (CVD) are the leading cause of death in Western countries, accounting for up to 30% of all deaths, and sudden cardiac death (SCD) is responsible for approximately 40–50% of these events (Mehra, 2007). In the United States alone, this accounts for up to 450,000 annual deaths, meaning millions of deaths globally (Adabag, Luepker, Roger, & Gersh, 2010). Coronary artery disease (CAD) is the most common cardiac disease predisposing to SCD. Fatal CAD events have declined substantially over the past several decades due to improved primary and secondary prevention (Fox, Evans, Larson, Kannel, & Levy, 2004). However, the global burden of cardiovascular diseases remains substantial. Therefore, medical professionals and scientists are striving for better risk evaluation methods to prevent premature deaths.

As SCD is considered a multifactorial event and often occurs with no preceding symptoms, the risk prediction is under constant evaluation (Huikuri, Castellanos, & Myerburg, 2001). Well over a century ago, Willem Einthoven developed a method to study electrical activity of the heart known as electrocardiogram (ECG) (Wellens & Gorgels, 2004). At the present era, ECG is still one of the most used diagnostic tools worldwide in clinical medicine for diagnosing acute coronary syndromes, arrhythmias, disturbances in the conduction system of the heart and in genetic cardiac diseases predisposing to arrhythmia. In addition, 12-lead ECG is widely used for scientific purposes aiming for better understanding, prediction and prevention of SCD and non-arrhythmic cardiac events (Aro et al., 2017; Deo et al., 2016; Waks et al., 2016).

During the most recent decade of ECG studies, fragmented QRS complex (fQRS) has been suggested as a risk marker for cardiac mortality and SCD (Das & El Masry, 2010; Rosengarten, Scott, & Morgan, 2015). However, a great majority of these studies had study participants with known heart disease such as coronary artery disease, heart failure and cardiomyopathies (Das et al., 2007; Korhonen et al., 2010; Pei et al., 2012). Our aim was to study the prevalence and prognostic value of fQRS in a general population sample for cardiac mortality. At present, there is an obvious need for better risk prediction for SCD. Consequently, we studied multiple risk variants observed in ECG in an effort to improve current risk models to predict fatal cardiac events in subjects without known cardiac disease.
2 Review of the literature

2.1 Cardiovascular diseases - morbidity and mortality

Cardiovascular diseases are the leading cause of mortality and morbidity despite advanced screening and treatment (Moran et al., 2014; Piepoli et al., 2016). The primary prevention of ischemic heart diseases (IHD), the most relevant part of the CVD disease group, has shifted the onset of these diseases to older ages (Moran et al., 2014). However, changing lifestyle, economic stress and other factors in low- and middle-income regions may lead to increased morbidity and mortality of IHD among middle-aged populations. The Global Burden of Diseases, Injuries, and Risk Factors is a systematic international study from 187 countries, 21 regions and 20 age groups of both sexes to evaluate disease burden of 291 different diseases and injuries (Murray et al., 2012). The number of disability-adjusted life years was used to measure the disease burden and was the sum of years of life lost and years lived with disability. Cardiovascular and circulatory diseases accounted for 11.8% of global disease burden and 5.2% were due to IHD. In the U.S, the prevalence of CVD in individuals $\geq 20$ years of age is estimated at 9.0% when including coronary artery disease, heart failure and stroke, and 48.8% if elevated blood pressure is included (Benjamin et al., 2019). The prevalence of CVDs increases with age in both genders. The mortality rates due to CVDs have dropped dramatically, up to 60–70%, in three decades (Mensah et al., 2017).

In 2016, cardiovascular diseases were responsible for approximately 17.6 million deaths globally, and CAD accounted for 43.2% of deaths attributable to CVDs (Benjamin et al., 2019). The prevalence of CAD (International Classification of Diseases 10th edition codes I20-25) in the U.S is 7.4% for males and 6.2% for females among population $\geq 20$ years of age with obvious age dependence. This disease group involves different clinical manifestations of impaired coronary circulation such as angina pectoris chest pain (AP), myocardial infarction (MI), and chronic ischemic heart disease. In the U.S. alone, the annual incidence of MI is estimated at 805,000, of which 200,000 are recurrent (Benjamin et al., 2019). The average age of MI in males is 65.6 years and in females 72.0 years.

During the past two decades, the incidence of ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI) in the U.S have declined up to 24%, and the incidence of STEMI alone decreased from 133/100,000 to 50/100,000 (Yeh et al., 2010). Statistics Finland maintains a
national registry of causes of death. From the early 2000 to 2016, the age-adjusted mortality for ischemic heart diseases in Finnish population declined markedly in both sexes: from over 250/100,000 to slightly over 100/100,000 in women and from over 450/100,000 to under 300/100,000 in men (Statistics Finland, Causes of Death, 2016).

2.1.1 Risk factors and prevention of coronary artery disease

As mentioned previously, the CAD is the most relevant single manifestation of CVDs. Coronary artery disease refers to accumulation of atherosclerotic plaque in the coronary arteries (Khera & Kathiresan, 2017; Shapiro & Fazio, 2016). From the 1980s to the turn of the millennium, the age-adjusted death rate dropped approximately 50% in both sexes (Ford et al., 2007). About half of this improvement is attributed to treatments, such as secondary prevention of CAD, while the other half is attributed to changes in risk factors such as reduced serum cholesterol, blood pressure, smoking and physical inactivity. However, increases in the body mass index (BMI) and the prevalence of diabetes are responsible for a negative development of deaths due to CAD (Ford et al., 2007).

The cellular and molecular basis of normal endothelial function and repair is a complex cascade of numerous enzymes and signaling pathways regulating intracellular Ca2+ and smooth muscle relaxation (Winzer, Woitek, & Linke, 2018). Endothelial function has a major role in regulating vascular tone and proliferation of smooth muscle tissue. Disturbed endothelial function leads to progressive infiltration of cholesterol in the arterial walls and remodeling of smooth muscle, ultimately resulting in a narrowed coronary artery and deficient blood flow. In the case of myocardial infarction, the surface of this plaque is ruptured, and the blood flow is decreased substantially, inducing lack of oxygen peripherally from the site of the event, causing death of myocytes and impaired pumping function of the heart.

The onset of this event begins early in life and many factors are responsible for the manifestation of CAD at some point of life. There is no single risk factor to lean on for predicting the risk of CAD. The risk of CAD is considered to depend on genetic background and lifestyle factors. Traditional risk factor of CAD are male gender, age, high blood pressure, hypercholesterolemia, diabetes, insulin resistance, and smoking (Assimes & Roberts, 2016). A recent review on physical activity and CAD prevention indicated the importance of good physical fitness, resulting in up to 20% decrease of cardiovascular events and elevation of life expectancy by up to 5 years (Winzer et al., 2018). Familiar hypercholesterolemia is a genetic disorder
of decreased uptake of low-density lipoprotein (LDL) into hepatocytes (liver cells) leading to markedly increased LDL concentration in the circulation (Harada-Shiba et al., 2018; Nordestgaard et al., 2013). In homozygous disease, subjects usually develop CAD under the age of 20 years and in heterozygous disease, at the age of 50 or above if not properly treated.

For many decades, lowering serum cholesterol with statin therapy has been the first line of treatment, and studies have found it cost-effective in primary and secondary prevention (Pearson, 1998; Taylor, Huffman, & Ebrahim, 2013; Wenger, 2014). It has been suggested that 10% reduction of serum cholesterol decreases CAD mortality by 15% and total mortality by 11%. Depending on the drug and dosage, statins lower blood cholesterol, especially LDL, by 30 to 50% and raise levels of high-density lipoprotein (HDL) concentration, therefore, lowering the risk of CAD substantially (Pearson, 1998; Wenger, 2014). Treatment of hypertension and decreased smoking in the community have had a positive impact on the prevalence and incidence of CAD. However, the current trend of increased prevalence of diabetes, obesity and blood pressure are major issues in modernized countries decelerating the prevention of CAD (Laslett et al., 2012). In the era of genetic research, the risk of CAD is under great interest. A Finnish Genome-Wide Association Study (GWA study) in 2010 estimated that up to 20% of individuals who are at roughly 70% risk of a first coronary artery disease event could be identified using a genetic risk score (Ripatti et al., 2010).

2.1.2 Sudden cardiac death – epidemiology, etiology and genetics

Sudden cardiac death is defined as unexpected death due to cessation of spontaneous circulation, generally within one hour after the onset of symptoms in a person with no prior clinical condition to explain the event (Zipes & Wellens, 1998). This definition includes variations depending on whether the event was witnessed or unwitnessed. In this thesis, we used the definition of the Cardiac Arrhythmia Pilot which is in line with the generally accepted classification of SCD events (Greene et al., 1989). This classification is greatly needed to separate SCD from other fatal cardiac events, for example myocardial infarction, in which preceding symptoms such as chest pain often occur.

The mechanism of SCD is regarded multifactorial and the chain of events leading to devastating outcome is not completely understood. Sudden death is a continuum of cardiac arrhythmia, most often preceded by ventricular tachycardia (VT) advancing to ventricular fibrillation (VF) leading to asystole (loss of pulse),
collapse of cardiac output, syncope and death if rapid intervention (e.g. defibrillation) is not received (Chugh et al., 2008; Huikuri et al., 2001; Zipes & Wellens, 1998). The initiation and continuation of arrhythmia need both a substrate and trigger to occur (Kusmirek & Gold, 2007). In most of the cases, the predisposing agent for ventricular arrhythmias, such as CAD, myocardial scar, cardiomyopathy and/or ion channel abnormality, can be detected with thorough clinical examination. However, in 5–13% of SCD cases, the predisposing factor is not obvious (Chugh, Kelly, & Titus, 2000; Kusmirek & Gold, 2007). Myocardial ischemia, ventricular ectopia, fluctuation of ventricular volume/pressure (pulmonary embolism, cardiac tamponade), the activity of the autonomic nervous system, electrolyte/metabolic variation and proarrhythmic drugs can serve as triggers leading to ventricular arrhythmias and SCD (Kusmirek & Gold, 2007). Coronary artery disease and its complications are responsible for the majority of SCD events. It has been noted that 80–90% of the SCD victims above 45 years of age have marked CAD with significant male dominance, whereas CAD is associated with SCD in 13–42% in the age groups of 20–30 and 30–40 years, respectively (Chugh et al., 2000; Shen et al., 1995).

During the past century, the number of fatal cardiovascular events has declined by as much as 70% (Mensah et al., 2017). Medical therapies to prevent CAD and improvements in the treatment of acute CAD events are major factors in this positive trend (Ford et al., 2007). These include multiple factors, such as initial revascularization after myocardial infarction (MI), secondary prevention to reduce recurrent events, and treatment of heart failure and unstable angina pectoris AP. However, SCD events accounting for approximately half of cardiovascular mortality still affect 4–5 million individuals annually (Adabag et al., 2010; Chugh, 2017). Prospective studies suggest that the incidence of SCD ranges from 50 to 100 per 100,000 in the general population (Deo & Albert, 2012).

The prevention strategies of SCD beyond traditional risk management of known risk factors are still a major challenge for clinical physicians. The main reason for the difficulty of predicting SCD is the multifactorial nature of these events (Huikuri et al., 2001; Zipes & Wellens, 1998). Because of structural coronary arterial abnormalities, epidemiological surveys have demonstrated that up to 80% of fatal arrhythmia events can be explained by either acute myocardial ischemia exposing to ventricular tachyarrhythmia or ventricular tachyarrhythmia related to myocardial scarring, generally indicating previous myocardial infarction. Subjects with dilated or hypertrophic cardiomyopathy are at high risk for SCD, as are those with valvular diseases and genetic ion-channel alterations. Even though
high-risk subjects are relatively easy to identify in general practice, the vast majority of SCD events occur in asymptomatic individuals with neither prior cardiac disease nor other known exposing agent for arrhythmia (Goldberger et al., 2008; Huikuri et al., 2001). It has been proposed that of SCD events, 45% occur in those without known cardiac disease with poor predictability, 40% in those with cardiac disease and preserved cardiac function (left ventricular ejection fraction [LVEF] >40%), 13% in subjects with cardiac disease and reduced LVEF, and 2% in those with genetically based arrhythmic disease (Wellens et al., 2014).

Fig. 1. The relation between the incidence and total number of sudden cardiac deaths in different populations. Published with permission of Woltsens Kluwer Health (Myerburg, Kessler, & Castellanos, 1992).

As the incidence of SCD increases substantially alongside with CAD, elderly population is more vulnerable to SCD in both men and women regardless of race or sex (Zipes & Wellens, 1998). Men are at 3 to 4 times higher annual risk for SCD compared to women in all age groups. It has been demonstrated that a great proportion of women suffering SCD have no prior cardiac disease or abnormal autopsy findings (50% or even up to two-thirds), whereas in men with SCD, structural heart disease or abnormal autopsy finding is more often present to explain the event (50% to 76%) (Chugh et al., 2008; Deo & Albert, 2012). Consequently, among cardiac arrest survivors, women seem to have less structural heart
abnormalities compared to men. With respect to race, the incidence of SCD seems to be higher and the survival rates from cardiac arrest poorer among black population in both men and women (Deo & Albert, 2012; Hayashi, Shimizu, & Albert, 2015). Sudden death is a rare event in children and those cases often are accompanied by congenital disease as a substrate for the event (Meyer et al., 2012).

Among adolescents and young adults, physical exercise is held as a predisposing factor for unexpected SCD. Approximately 20 to 25% of SCD cases among young subjects occur during physical exercise and in most of these cases, an underlying cardiac disease can be determined (Gajewski & Saul, 2010). The incidence of exercise-related SCD events is somewhat underestimated and is thought to be underestimated (Maron, 2003). In sports-related SCD events among young athletes, the most common structural abnormalities are hypertrophic cardiomyopathy (HCM) and congenital coronary artery anomalies, accounting for over 40–50% of all cases, and a great majority of these events occur in males (Maron et al., 1996; Maron, 2003). Multiple other predisposing cardiac conditions include valvular anomalies, Marfan’s syndrome, arrhythmogenic right ventricular cardiomyopathy (ARVC), myocarditis, dilated cardiomyopathy, left ventricular hypertrophy ([LVH] without criteria for cardiomyopathy) and CAD. As for the 2% with neither abnormal autopsy findings nor other explanation for SCD, these subjects are thought to have possible ion-channel disorders such as Brugada syndrome (BrS), long QT-syndrome (LQTS) and Wolff-Parkinson-White disease (WPW) exposing to arrhythmia (Maron, 2003; Priori et al., 2003; Wilde & Amin, 2018). Regarding exercise-related SCD events in young population, commotio cordis, referring to nonpenetrating external force to the chest, is held as a major risk factor for SCD (Maron, Gohman, Kyle, Estes, & Link, 2002). Moreover, a family history of SCD is found as a significant risk marker in the population (Friedlander et al., 1998; Jouven, Desnos, Guerot, & Ducimetiere, 1999).

As pointed out above, the majority of SCD and SCA events occur in subjects without a known underlying cardiac disease. The GWA studies, investigating single-nucleotide polymorphisms and their relationship to certain diseases, are regarded as a revolution of genetic research (Manolio, 2010). These studies have shown promising results on genetic testing and risk stratification of SCD (Albert et al., 2010; Arking et al., 2011). In 2018, the largest GWA study thus far was published to identify potential loci associated with SCA and to identify risk factors causally associated with SCA (Ashar et al., 2018). A total of 3,939 cases and 25,989 controls were examined. This study did not find evidence on arrhythmia genes associated with SCA in the general population. However, during the past decade
the field of genetic testing has taken dramatic steps towards definitive understanding of genetic disorders predisposing to arrhythmias and SCD. This field of research is considered as one of the most promising directions for future risk stratification (Wellens et al., 2014).

### 2.1.3 Heart failure and ventricular function

The LVEF is probably the most used variable of cardiac function in clinical trials and in clinical practice. In heart failure (HF) the LVEF is reduced due to structural and/or functional cardiac abnormality, and detecting the underlying cause of HF is crucial for proper treatment (Ponikowski et al., 2016). In most cases, the cause of HF is due to myocardial abnormalities; however, valvular, pericardial, endocardial, heart rate and conduction abnormalities can also lead to decreased systolic/diastolic ventricular function. In the early stage of HF, most subjects are asymptomatic although decreased ventricular function could be present. The early symptom of HF is usually atypical shortness of breath in physical exercise and fatigue. Ankle swelling may occur in progressed disease. The New York Heart Association (NYHA) classification is widely used to determine the extent and severity of HF. The estimated prevalence of HF in the adult population is 1–2% and ≥10% among people >70 years of age (Ponikowski et al., 2016).

Subjects with decreased systolic ventricular function are at increased risk for SCD, and the severity of the dysfunction is associated with worse outcome (Maggioni et al., 2013; Middlekauff, Stevenson, Stevenson, & Saxon, 1993). Reduced LVEF significantly modifies the impact of other factors related to SCD; however, there is no evidence of direct interaction between LVEF and arrhythmia mechanisms (Wellens et al., 2014). The depressed LVEF in post-MI patients is proposed as a risk factor for increased mortality. In a study in the early 1980s, a total of 866 post-MI patients underwent 24h Holter monitoring and ejection fraction was determined (Multicenter Postinfarction Research Group, 1983). One-year cardiac mortality in subjects with LVEF <20% was greatly elevated, whereas those with preserved (>40%) LVEF had a low risk for the endpoint. The risk for cardiac death after 12 to 36 months of discharge was over two-fold (P<0.001) for those with LVEF <40%. Later, an international multicenter study (ATRAMI) with more than 1,200 post-MI patients yielded parallel results with over 7- and 5-fold risk of cardiac mortality for those with LVEF <35% in univariate and multivariate analysis, respectively (La Rovere, Bigger, Marcus, Mortara, & Schwartz, 1998).
At the turn of the millennium, a series of randomized controlled trials associated decreased left ventricular function to ventricular arrhythmias. In 1996, a total of 196 subjects with previous non-sustained VT, myocardial infarction and LVEF <35% were treated with implantable cardioverter/defibrillator (ICD) or antiarrhythmic drug therapy; the baseline characteristics of the subjects were similar (Moss et al., 1996). The ICD group had 54% lower risk of death (P=0.009) compared to those without, whereas amiodarone, beta-blockers or other antiarrhythmic therapy had no influence on survival. A few years later, a study with 704 CAD patients with LVEF ≤40% concluded significantly lower incidence of cardiac arrest and SCD in subjects with antiarrhythmic therapy (antiarrhythmic drugs and ICD) compared to those who did not receive antiarrhythmic therapy (incidence 25% vs. 32% and 5-year mortality 42% vs. 48%, respectively) (Buxton et al., 1999). The incidence of cardiac arrest or SCD was 66% lower among subjects receiving ICD therapy than those with or without antiarrhythmic drug therapy. Consequently, ICD therapy was concluded as the only treatment to reduce the risk of SCD in this population. Parallel results followed soon after in another trial (MADIT) with more than 1200 post-MI participants and LVEF <30% (Moss et al., 2002). The participants were randomly assigned to either ICD or medical therapy group. The baseline characteristics of the subjects in both groups were similar and the average follow-up was 20 months. All-cause mortality in the ICD group was significantly lower compared to the medical therapy group (14.2% vs. 19.8%). During the trial, 4.5% of the subjects in the medical therapy group received an ICD because of suspected or documented malignant ventricular arrhythmias. These observations were strengthened in 2005 when Bardy and colleagues executed a randomized trial (SCD-HeFT) with a cohort of 2,521 HF subjects (NYHA II-III) and LVEF ≤35% (Bardy et al., 2005). The ICD therapy group had a 23% decrease in mortality whereas placebo and amiodarone shared a similar elevated risk of death.

The previously mentioned randomized controlled studies have provided indisputable evidence of increased cardiac mortality and risk of ventricular arrhythmia among those with underlying cardiac disease and decreased left ventricular function. It has been proposed that in subjects with CAD, each 10% reduction in LVEF <40% increases all-cause mortality by 42%, SCD by 39%, and non-arrhythmic mortality by 49% over a two-year period (Yap et al., 2007). Moreover, the use of reduced LVEF as a sole risk factor for SCD has limitations. As the treatment of acute MI and heart failure has advanced substantially over the years, only a minority of the patients have significantly depressed LVEF (Dagres & Hindricks, 2013). Secondly, despite significantly reduced LVEF, and therefore,
classified as high-risk patients, only a portion of these subjects will benefit from ICD therapy because a great proportion of deaths are non-arrhythmic. In addition, LVEF has limited sensitivity and specificity for SCD (Dagres & Hindricks, 2013).

2.2 Electrophysiology of the heart and electrocardiogram

The function of the heart is based on a self-regulated electrical conduction system. This cascade of events consists of pacemaker cells, heart muscle cells and the electrical conduction pathway is enabled by ions travelling back and forth across the cell membrane. The usability and interpretation of an ECG is based on this ongoing flow of current. As briefly mentioned in the introduction, Willem Einthoven (1860–1927) is regarded as the developer of modern ECG, and he received a Nobel prize in medicine for his discovery in 1924. Although the field of cardiac research has widened substantially to more specific factors, such as genetics and molecular science, the ECG remains essential for the clinical examination.

2.2.1 Electrical conduction system of the heart and action potential

The electrical impulse is generated by the pacemaker cells in the sinoatrial node (SA node) localized in the upper part of the right atrium, resulting in contraction of both right and left atriaums. This impulse travels to the atrioventricular node (AV node), and after a short delay, proceeds to the bundle of His, which is divided into left and right bundle branches. Small Purkinje fibers conduct the electric impulse to cover the entire heart muscle cells, often called myocytes, and this activity spreads via gap junctions between cells. In systole, heart muscle contracts and in diastole, it relaxes. This cycle of electrical activity of the heart enables continuous circulation.

On a cellular level, myocytes have voltage on their phospholipid membrane. The voltage is maintained by differences in ion (charged atoms) concentrations between extra- and intracellular fluid. This voltage is regulated with a great number of variable ion pumps and exchangers for rapid transfer of ions across the cell membrane. Cardiac action potential is divided into five phases. This chain of events includes rapid changes in the membrane potential due to ion flow across the cell membrane. The action potential of a myocyte is presented in Figure 2.

In phase 0, this activation induces opening of Na⁺ channels causing influx of sodium and a positive change in the membrane voltage. After the membrane
potential reaches the threshold value (approximately -70mV), a greater amount of Na⁺ channels open, leading to rapid change of membrane voltage. At the end of phase 0, there is an inactivation of sodium channels decelerating the influx of Na⁺. As seen in Figure 2, there is a notch in phase 1 which is a result of potassium efflux making the membrane potential slightly more negative. After this in phase 2 (plateau), the membrane potential almost remains constant, and gradually a phase of repolarization begins. Phase 2 is characterized mainly with influx of Ca²⁺ via L-type calcium channels. This causes the contraction of the myocytes. Phase 3 can be regarded as the repolarization stage. L-type calcium channels close while potassium channels allow efflux of K⁺. This causes a shift of membrane potential towards resting potential. Phase 4 is also known as the resting stage of the cell or diastole. During this period, heart muscle is relaxed before starting a new cycle of cardiac action potential.

Fig. 2. Cardiac action potential and ion currents.

2.3 12-lead electrocardiogram as a clinical tool

Since action potential consists of voltage changes, this event can be detected with electrodes placed on the skin. A normal 12-lead ECG consists of electrodes which are placed on the limbs and chest. This enables monitoring of the heart from different angles.
The cardiac action potential cycle generates various waveforms on ECG. At the beginning, there is a small positive deflection (P-wave) on ECG resulting in depolarization and activation of both atriums, followed by a short pause of conduction in the AV node before depolarization proceeds to ventricles. Depolarization of the ventricles creates a waveform referred to as the QRS complex. Ventricles remain depolarized for a while; this stage is shown as ST-segment. Finally, T-wave represents repolarization of ventricles. The cycle of the heart can be divided into systole (contraction) and diastole (relaxation).

In addition to various morphologies seen on 12-lead ECG, placing of the electrodes enables clinicians to observe different locations of the heart, often essential especially in acute medical emergencies such as acute coronary syndromes. A normal 12-lead ECG consists of six precordial leads (V1 to V6) and six limb leads (I, II, III, aVR, aVL, aVF). These are further divided into three groups corresponding to major coronary arteries: Lateral leads I, aVL, V4-V6; anterior leads V1-V3; inferior leads II, III, aVF and abnormal electrical activity of the myocardium can be localized using this division.

Since the invention of the ECG over a century ago, it still has invaluable meaning in clinical medicine for the investigation of arrhythmias, acute coronary artery syndromes, genetic channelopathies and cardiomyopathies. The risk of CVD diseases (cerebrovascular disease, peripheral vascular disease and heart failure) is often screened using the generally accepted algorithms with known risk factors, yet ECG is suggested as a tool for improved risk assessment beyond these traditional factors (Chou et al., 2011; D'Agostino RB et al., 2008). The research on electrocardiogram has held its position in the field of cardiac research. In the upcoming chapters we will review important electrocardiographic abnormalities from the clinical perspective concerning this thesis and discuss current advances and risk management strategies.
2.3.1 QRS-duration

The QRS-complex represents depolarization of the ventricles. The term intraventricular conduction disturbances (IVCD) refers to abnormalities in the intraventricular propagation of supraventricular impulses that give rise to changes in the shape and/or duration of the QRS-complex (Surawicz et al., 2009). These abnormalities may be caused by abnormalities in the His-Purkinje conduction system or ventricular myocardium that result from necrosis, fibrosis, calcification, infiltrative lesions, or impaired vascular supply. Additionally, QRS prolongation may be functional due to supraventricular impulse during the relative refractory period in a portion of the conduction system (aberrant ventricular conduction). The generally accepted definition of prolonged QRS-duration is over 110 ms (Surawicz et al., 2009).

A community-based study with population from the Framingham Heart Study, free of heart failure and prior MI, noticed that prolonged QRS-duration was
positively associated with left ventricular mass (i.e. left ventricular mass increased with the extent of QRS prolongation) and ventricular wall thickness (Dhingra et al., 2005). From this perspective, the evolution of QRS prolongation is due to evolving cardiac disease and can predict future cardiac events. A large general population-based Finnish study in 2011 concluded that IVCD was a risk marker for all-cause mortality and arrhythmic death with 2- and 3-fold risks, respectively (Aro et al., 2011). Subsequently, QRS-duration was studied for SCD and VT/VF episodes in a cohort of over 2,000 men (Kurl, Makikallio, Rautaharju, Kiviniemi, & Laukkanen, 2012). Each 10-ms increase in QRS duration was associated with a 27% higher risk for SCD and subjects with QRS duration over 110 ms had a 2.5-fold risk for SCD in multivariate regression analysis. The above-mentioned studies suggest that QRS prolongation might be an independent risk factor for mortality in the general population.

The prevalence of QRS prolongation in congestive HF is estimated to be between 20% and 50% and regarded as a sign of more advanced heart disease (Goldberger et al., 2008). In HF patients the presence of IVCD is suggested as a significant marker of poor prognosis (Shamim et al., 1999). Among CAD patients, bundle branch blocks are regarded as signs of more extensive coronary artery disease, worse left ventricular function, and poorer prognosis (Freedman, Alderman, Sheffield, Saporito, & Fisher, 1987; Zimetbaum et al., 2004). Moreover, QRS prolongation is associated with over 3-fold risk of short-term mortality in acute MI patients (Hansen et al., 2017).

Complete or incomplete right bundle branch block (RBBB) and left bundle branch block (LBBB) are common causes of QRS prolongation. Electrocardiographically, the complete blocks are characterized by QRS duration ≥120ms and represent different QRS waveforms and ST-T segment abnormalities often easily detectible on ECG (Surawicz et al., 2009). In incomplete blocks, the QRS duration is between 110–120ms with defined abnormalities observed on ECG. The term nonspecific intraventricular conduction disturbance is used when QRS duration is greater than 110 ms but in the absence of criteria for LBBB or RBBB.

2.3.2 Fragmented QRS complex

Inspired by the growing evidence of non-detectible ECG variants on traditional recordings, Langner and co-workers studied high-frequency components of ECG by using low-frequency filtering in 1960 (Langner & Geselowitz, 1960). They recruited a reference group of 18 subjects, aged between 32 and 68 years, without
known cardiac disease or symptoms to assume so. Another 21 patients, aged 40 to 70 years, had clinically confirmed prior MI. They noticed increased notching and slurring of the QRS complex in the post-MI subjects, suggesting presence of a myocardial scar and fibrous tissue replacement of the normal myocardium as a cause of this abnormal ECG phenomenon. Some years later, notching and slurring of the QRS complex was discovered to be more prevalent in subjects with prior MI and ventricular enlargement verified by post-mortem dissection, thus supporting prior findings (Flowers, Horan, Tolleson, & Thomas, 1969).

Traditionally, the observation of pathological Q-waves on ECG indicates a myocardial scar due to prior MI (Thygesen et al., 2018). Since the development of medical intervention strategies with early revascularization and anticoagulative drug therapy, the Q-waves have presented substantial regression over time and even disappearance (Florian, Slavich, Masci, Janssens, & Bogaert, 2012; Voon, Chen, Hsu, Lai, & Sheu, 2004). By regarding this knowledge, in 2006 a study was conducted in which fragmentation of the QRS complex (fQRS) was evaluated as an ECG sign of myocardial scar (Das, Khan, Jacob, Kumar, & Mahenthiran, 2006). A cohort of 479 subjects with CAD or being evaluated for CAD underwent single photon emission tomography (SPECT) imaging to detect regional perfusion abnormalities. The study compared the sensitivity and specificity of Q-waves and fQRS for myocardial scar. The fQRS showed significantly higher sensitivity (85.6% vs. 36.3%) and negative predictive value (94.2% vs. 70.8%) for myocardial scar confirmed by SPECT. At present, the generally accepted definition of fQRS is described as the presence of various RSR’ patterns (≥1 R’ prime or notching of the R or S wave) within a single QRS complex and with no typical morphology of a bundle branch block (Brenyo et al., 2012; Das et al., 2007). The different morphologies are presented in Figure 4.

Since then, the fQRS has been evaluated in multiple studies and different populations. Patients with CAD and acute ischemic events are probably the most evaluated groups in which this abnormal ECG finding has been considered. In post-MI patients, the fQRS has been associated with increased mortality rates (all-cause and cardiac mortality, SCD), arrhythmic events (VT/VF), hospitalization due to heart failure, lower LVEF, recurrent cardiac events and adverse left ventricular remodeling (Akbarzadeh, Pourafkari, Ghaffari, Hashemi, & Sadeghi-Bazargani, 2013; Akgul et al., 2015; Ari, Cetinkaya, Ari, Koca, & Bozat, 2012; Brenyo et al., 2012; Chew et al., 2018; Das et al., 2009; Erdem et al., 2013; Korhonen et al., 2006; Korhonen et al., 2010; Lorgis et al., 2013; Pietrasik, Goldberg, Zdziekcka, Moss, & Zareba, 2007; Stavileci et al., 2014). The predictive value of fQRS for
myocardial scar has been evaluated in CAD patients with parallel results: negative predictive value 84–94.2%; positive predictive value 88–92%; sensitivity 75–91.4%; specificity 89–94% (Das et al., 2006; Das et al., 2008; Mahenthiran, Khan, Sawada, & Das, 2007). However, not all studies are in line with the above-mentioned results suggesting lower predictive value of fQRS for myocardial scar (Ahn et al., 2013).

Subjects with prior idiopathic VF episode and co-existing fQRS and J-waves on resting ECG have a three-fold risk for recurrent VF episode (J. Wang et al., 2012). In hypertensive patients, fQRS is noticed as a marker of LVH and reduced systolic and diastolic function (B. Zhang, Zhen, Shen, & Zhang, 2015). An interesting case-control study was published in 2015 aiming to evaluate the risk of SCD among 590 overweight (BMI >25kg/m²) subjects from the general population with fQRS on ECG (Narayanan et al., 2015). Fragmentation was more commonly observed on ECG of subjects who suffered SCD and in those surviving SCA. The risk of SCD was over 2-fold for those with lateral fQRS even after multivariate adjustments for reduced LVEF and other ECG risk markers (Q-waves, QTc prolongation, heart rate, QRS duration). A subsequent study related increased prevalence of fQRS to diabetes mellitus, hypertension, waist circumflex, and decreased left ventricular systolic and diastolic function (Bayramoglu et al., 2017).

Moreover, the predictive value of fQRS in subjects with cardiomyopathies and channelopathies has been studied to some extent. In ARVC the presence of fQRS is suggested to significantly increase the risk of VT, VF and SCD (Canpolat et al., 2013) and fQRS is suggested of being a sign of possible substrate for VF in Brugada syndrome (BrS) with almost four-fold risk (Morita et al., 2008; Morita et al., 2017). In subjects with hypertrophic cardiomyopathy (HCM), the risk of VT/VF and SCD is suggested to be over 4-fold (P=0.02) for those with fQRS in ≥3 territories, and fQRS increases the risk of arrhythmic events in subjects with non-compaction cardiomyopathy (Cetin et al., 2016; Debonnaire et al., 2015).

As a conclusion of the reviewed literature, the following statements are justified: 1) fQRS on ECG is related to detection of myocardial scar and prior MI; 2) fQRS is a sign of a probable substrate for arrhythmic events in subjects with underlying cardiac disease; 3) fQRS is a possible sign of decreased left ventricular function in subjects with cardiac disease; 4) fQRS on ECG after acute ischemic event is associated with increased mortality and recurrent cardiac events; 5) fQRS is quite a common finding in the general population and the evaluation of its prognostic significance requires further studies.
Table 2. A review of prior studies on fQRS among subjects with acute or chronic ischemic disease and other cardiac/metabolic conditions.

<table>
<thead>
<tr>
<th>Author(s), year</th>
<th>Study population</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Das, 2006</td>
<td>479 CAD/suspected CAD patients</td>
<td>SPECT: fQRS is a sign of a prior MI, high sensitivity (91.4%) and NPV (94.2%) for myocardial scar</td>
</tr>
<tr>
<td>Korhonen, 2006</td>
<td>158 post-MI patients, LVEF &lt;50%</td>
<td>fQRS exposes to VT, VF, SCD</td>
</tr>
<tr>
<td>Das, 2007</td>
<td>998 suspected CAD patients</td>
<td>1.6-fold risk of cardiac events (arrhythmias, MI, HF and SCD) for those with fQRS</td>
</tr>
<tr>
<td>Mahenthiran, 2007</td>
<td>409 CAD/suspected CAD patients</td>
<td>fQRS on ECG is a significant marker of abnormal myocardial perfusion imaging, lower LVEF and myocardial regional scar</td>
</tr>
<tr>
<td>Pietrasik, 2007</td>
<td>350 Q-wave MI or UAP patients</td>
<td>Over 2-fold risk for recurrent cardiac event in those with resolved Q-waves and fQRS</td>
</tr>
<tr>
<td>Das, 2008</td>
<td>879 CAD patients with wide-fQRS (f-wQRS&gt;120 ms)</td>
<td>1.4-fold risk for mortality, moderate sensitivity (86.8%) and high specificity (92.5%) for myocardial scar.</td>
</tr>
<tr>
<td>Das, 2009</td>
<td>449 STEMI or NSTEMI and 455 UAP patients</td>
<td>1.7-fold higher risk of death for those with fQRS</td>
</tr>
<tr>
<td>Korhonen, 2010</td>
<td>158 post-MI patients with LV dysfunction</td>
<td>Increased risk of cardiac death and hospitalization for those with fQRS and reduced LVEF</td>
</tr>
<tr>
<td>Ari, 2012</td>
<td>85 acute STEMI patients after PCI</td>
<td>7-fold risk for cardiac death, MI and revascularization, lower LVEF for those with fQRS</td>
</tr>
<tr>
<td>Akbarzadeh, 2013</td>
<td>100 patients with STEMI, NSTEMI, UAP</td>
<td>fQRS predicts mortality and lower LVEF after 6 months of the cardiac event</td>
</tr>
<tr>
<td>Erdem, 2013</td>
<td>100 acute STEMI patients treated with thrombolysis</td>
<td>fQRS patients have lower LVEF and fQRS is associated with inadequate myocardial reperfusion.</td>
</tr>
<tr>
<td>Lorgis, 2013</td>
<td>307 patients with acute MI</td>
<td>Persistent fQRS after MI is a risk factor for increased mortality</td>
</tr>
<tr>
<td>Ahn, 2013</td>
<td>190 MI patients</td>
<td>fQRS is a poor indicator of myocardial injury. fQRS is related to reduced LVEF after acute MI</td>
</tr>
<tr>
<td>Stavileci, 2014</td>
<td>296 acute STEMI patients</td>
<td>fQRS subjects have significantly lower LVEF, more global CAD and poorer prognosis after acute STEMI</td>
</tr>
<tr>
<td>Akgul, 2014</td>
<td>414 STEMI patients</td>
<td>fQRS predicts lower LVEF and increased risk of mortality, revascularization and advanced HF</td>
</tr>
<tr>
<td>Author(s), year</td>
<td>Study population</td>
<td>Key findings</td>
</tr>
<tr>
<td>----------------</td>
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<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Chew, 2018</td>
<td>705 post-MI patients</td>
<td>fQRS after acute MI: a 2-fold risk of adverse LV remodeling</td>
</tr>
<tr>
<td>Cho, 2019</td>
<td>150 subjects with myocardial ischemia</td>
<td>fQRS is a predictor of myocardial ischemia without a detectible myocardial scar tissue</td>
</tr>
<tr>
<td>Wang, 2012</td>
<td>21 cases subjects with idiopathic VF</td>
<td>Combined J waves and fQRS increase the risk of idiopathic VF</td>
</tr>
<tr>
<td>Zhang, 2015</td>
<td>236 patients with hypertension</td>
<td>fQRS is an independent predictor of LVH in hypertensive patients</td>
</tr>
<tr>
<td>Narayanan, 2015</td>
<td>590 overweight subjects</td>
<td>Overweight subjects with lateral fQRS have over 2-fold risk for SCD.</td>
</tr>
<tr>
<td>Bayramoglu, 2017</td>
<td>164 subjects with metabolic syndrome</td>
<td>fQRS is significantly related to diabetes mellitus, systolic and diastolic LV dysfunction</td>
</tr>
</tbody>
</table>

Fig. 4. Examples of different fragmented QRS complex morphologies

2.3.3 Q-waves

The Q-waves are located at the beginning of the QRS complex as the first negative reflection on ECG after the P-wave. In the absence of left ventricular hypertrophy and left bundle branch block, pathological Q-waves are defined as 1) any Q-wave (or QS) in leads V2-V3 >0.02s; 2) Q-wave ≥0.03s and ≥1mm deep or QS in two consecutive leads corresponding to major coronary artery territory (Thygesen et al., 2018). However, QS complex and Q-waves can be interpreted as normal depending on the leads observed, the duration and compared ratio of the R-wave amplitude. There is histologic evidence that the presence of pathological Q-waves on ECG is
associated with lesion of infarcted myocardium (Horan, Flowers, & Johnson, 1971; Savage, Wagner, Ideker, Podolsky, & Hackel, 1977). In addition, the presence of Q-waves can be due to myocardial damage other than ischemia, such as myocarditis (Deluigi et al., 2013).

Pathological Q-waves may occur during an acute MI or can be indicators of prior silent MI (Burgess et al., 2010). In subjects with high cardiovascular risk, such as individuals with diabetes mellitus, silent events can account for over 35% of total MIs. In the general population, the estimated prevalence of silent MI is 0.18% and the proportion of all MI events 8.1% (Ramos et al., 2016). The overall positive predictive value of Q-wave for actual silent Q-wave MI is estimated at 30% whereas in subjects with high 10-year risk (≥10%) of CHD the positive predictive value is substantially higher. A large community-based study examined four different cohorts from Belgium and found Q/QS to be more prevalent in men than women (3.2% vs. 2.3%) and the prevalence was strongly age-dependent (De Bacquer, De Backer, & Kornitzer, 2000).

After Q-wave MI, pathological Q-waves may disappear over time. The persistence of Q-waves varies depending on the study but is estimated at approximately 70% (Wong, Levy, & Kannel, 1990). Interestingly, subjects who lose the Q-wave evidence of MI are suggested of being at higher risk of cardiac death than those with persistent Q-waves. Patients with non-Q wave infarction are proposed to have almost 2-fold risk of reinfarction; however, subjects with Q-wave infarction are at higher risk for congestive heart failure (Berger, Murabito, Evans, Anderson, & Levy, 1992). As Q-waves may denote prior MI, silent or not silent, the myocardial scarring can predispose to re-entrant arrhythmia and SCD (Narayanan & Chugh, 2015). In 2014, almost 7,000 subjects from the general population aged 65 years or above and without known cardiac disease were examined, aiming to conclude whether abnormal ECG findings had prognostic value (Jorgensen et al., 2014). The Q-waves were associated with almost 3.5-fold risk of cardiovascular mortality compared to those without Q-waves.

2.3.4 ST-segment and T-wave abnormalities

The ST-segment represents the phase of depolarized ventricles during the cardiac cycle. Traditionally, ST-segment elevation is interpreted in acute STEMI as indicating total occlusion due to ruptured plaque and formation of thrombosis in a coronary artery. Myocardial ischemia often manifests as other ECG abnormalities, most known of which are pathological Q-waves, ST-segment depression and T-
wave inversions. The following ECG manifestations are recommended as suggestive of acute myocardial ischemia in the absence of LVH and BBB: new ST elevation $\geq 2$ mm at the J-point in two contiguous leads other than V2-V3 in men $\geq 40$ years; ST-elevation $\geq 2.5$ mm in men $< 40$ years or $\geq 1.5$ mm in women regardless of age (Thygesen et al., 2018). The ischemic ST-segment elevation should be demerged from other causes of ST-elevation such as early repolarization. New horizontal or downsloping ST-depression $\geq 0.5$ mm in two contiguous leads and/or T-wave inversion $> 1$ mm in two contiguous leads are also markers of myocardial ischemia. In children over one month of age, the T-wave is often inverted in leads V1-V3 (Rautaharju et al., 2009). In adolescents 12 years and above and in young adults less than 20 years of age, the T-wave may be inverted in aVF and V2. In adults the T-wave is usually codirectional with the QRS-complex, thus inverted in aVR, may be inverted in III, aVL, V1, and should be upright in I, II and V3-V6.

However, in clinical practice ST-segment abnormalities and T-wave inversions (TWI) on ECG are common findings also in the absence of acute coronary syndrome. The prevalence of nonspecific TWIs in general population is suggested at 0.5–2.4% depending on the leads involved (Aro, Anttonen et al., 2012; Laukkanen et al., 2014). In a general population cohort of over 10,000 middle-aged subjects, precordial (V1-V3) TWI did not associate with adverse events (Aro et al., 2012). However, TWI in other leads than V1-V3 showed over 2.5-fold risk for cardiac mortality and over 3-fold risk of SCD compared to those without TWI. Parallel observations were established in a cohort of 1,954 Finnish middle-aged men after adjustment for age and clinical risk factors (Laukkanen et al., 2014). The Atherosclerosis Risk Study in Communities (ARIC) and Cardiovascular Heart Study (CHS), population-based studies investigating cardiovascular events in the U.S. with over 18,000 middle-aged participants (58% women, 24% black) demonstrated that TWI, ST-elevation in V2 and ST-segment depression increase the risk of SCD and incidence of CHD (Soliman et al., 2011).

Brugada syndrome is a genetically transmitted channelopathy with variable genetic background and penetrance (Juang & Horie, 2016; Raharjo et al., 2018; Wilde & Amin, 2018). According to current knowledge, 20–25% of this disease is transmitted via mutations in SCN5A gene responsible for the normal function of sodium channels and intake of Na+ into the cells. The typical onset of symptoms is at middle age with at least 8-fold male dominance (Priori et al., 2013; Priori et al., 2015). Brugada syndrome is classified into three types. Type 1 BrS represents ECG pattern of coved ST-segment elevation $\geq 2$ mm in $\geq 1$ precordial leads V1-V3
followed by a negative T-wave either spontaneously or under provocative antiarrhythmic drug testing (Antzelevitch et al., 2005; Priori et al., 2015). Type 2 and 3 ECG abnormalities (high take-off ST-elevation of $\geq 2$ mm with continuing ST-elevation $\geq 1$ mm with positive/biphasic T-wave or ST-elevation $<1$ mm in the right precordial leads, respectively) are suggestive of BrS. Brugada syndrome predisposes to malignant ventricular arrhythmia, mainly VT, and is therefore a major risk factor for SCD (Brugada & Brugada, 1992; Fauchier et al., 2013). It has been estimated that BrS is responsible for 4% of all SCD events and up to 20% of SCDs of those with structurally normal hearts (Antzelevitch et al., 2005).

### 2.3.5 Early repolarization

The early repolarization (ER) pattern has been studied for several decades and was regarded as a normal benign variant often observed among healthy adults (Edeiken, 1954; Goldman, 1953; Kambara & Phillips, 1976; Wasserburger & Alt, 1961). In 1953, Osborn noticed J-waves in dogs exposed to hypothermia and referred to them as “current of injury” (Osborn, 1953). The experiment showed the ER ECG pattern in most cases preceded VF. Several decades later, case report studies linked inferior and/or lateral ER pattern to increased risk of spontaneous VF in the absence of BrS or other known cardiac disease (Ogawa, Kumagai, Yamanouchi, & Saku, 2005; Shinohara, Takahashi, Saikawa, & Yoshimatsu, 2006). It is proposed that ER is a result of unequal ion currents between endo- and epicardium during phase 1 of the action potential, inducing a transmural voltage gradient and typical J-wave manifestation on ECG (Bourier et al., 2018).

Early repolarization pattern refers to the generally acknowledged morphological J-wave variations on 12-lead ECG located at the junction between the end of the QRS complex and the beginning of the ST interval (Macfarlane et al., 2015). The J-wave ECG manifestation can be represented as end-QRS slurring or notching and may be accompanied by elevation, isoelectric or downsloping ST-interval. When ER pattern is observed in $\geq 2$ consecutive inferior/lateral leads on ECG monitoring, the possibility of early repolarization syndrome (ERS) should be acknowledged. (Antzelevitch et al., 2016; Mazzanti, Underwood, Nevelev, Kofman, & Priori, 2017).

Early repolarization syndrome and BrS share quite a few clinical features; the underlying pathophysiology is thus thought to be similar (Antzelevitch et al., 2016; Casado Arroyo et al., 2018; Junttila et al., 2012). In both, the usual manifestation of VT or SCD occurs after the age of 30 years with obvious male dominance (over
70%) and the onset of arrhythmia often occurs during low intensity physical activity or sleep (Antzelevitch et al., 2016). Similar genetic mutations in genes regulating myocyte ion transportation have been recognized. Despite many shared features, these conditions have differences. In the ERS, the most affected area is the inferior left ventricular wall and ECG abnormalities are observed in inferolateral (II, III, aVF, I, aVL, V4-V6), whereas in Brugada syndrome, the area of disturbed electrical activity is the right ventricular outflow tract deflecting abnormalities in precordial (V1-V3) leads.

In 2008, Haïssaguerre et al. published an article which prompted wide interest towards the prognostic significance of the ER pattern (Haïssaguerre et al., 2008). They studied over 200 subjects with prior cardiac arrest due to idiopathic VF; the control group consisted of over 400 subjects without known cardiac disease and similar demographical background in the absence of arrhythmic events. The ER was defined as J-point elevation of $\geq 0.1$ mV, observed in at least two consecutive leads, in the inferior or lateral territories. The prevalence of ER was significantly higher among subjects with prior VT (31% vs. 5%) and the risk for recurrent VT was found to be elevated (RR 2.1, $P=0.008$). A year later, this was followed by a study of ER in the general population (Tikkanen et al., 2009). The prevalence of ER was 5.8% and subjects with ER $\geq 0.2$ mV (0.3%) had significantly higher risk for arrhythmic death (RR 2.9, $P=0.01$). The same group suggested horizontal or descending ST-segment after ER as a sign of increased risk for arrhythmic events, whereas ER followed by rapidly ascending ST-segment seemed a more benign variant (Tikkanen et al., 2011). Subsequent publications have yielded similar results suggesting that ER pattern increases the risk of cardiovascular mortality and SCD, and recurrence of VT/VF (Haruta et al., 2011; Junttila et al., 2014; Rollin et al., 2012; Siebermair et al., 2016; Sinner et al., 2010).

An interesting meta-analysis was published in 2016 aiming to clarify the association of ER with the defined endpoints: SCD/VF, cardiac and all-cause mortality (Cheng et al., 2016). The study included a total of sixteen studies and 334,524 subjects (60.6% men) with an average follow-up of over 10 years. The ER pattern significantly increased the risk of SCD/VF (RR 2.18, $P=0.003$), cardiac death (RR 1.48, $P=0.02$) and all-cause mortality (1.21, $P=0.03$). Interestingly, the increased risk was observed mainly among Asians and whites but not African Americans. A year later, another meta-analysis by the same study group was published in which they aimed to evaluate the prognostic significance of ER in patients with structural heart disease (Cheng et al., 2017). Nineteen publications including 7,268 subjects with coronary artery disease, acute coronary syndrome,
cardiomyopathy and chronic heart failure were reviewed. Patients with known cardiac disease and ER pattern on ECG had almost 5-fold risk for SCD and ventricular arrhythmias. The risk was higher in those with inferior ER with notched morphology, higher magnitude J-point elevation, and horizontal/descending ST-segment (Cheng et al., 2017).

As a primary objective in prevention strategies, the overall risk for arrhythmic events should be evaluated in patients with ER pattern. As the risk of SCD and VF in asymptomatic subjects with ER pattern is low and the prevalence of ER in the general population high, there are no general recommendations for treatment in such cases (Priori et al., 2013; Priori et al., 2015). However, there is a class I indication for ICD implantation for patients with VF episode and documented J waves.

Fig. 5. Examples of abnormal ECG findings. A. Early repolarization in inferior leads; B. intraventricular conduction disturbance; C. T-wave inversions

2.3.6 QT-interval

The QT-interval represents the interval from the onset of ventricular depolarization to the end of the ventricular repolarization; it is thus measured from the beginning of the QRS-complex to the end of the T-wave (Rautaharju et al., 2009). Although
calculating the QT-interval is commonly straightforward, the recognition of the beginning of the QRS-complex and the end of the T-wave can cause error as well as variability between the leads under examination.

QT interval is dependent on heart rate and in clinical practice, Bazett’s formula is most commonly used for heart rate-corrected QT-interval (QTc). The recommended limits for normal QTc are <460 ms in women and <450 ms for men (Rautaharju et al., 2009). A large sample of Danish conscripts found 0.5% of men and 0.6% of women having prolonged QTc (Kobza et al., 2009). The QTc prolongation can be acquired or genetic.

In the general population, prolonged QTc has been noted as an independent predictor of all-cause mortality, cardiovascular mortality, and ischemic heart disease in both sexes (Karjalainen, Reunanen, Ristola, & Viitasalo, 1997; Schouten et al., 1991). A study with 877 middle-aged men suggested that subjects with QTc ≥420 ms had a 3-fold risk of death due to CAD, independent of other cardiovascular risk factors, compared to those with QTc <385 ms (Dekker, Schouten, Klootwijk, Pool, & Kromhout, 1994). A subsequent study with elderly population (average age 68 years, 2,083 men and 3,158 women) found a 70% increase in risk for both all-cause mortality and cardiac mortality in subjects with prolonged (>437 ms in men, >446 ms in women) QTc compared to those with normal QTc (<406 ms for men, <418 ms for women). In this study, QTc prolongation was an independent risk factor especially among women (de Bruyne et al., 1999). A random sample study of 3,455 (52% men) Danish citizens aged 30 to 60 years revealed an almost 3-fold risk of cardiovascular mortality and hospitalization due to cardiac causes (Elming et al., 1998). The prognostic value of QTc prolongation for mortality is stronger in subjects with underlying cardiac disease (Karjalainen et al., 1997; Robbins, Nelson, Rautaharju, & Gottdiener, 2003).

The association of prolonged QTc and the risk of SCD has also been a common study setting. The prospective Rotterdam study with 3,105 men and 4,878 discovered that those with QTc prolongation (>450 ms for men and >470 ms for women) had an almost 3-fold risk for SCD compared to those with normal QTc after adjusting for relevant clinical risk factors (Straus et al., 2006). Among subjects aged under 68 years of age the risk increased to 8-fold. The association of QTc prolongation and increased risk for SCD has been observed in many studies, supporting the proarrhythmic nature of this abnormal ECG finding (Wellens et al., 2014; Y. Zhang et al., 2011).

The long-QT (LQTS) and short-QT syndromes (SQTS) are rare genetic diseases characterized by abnormal QT intervals. The estimated prevalence of
LQTS is 1/2,500 to 1/2,000 individuals, whereas only up to 250 cases of SQTS have been reported worldwide (Campuzano et al., 2018; Schwartz et al., 2009). The diagnosis of LQTS is based on QT-interval prolongation observed on ECG. The recommendation is to use QTc interval according to Bazett’s formula, and values $\geq 480$ms are strongly indicative of LQTS (Priori et al., 2015). Nonetheless, LQTS may be present even if QTc is within normal range; for this reason, other criteria for this syndrome are fundamental in clinical practice. The diagnostic criteria or risk score for LQTS which are used today were demonstrated by Schwartz and colleagues in 1993 (Schwartz, Moss, Vincent, & Crampton, 1993). These criteria involve ECG abnormalities (e.g. QTc interval, Torsade De Pointes, T-wave alternans), clinical history (syncope with or without stress, congenital deafness) and family history of immediate relatives (definite LQTS, unexplained SCD under the age of 30 years). Fatal arrhythmic events can occur during exercise, sleep or emotional stress, and occurrence is dispersed depending on the LQTS subtype present (Schwartz, Ackerman, George, & Wilde, 2013). The annual incidence of SCD or first cardiac arrest in LQTS (three main genetic mutations) is 0.3–0.6% and the combined incidence of syncope, SCD or cardiac arrest before the age of 40 years is 36% (Priori et al., 2003). The cumulative risk increases substantially when QTc interval exceeds 500 ms.

The SQTS is characterized by accelerated cardiac repolarization and diagnosed in the presence of QTc $\leq 340$ ms (Mazzanti et al., 2017; Priori et al., 2015). Family history of definite SQTS/SCD under the age of 40 years, confirmed genetic mutation of known susceptibility genes, or previous unexplained VT/VF episode can lead to diagnosis if QTc $\leq 360$ ms is observed. The cumulative incidence of cardiac arrest if untreated is estimated to be as high as 40% during the first four decades of life and over 80% of SQTS patients develop symptoms which may include palpitations, atrial fibrillation/flutter and syncope (El-Battrawy et al., 2018).

2.3.7 Left ventricular hypertrophy

Left ventricular hypertrophy is an ECG marker for abnormal myocardial wall thickness of the left ventricle. Arterial hypertension, with an estimated prevalence of 30–45% in the adult population, is the most common cause leading to LVH (Williams et al., 2018). The evaluation of LVH in ECG includes 1) Sokolow-Lyon index $>35$ mm ($S_{V1}+R_{V5}$) or $R_{AVL} \geq 11$ mm; 2) Cornell voltage criteria $>2,440$ mm.ms ($S_{V3}+R_{AVL} \times$ QRS duration). In addition, the Romhilt-Estes scoring was one of the first efforts to improve ECG LVH prediction for LV mass (Romhilt & Estes, 42
Although not commonly used in general practice, the Romhilt-Estes scoring might add prognostic value for risk prediction (Darouian et al., 2017; Estes, Zhang, Li, Tereschenko, & Soliman, 2015).

One of the early studies on the prognostic significance of LVH for ventricular arrhythmias was the Framingham Heart Study with over 6,000 participants in the late 1980s (Levy et al., 1987). Subjects with LVH were older, more commonly men, had higher systolic blood pressure, and had higher LV mass than those without LVH. Hypertrophy was associated with increased incidence of ventricular arrhythmias on ambulatory electrocardiograms. Subsequent studies supported these findings (Bayes-Genis et al., 1995; Ghali, Kadakia, Cooper, & Liao, 1991; Levy, Garrison, Savage, Kannel, & Castelli, 1990).

The progression of LVH in hypertension can be divided into three stages: 1) preclinical phase with normal LVEF; 2) LV remodeling and normal LVEF, progression of diastolic dysfunction; 3) advanced heart failure with reduced LVEF (Shenasa & Shenasa, 2017). In stages 2 and 3, the myocardium becomes vulnerable to arrhythmia due to an increase of fibrosis and myocardial remodeling. Progression of LVH causes microvascular changes and subendocardial ischemia predisposing to SCD. Both inflammation and fibrosis are the source of arrhythmogenesis also in diabetes mellitus, cardiac aging and sleep apnea.

The sensitivity and specificity of ECG to detect LVH varies greatly depending on the criteria used, and individual characteristics, such as body weight, should be regarded (Bacharova, Schocken, Estes, & Strauss, 2014; Porthan et al., 2019; Williams et al., 2018). In summary, ECG LVH predisposes to arrhythmia, is a risk factor for cardiovascular events, should be screened in every patient with hypertension or cardiac symptoms, and the underlying etiology should be identified for targeted treatment.

Hypertrophic cardiomyopathy is an inherited genetic disorder of the myocytes with the highest prevalence of all cardiomyopathies. It is characterized by non-dilated hypertrophy of the left ventricle in the absence of a secondary explanation (e.g. high blood pressure) and normal or increased LVEF (Marian & Braunwald, 2017). The specificity of ECG abnormalities related to HCM is low when found in isolation (Caselli & Pelliccia, 2019). These possible abnormalities include negative T-waves and LVH, of which the first mentioned could be the initial phenotypic expression of HCM (Caselli & Pelliccia, 2019; Pelliccia et al., 2008). The clinical features vary greatly, from symptoms such as dyspnea, chest pain, palpitations, presyncope and syncope, to being almost asymptomatic (Marian & Braunwald, 2017). Hypertrophic cardiomyopathy is the most common cause of SCD in young
healthy adults and athletes, the annual risk of SCD being 0.5–2% (Marian & Braunwald, 2017; Maron, Doerer, Haas, Tierney, & Mueller, 2009).

### 2.3.8 Frontal QRS-T angle

In cardiac depolarization and repolarization, each of the billions of cardiac myocytes generates an individual electrical vector. The frontal QRS-T angle can be measured by using 12-lead ECG and calculating the absolute value of the difference between cardiac depolarization (QRS-complex) and repolarization (T-wave). (Oehler, Feldman, Henrikson, & Tereshchenko, 2014). Parallel orientation of the QRS-complex and T-wave in 12-lead ECG results in lower QRS-T angle values. The definition of abnormal QRS-T angle varies somewhat depending on gender (lower in women) and study; however, the definition of abnormal value is around 100-120° (Oehler et al., 2014).

The prevalence of abnormal QRS-T angle in the general population is estimated at 2–2.5% (Aro, Huikuri et al., 2012; Walsh et al., 2013). In the general population, QRS-T angle \(\geq 100^\circ\) increases the risk of SCD over 2-fold, and there is evidence that this might primarily be a result of altered T-wave axis (Aro et al., 2012; Laukkanen et al., 2014; Walsh et al., 2013). A community-based study of 666 SCA victims and 863 controls demonstrated that frontal QRS-T angle \(>90^\circ\) is an independent predictor of SCA with over 2-fold risk in multivariate adjusted regression analysis (age, gender, heart rate, hypertension, diabetes mellitus, prior MI, IVCD, LVH) even after adding LVEF to the analysis (Chua et al., 2016). Moreover, there is evidence that abnormal frontal QRS-T angle increases arrhythmic events in patients with non-ischemic cardiomyopathy (Pavri et al., 2008).
Fig. 6. Measurement of frontal QRS-T angle
3  Aims of the study

The fragmented QRS-complex is suggested to possess prognostic value in risk prediction among patients with coronary artery disease. Our first goal was to the evaluate prevalence and prognostic value of this abnormal ECG morphology in the general population with and without known cardiac disease. Moreover, this thesis aimed to evaluate known ECG risk factors for fatal and non-fatal endpoints. A summary of the study aims is listed below:

1. To evaluate the prevalence and long-term prognostic significance of fQRS in Finnish middle-aged general population with and without a history of cardiac disease.
2. To assess the role of major ECG abnormalities for cardiac death and non-fatal cardiac in middle-aged population without known cardiac disease. Non-fatal event included hospitalization due to ischemic heart disease complications using national registries.
3. To examine the short- and long-term prognostic value of abnormal ECG findings for sudden cardiac death among apparently healthy middle-aged population.
4 Population and methods

4.1 Study population

All publications of the thesis are based on the Finnish Mobile Clinic Health Examination Survey, which was performed between 1966 and 1972. As part of this wide study, the Coronary Artery Disease Study was carried out to gain better understanding to prevent future cardiac events. Subjects were invited to the study by a letter, including instructions for preparation. Participation rate was 89%. Of the participants invited, a total of 10,962 subjects aged 30–59 years took part in the study (52.3% men, mean age 44±8). Subjects were drawn from 12 Finnish cohorts to represent different geographical areas of Finland. All participants underwent an examination by trained nurses supervised by a medical doctor; the examination included the Rose angina questionnaire, possible other symptoms, prior diagnosed diseases, smoking status and medication use. A clinical examination included measurements such as blood pressure, BMI, blood cholesterol and triglycerides, urine sample and one-hour glucose tolerance test.

For the first study, a total of 10,904 (52% men, mean age 44±8.5 years) subjects were available from the original cohort. For the purpose of the second and third publications, the studied population was 9,511 subjects (mean age 43±8.2 years, 52% males) after exclusions. To evaluate the significance of fQRS (study I) in apparently healthy population we excluded those with known cardiac disease, defined as use of cardiac medication (N=253), clinical history of prior MI/CAD (N=895) and those with ECG evidence of cardiac disease (Minnesota codes 1.1 to 1.3, 4.1 to 4.3, 5.1 to 5.2, 7.1, and 7.4). To avoid overlapping between fQRS and ER, we excluded those with ER pattern in inferior/lateral leads (N=215). Subjects with bundle branch blocks (N=227) were excluded, in addition to missing or unreadable data (N=53). For studies II-III, the exclusion criteria involved subjects with symptoms attributable to cardiac disease (N=245), those with known cardiac disease (N=895), usage of cardiac medication (N=253), ECG-pattern of Wolff-Parkinson-White syndrome (N=8)/atrial fibrillation (N=21) and those with unreadable or missing data (N=53). The study populations are presented in Figure 7.
4.2 Follow-up and endpoints

The total follow-up was 30±11 years. The data was gathered until the year 2007. During the follow-up period, less than 2% of the subjects were lost. Causes of death and/or hospitalization were determined according to data from Statistics Finland. Unaware of the follow-up data, all death certificates and hospitalization records were analyzed by experienced cardiologists. To determine death as arrhythmic or non-arrhythmic, they used the definition of the Cardiac Arrhythmia Pilot study (Greene et al. 1989). According to this criterion, death was classified as arrhythmic in the case of spontaneous cessation of respiration and circulation, either witnessed or unwitnessed, as follows: 1) witnessed and instantaneous without new and/or progressive symptoms; 2) witnessed and preceded or accompanied by symptoms attributable to myocardial ischemia in the absence of heart failure; 3) witnessed and preceding symptoms of cardiac arrhythmia; 4) unwitnessed with no evidence of other cause of the event. During the follow-up, 6,159 (56.5%) subjects died. Cardiac death was responsible for 32.2% of all deaths and SCD accounted for 13.3% of all fatal events.

Four different endpoints were used. In the first publication, our primary endpoints were death due to cardiac and arrhythmic causes and all-cause mortality. In the second study with multiple ECG risk markers included, the primary end point
was death from cardiac causes (ICD I20-25, ischemic heart disease) and the secondary end point was hospitalization due to coronary artery disease (ICD I20-25). To study short- and long-term prognosis, we used 10- and 30-year follow-up cutoff points in both study II and study III. In study III, the primary end point was death due to arrhythmia.

4.3 Electrocardiographic measurements

The 12-lead ECG measurements were recorded with a paper speed of 50 mm/s. Electrocardiographic variables were coded according to the Minnesota coding system. For most of the original participants, a re-examination was performed during the years 1973–1976. A total of 10,904 ECGs were re-analyzed for this thesis by six physicians unaware of the outcome data. Study exclusions are presented in Figure 7. For further evaluation of fQRS in subjects free of cardiovascular disease, the exclusions were executed as described earlier. Unreadable ECGs were excluded from the analysis (I, II, II). Those with atrial fibrillation, Wolf-Parkinson White ECG pattern or pacemaker rhythm were also excluded (II, III), in addition to the criteria mentioned earlier and presented in Figure 7.

Fragmentation of the QRS complex was defined as various RSR’ patterns in at least two consecutive leads corresponding to the major coronary arteries (inferior II, III, aVF; lateral I, aVL, V4 to V6; anterior V1 to V3). The criteria included additional R-waves (R’) or notching of the R- or S-wave. The pattern of ER was defined as J-point (junction between the end of the QRS complex and the beginning of the ST segment) elevation in at least two consecutive leads: inferior (II, III, aVF), and lateral (I, aVL, V4-V6). In addition, the amplitude of J-point elevation was measured and divided, being ≥0.1mV or >0.2mV. ST-segment was characterized into two categories: 1) ascending ST segment; 2) horizontal or descending ST segment. The ST segment depression (at least 0.5mm deep) was evaluated according to Minnesota coding (codes 4-1, 4-2). T-wave inversion (≥1.0 mm deep in other leads than aVR, codes 5-1 to 5-2) was also included. Prolonged QTc interval was defined as ≥440 ms for men and ≥460 ms for women. Left ventricular hypertrophy was evaluated with Sokolow-Lyon criteria or Romhilt-Estes points ≥5. A frontal QRS-T angle >100° was defined as abnormal.
4.4 Statistical analysis

All continuous variables are presented as mean ± standard deviations. The general regression model was used to compare the age- and sex-adjusted mean values for continuous variables and the prevalence of categorical variables among different groups. The Cox proportional-hazard model (I) and competing risk regression model (II, III) were used to calculate hazard ratios and confidence intervals. The multivariate analyses included age, gender, systolic blood pressure, BMI, cholesterol levels, QTc interval (I), QRS-duration (I), smoking, and diabetes (II, III). Information about history/symptoms or ECG signs of cardiovascular disease (MI, congestive HF) and use of chronotropic medication was used to identify subjects with underlying cardiac disease. Kaplan-Meier with the log-rank test (I, III) and cumulative incidence curves with Gray’s test (II) were plotted for further statistical evaluation.

The C-index is equivalent to the area under the receiver operating characteristics curve with values between 0.5 (random prediction) and 1 (perfect prediction) (Harrell, Lee, & Mark, 1996). The Integrated Discrimination Increment (IDI) estimates whether a tested marker, in this thesis, abnormal ECG, improves the level of discrimination between groups of individuals with and without the tested variable (Kentta et al., 2012). The C-statistics and IDI analyses were used (II, III) to test ECG’s ability in risk prediction using novel statistical methods. The original model included age, gender, systolic blood pressure, cholesterol, smoking, diabetes and BMI, and abnormal ECG was added to this model. Statistical analyses were performed with Statistical Package for Social Sciences and R statistical software (The R Foundation for Statistical Computing, Vienna, Austria). All two-sided P-values <0.05 were considered significant.
5  Results

5.1  Fragmented QRS complex – prevalence and prognosis in the general population

The fQRS was evaluated in two groups: 1) subjects without known cardiac disease and 2) subjects with known cardiac disease. The overall prevalence of fQRS was 19.7% (N=2,147). The fQRS was most commonly observed in the inferior territory (15.7%, N=1,714) whereas lateral territory was the most uncommon region (0.8%, N=84). The baseline characteristics are presented in Table 3. In brief, subjects with fQRS were more commonly men, were older, and had higher BMI, higher blood pressure and longer QRS-duration than those without fQRS.

Table 3. Demographic comparison of the fQRS and non-fQRS group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>fQRS</th>
<th>Non-fQRS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>8757 (80.3%)</td>
<td>2147 (19.7%)</td>
<td></td>
</tr>
<tr>
<td>Malea</td>
<td>50.2%</td>
<td>61.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years)b</td>
<td>43.8±8.4</td>
<td>44.9±8.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smokerc</td>
<td>33.8%</td>
<td>34.5%</td>
<td>0.001</td>
</tr>
<tr>
<td>Cholesterol mmol/Lc</td>
<td>6.49±1.31</td>
<td>6.53±1.34</td>
<td>0.810</td>
</tr>
<tr>
<td>(251±50.7mg/dl)</td>
<td>(253±51.8mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)c</td>
<td>25.8±3.9</td>
<td>26.4±3.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate (bpm)c</td>
<td>76±15</td>
<td>75±15</td>
<td>0.200</td>
</tr>
<tr>
<td>Blood pressure (mmHg)c</td>
<td>138±21</td>
<td>140±22</td>
<td>0.290</td>
</tr>
<tr>
<td>Systolic</td>
<td>82±12</td>
<td>83±13</td>
<td>0.003</td>
</tr>
<tr>
<td>Diastolic</td>
<td>31.9%</td>
<td>28.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVHf</td>
<td>408±27</td>
<td>408±28</td>
<td>0.600</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>84±11</td>
<td>88±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>322±28</td>
<td>319±30</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

+ fQRS present; - fQRS absent; BMI=body mass index; LVH=left ventricular hypertrophy; *Adjusted for age; 1Adjusted for gender; 2Adjusted for age and gender; values are shown as mean ± standard deviations (SD) for continuous variables

In a population without known cardiac disease, the fQRS did not increase the risk of any endpoints, i.e. all-cause, cardiac or arrhythmic mortality. However, among subjects with ECG evidence of underlying cardiac disease the lateral territory fQRS was associated with the risk of all-cause mortality (RR 1.9, 95% CI 1.27–2.70,
P=0.001), cardiac mortality (RR 2.5, 95% CI 1.45–4.22, P=0.001) and arrhythmic mortality (RR 3.0, 95% CI 1.43–6.56, P=0.004). In conclusion, the fQRS had no prognostic value for predicting fatal events in subjects without a known cardiac disease, whereas lateral fQRS was associated with the risk of future events among subjects with a present cardiac disease. Overall, the prevalence of fQRS was common in the general population and most often observed in the inferior leads.

Fig. 8. Kaplan-Meier curves of cardiac mortality for subjects without known cardiac disease and with or without fQRS in any lead (A) and for those with clinical and/or ECG evidence of cardiac disease and with or without fQRS in lateral leads (B). Published with the permission of the American Journal of Cardiology.
5.2 Electrocardiographic risk markers for fatal and non-fatal cardiac events

The exclusion criteria for the purpose of study II are presented in Figure 7. The remaining 9,511 subjects were included in the study. This population was examined for major ECG abnormalities. The ECG was defined as abnormal if one or more of the following abnormalities were present: 1) Q-waves/QS complexes (comparable to pathological Q-waves); 2) $\geq 1$ mm deep T-wave inversion in other leads than aVR, aVL, III, and VI-V3; 3) horizontal or downsloping ST-segment depression at least 0.5 mm deep; 4) LVH; 5) QRS-duration $\geq 110$ ms; 6) IVCD; 7) LBBB or RBBB; 8) ER $\geq 0.1$ mV with a horizontal or downsloping ST-segment. In general, subjects with abnormal ECG findings were older, more commonly men, and had higher blood pressure than those with normal ECG.
Table 4. Characteristics of subjects with and without major ECG abnormalities at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal ECG (N=8,380)</th>
<th>Any ECG abnormality (N=1,131)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (%)</td>
<td>52.1</td>
<td>59.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>42.9±8.2</td>
<td>44.7±8.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>34.5</td>
<td>35.1</td>
<td>0.186</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>1.4</td>
<td>1.8</td>
<td>0.646</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>6.46±1.3</td>
<td>6.44±1.3</td>
<td>0.479</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8±3.7</td>
<td>25.2±3.6</td>
<td>0.008</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>76±15</td>
<td>76±15</td>
<td>0.067</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>136±19</td>
<td>143±19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>81±12</td>
<td>83±12</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

1Adjusted for age; 2Adjusted for gender; 3Adjusted for age and gender; ± values are means and standard deviations; BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure

The prevalence of any ECG abnormality was 11.9% (N=1,131). Cardiac mortality was 1.7% (N=158) during the 10-year follow-up and 16.3% (N=1,548) during the 30-year follow-up. The incidence of cardiac death was higher among those with abnormal ECG compared to those without (7.9/1,000 person years vs. 4.9/1,000 person years). During the 10- and 30-year follow-ups, subjects with any ECG abnormality had increased risk of cardiac mortality compared to those without after adjusting for other risk factors (HR 1.7, 95% CI 1.1–2.5, P=0.009; HR 1.3, 95% CI 1.1–1.5, P<0.001, respectively).

For further evaluation of abnormal ECG to predict cardiac death, C-statistics and IDI analyses were performed. A minor improvement was seen on C-statistics (0.851 to 0.853 and 0.742 to 0.743 for 10 and 30 years of follow-up, respectively) and IDI (0.0027, P=0.072 and 0.0017, P=0.002 for 10 and 30 years of follow-up, respectively) when abnormal ECG was added to the risk model with conventional risk variables (age, gender, systolic blood pressure, cholesterol, diabetes, and BMI).
Table 5. Hazard ratios (95% confidence intervals) for cardiac death.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of events</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Cardiac death, 10-year follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal ECG (n=1,131)</td>
<td>39 (3.4%)</td>
<td>1.7 (1.1 - 2.5)</td>
</tr>
<tr>
<td>Q-waves (n=36)</td>
<td>3 (8.3%)</td>
<td>3.6 (1.1 - 11.9)</td>
</tr>
<tr>
<td>T-inversion (n=284)</td>
<td>12 (4.2%)</td>
<td>2.2 (1.1 - 4.1)</td>
</tr>
<tr>
<td>ST-depression (n=212)</td>
<td>12 (5.7%)</td>
<td>2.5 (1.3 - 4.8)</td>
</tr>
<tr>
<td>LVH (n=395)</td>
<td>16 (4.1%)</td>
<td>1.4 (0.8 - 2.5)</td>
</tr>
<tr>
<td>QRS110 (n=110)</td>
<td>8 (7.3%)</td>
<td>2.3 (1.1 - 5.1)</td>
</tr>
<tr>
<td>IVCD (n=51)</td>
<td>3 (5.9%)</td>
<td>2.0 (0.6 - 6.9)</td>
</tr>
<tr>
<td>RBBB (n=37)</td>
<td>2 (5.4%)</td>
<td>1.3 (0.3 - 5.9)</td>
</tr>
<tr>
<td>LBBB (n=20)</td>
<td>3 (15%)</td>
<td>5.7 (1.7 - 19.7)</td>
</tr>
<tr>
<td>ER (n=351)</td>
<td>7 (2.0%)</td>
<td>0.9 (0.4 - 2.0)</td>
</tr>
<tr>
<td>Cardiac death, 30-year follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal ECG (n=1,131)</td>
<td>258 (22.8%)</td>
<td>1.3 (1.1 - 1.5)</td>
</tr>
<tr>
<td>Q-waves (n=36)</td>
<td>16 (44.4%)</td>
<td>2.2 (1.3 - 3.7)</td>
</tr>
<tr>
<td>T-inversion (n=284)</td>
<td>66 (23.2%)</td>
<td>1.4 (1.1 - 1.8)</td>
</tr>
<tr>
<td>ST-depression (n=212)</td>
<td>53 (25.0%)</td>
<td>1.3 (0.9 - 1.7)</td>
</tr>
<tr>
<td>LVH (n=395)</td>
<td>96 (24.3%)</td>
<td>1.3 (1.0 - 1.6)</td>
</tr>
<tr>
<td>QRS110 (n=110)</td>
<td>30 (27.3%)</td>
<td>1.3 (1.0 - 1.6)</td>
</tr>
<tr>
<td>IVCD (n=51)</td>
<td>13 (25.5%)</td>
<td>1.3 (0.7 - 2.4)</td>
</tr>
<tr>
<td>RBBB (n=37)</td>
<td>11 (29.7%)</td>
<td>1.2 (0.6 - 2.2)</td>
</tr>
<tr>
<td>LBBB (n=20)</td>
<td>6 (30.0%)</td>
<td>1.5 (0.5 - 4.0)</td>
</tr>
<tr>
<td>ER (n=351)</td>
<td>79 (22.5%)</td>
<td>1.3 (1.0 - 1.6)</td>
</tr>
</tbody>
</table>

Multivariate hazard ratios (HR) are adjusted for age, gender, systolic blood pressure, body-mass-index, cholesterol, smoking and diabetes.

Hospitalization due to non-fatal coronary heart disease event occurred in 6.2% (N=537) and 33.9% (N=3,912) during the 10- and 30-year follow-up periods, respectively. The abnormal ECG did not increase the risk of non-fatal events. However, T-wave inversion and ST-segment depression had a minor prognostic value for a non-fatal event in the 10-year analysis.
Table 6. Competing risk regression model and hazard ratios (95% confidence intervals) for non-fatal coronary heart disease events

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of events</th>
<th>Multivariate</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Multivariate</td>
<td>P-value</td>
</tr>
<tr>
<td></td>
<td>Number of events</td>
<td>HR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>CHD event, 10-year follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal ECG (n=1,131)</td>
<td>86 (7.6%)</td>
<td>1.3 (1.0 - 1.7)</td>
<td>0.063</td>
</tr>
<tr>
<td>Q-waves (n=36)</td>
<td>4 (11.1%)</td>
<td>2.0 (0.8 - 5.3)</td>
<td>0.160</td>
</tr>
<tr>
<td>T-inversion (n=284)</td>
<td>26 (9.2%)</td>
<td>1.7 (1.1 - 2.7)</td>
<td>0.021</td>
</tr>
<tr>
<td>ST-depression (n=212)</td>
<td>27 (12.7%)</td>
<td>2.0 (1.3 - 3.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>LVH (n=395)</td>
<td>37 (9.4%)</td>
<td>1.4 (1.0 - 2.1)</td>
<td>0.074</td>
</tr>
<tr>
<td>QRS110 (n=110)</td>
<td>7 (6.4%)</td>
<td>0.7 (0.3 - 1.6)</td>
<td>0.370</td>
</tr>
<tr>
<td>IVCD (n=51)</td>
<td>2 (3.9%)</td>
<td>0.3 (0.1 - 2.4)</td>
<td>0.270</td>
</tr>
<tr>
<td>RBBB (n=37)</td>
<td>2 (5.4%)</td>
<td>0.3 (0.1 - 2.4)</td>
<td>0.280</td>
</tr>
<tr>
<td>LBBB (n=20)</td>
<td>3 (15%)</td>
<td>2.2 (0.7 - 7.2)</td>
<td>0.210</td>
</tr>
<tr>
<td>ER (n=351)</td>
<td>20 (5.7%)</td>
<td>1.0 (0.6 - 1.6)</td>
<td>0.950</td>
</tr>
<tr>
<td>CHD event, 30-year follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal ECG (n=1,131)</td>
<td>482 (42.6%)</td>
<td>1.1 (0.9 - 1.2)</td>
<td>0.420</td>
</tr>
<tr>
<td>Q-waves (n=36)</td>
<td>23 (63.9%)</td>
<td>1.6 (1.0 - 2.6)</td>
<td>0.053</td>
</tr>
<tr>
<td>T-inversion (n=284)</td>
<td>139 (48.9%)</td>
<td>1.3 (1.1 - 1.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>ST-depression (n=212)</td>
<td>105 (49.5%)</td>
<td>1.3 (1.0 - 1.6)</td>
<td>0.029</td>
</tr>
<tr>
<td>LVH (n=395)</td>
<td>159 (40.3%)</td>
<td>1.0 (0.8 - 1.2)</td>
<td>0.730</td>
</tr>
<tr>
<td>QRS110 (n=110)</td>
<td>45 (40.9%)</td>
<td>0.8 (0.6 - 1.2)</td>
<td>0.290</td>
</tr>
<tr>
<td>IVCD (n=51)</td>
<td>18 (35.3%)</td>
<td>0.6 (0.4 - 1.2)</td>
<td>0.140</td>
</tr>
<tr>
<td>RBBB (n=37)</td>
<td>16 (43.2%)</td>
<td>0.9 (0.5 - 1.5)</td>
<td>0.590</td>
</tr>
<tr>
<td>LBBB (n=20)</td>
<td>10 (50.0%)</td>
<td>1.2 (0.5 - 2.5)</td>
<td>0.700</td>
</tr>
<tr>
<td>ER (n=351)</td>
<td>139 (41.1%)</td>
<td>1.0 (0.8 - 1.2)</td>
<td>0.660</td>
</tr>
</tbody>
</table>

Multivariate hazard ratios (HR) are adjusted for age, gender, systolic blood pressure, body-mass-index, cholesterol, smoking and diabetes.
5.3 Electrocardiographic abnormalities and the risk of sudden cardiac death

A total of 9,511 participants met the inclusion criteria (see Figure 7). Abnormal ECG was defined as 1) QRS-duration $\geq 110$ ms; 2) QRS-T angle $>100^\circ$; 3) QTc interval over 440 ms in men and 460 ms in women; 4) LVH (Sokolow-Lyon criteria or Romhilt-Estes point $\geq 5$); 5) early repolarization $\geq 0.1$ mV and $\geq 0.2$ mV in inferior/lateral leads with a descending or horizontal ST-segment. The prevalence of any ECG abnormality was 16.3% (N=1,548). Those with ECG abnormalities were older, more commonly men, had higher BMI and higher systolic blood pressure, and were more frequently cigarette smokers than those without ECG abnormalities.
Table 7. Characteristics of subjects at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal ECG (N=7,963)</th>
<th>Any ECG abnormality (N=1,548)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (%)</td>
<td>50.8</td>
<td>63.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>42.8±8.1</td>
<td>44.5±8.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>33.9</td>
<td>38.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>1.3</td>
<td>1.9</td>
<td>0.369</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>6.46±1.3</td>
<td>6.49±1.3</td>
<td>0.695</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>25.8±3.7</td>
<td>25.2±3.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>135±19</td>
<td>144±23</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\(^{a}\)Adjusted for age; \(^{b}\)Adjusted for gender; \(^{c}\)Adjusted for age and gender

The multivariate regression model was executed at 10-year and 30-year cut-points. Subjects with abnormal ECG had a borderline risk (HR 1.62, 95% CI 1.00–2.62, P=0.052) of SCD in the 10-year analysis. Significant predictors of SCD were QRS-duration \(\geq 100\) ms (HR 3.09, P=0.013), frontal QRS-T angle \(>100^\circ\) (RR 3.40, P=0.009), LVH (HR 2.67, P=0.002) and T-wave inversions (HR 2.98, P=0.010).

After 30 years of follow-up, subjects with abnormal ECG had moderately increased risk of SCD (HR 1.30, 95% CI 1.07–1.57, P=0.007). The strongest single predictors of SCD were QRST angle \(>100^\circ\) (HR 1.79, P=0.023), LVH (HR 1.52, P=0.007), ER \(\geq 0.1\) mV and ER \(\geq 0.2\) mV (HR 1.6, P=0.005; HR 2.6, P=0.009, respectively). Subjects with \(\geq 2\) abnormal ECG variants had significantly increased risk for SCD over 10 and 30 years of follow-up (HR 3.22, 95% CI 1.57–6.62, P=0.001; HR 2.97, 95% CI 2.09–4.20, P<0.001, respectively).

For further evaluation, abnormal ECG was added to the original model of known CVD risk factors (age, gender, systolic blood pressure, diabetes, and smoking). The C-index yielded no significant improvement, whereas IDI yielded minor improvement in risk prediction during 10 and 30 years of follow-up (IDI 0.0033, P=0.032; IDI 0.0027, P=0.003, respectively).
Table 8. Competing risk regression model and hazard ratios (HR) in 10- and 30-year follow-up periods

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
<th>10-year follow-up</th>
<th>30-year follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Multivariate HR*</td>
<td>p-value</td>
<td>Multivariate HR*</td>
</tr>
<tr>
<td>Normal ECG</td>
<td>7963 (83.7%)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Abnormal ECG</td>
<td>1548 (16.3%)</td>
<td>1.62 (1.00 - 2.62)</td>
<td>0.052</td>
</tr>
<tr>
<td>QRS≥110 ms</td>
<td>110 (1.2%)</td>
<td>3.09 (1.27 - 7.52)</td>
<td>0.013</td>
</tr>
<tr>
<td>QTc</td>
<td>534 (5.6%)</td>
<td>1.26 (0.64 - 2.48)</td>
<td>0.500</td>
</tr>
<tr>
<td>QRS-T angle &gt;100°</td>
<td>125 (1.3%)</td>
<td>3.40 (1.37 - 8.44)</td>
<td>0.009</td>
</tr>
<tr>
<td>LVH</td>
<td>395 (4.2%)</td>
<td>2.67 (1.42 - 5.01)</td>
<td>0.002</td>
</tr>
<tr>
<td>ER≥0.1 mV</td>
<td>351 (3.7%)</td>
<td>0.86 (0.27 - 2.72)</td>
<td>0.800</td>
</tr>
<tr>
<td>ER≥2 mV</td>
<td>N=40 (0.4%)</td>
<td>0.00 (0-0) N/A</td>
<td>2.60 (1.28 - 5.29)</td>
</tr>
<tr>
<td>T-wave inversion</td>
<td>N=284 (3.0%)</td>
<td>2.98 (1.30 - 6.79)</td>
<td>0.010</td>
</tr>
<tr>
<td>≥2 ECG abn</td>
<td>186 (2.0%)</td>
<td>3.22 (1.57-2.30)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, systolic blood pressure, diabetes, BMI and cholesterol.

ECG=electrocardiogram, ER=early repolarization, LVH = left ventricular hypertrophy, QTc = heart rate corrected QT-interval, abn=abnormalities. HRs for ER>0.2 mV could not be analyzed as no events occurred in this group during the 10-year follow-up.

Fig. 11. Kaplan-Meier curves for SCD in subjects with and without abnormal ECG. Published with the permission of the International Journal of Cardiology Heart and Vasculature.
6 Discussion

6.1 Fragmented QRS complex

The purpose of the first study was to determine 1) the prevalence of fQRS in the general population and 2) resolve the prognostic value of fQRS in subjects with and without underlying cardiac disease. The overall prevalence of fQRS in the general population was high (19.7%) and it was most often observed in the inferior leads. In apparently healthy subjects fQRS was not associated with increased risk of death. In subjects with suspected or known cardiovascular disease and lateral fQRS on ECG the risk of cardiac death was 2.5-fold and the risk of arrhythmic death 3-fold. Fragmentation in the anterior or inferior territory did not predict future fatal events even in subjects with cardiac disease during the average follow-up of 30 years. Our findings are in line with prior studies suggesting that fQRS is associated with cardiac and arrhythmic death in subjects with cardiac disease; however, in our population, only lateral fQRS had prognostic significance. The fQRS was more common in males and the subjects were older than those without fQRS; consequently, there is a probability that fQRS represents underlying CAD.

Most of the prior studies on fQRS have included populations with coronary artery disease and prior myocardial infarction. In subjects with CAD, fQRS on 12-lead ECG has been associated with detection of myocardial scarring and increased total mortality (Das et al., 2006; Das et al., 2008; Mahenthiran et al., 2007). The association of fQRS in acute coronary events has been studied in a substantial number of articles for short- and long-term prognosis. In these populations, fQRS is associated with decreased systolic left ventricular function (Akbarzadeh et al., 2013; Ari et al., 2012; Stavileci et al., 2014), increased risk of arrhythmic events and SCD (Korhonen et al., 2006), and increased risk of total mortality and hospitalization due to heart failure (Das et al., 2009; Korhonen et al., 2010; Lorgis et al., 2013; Pietrasik et al., 2007). Some studies disagree on fQRSs’ sensitivity and specificity for detecting myocardial scar (D. D. Wang, Buerkel, Corbett, & Gurm, 2010); however, fQRS might have prognostic value for future ischemic events without detectible myocardial scarring (Cho et al., 2019).

In addition to subjects with CAD, fQRS has been evaluated in other populations as well. Cardiomyopathies are a diverse group of heart diseases with variable clinical manifestation and prognosis. In subjects with hypertrophic cardiomyopathy, fQRS is associated with VT/VF and SCD with a 3-fold risk.
An increased risk of arrhythmic events in subjects with non-compaction cardiomyopathy, ischemic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy has also been reported (Brenyo et al., 2012; Canpolat et al., 2013; Cetin et al., 2016). A meta-analysis of fQRS in subjects with Brugada syndrome concluded that fQRS increases the risk of arrhythmia in this population (Meng et al., 2017). Overweight subjects with lateral fQRS are suggested to have 2-fold risk of SCD (Narayanan et al., 2015), and fQRS has been related to LVH in hypertensive patients (B. Zhang et al., 2015), diabetes mellitus, and decreased systolic and diastolic left ventricular function (Bayramoglu et al., 2017).

Clinical trials thus far have provided codirectional data that fQRS might add value to risk prediction of future cardiac events. For example, post-MI patients with fQRS have shown to have lower LVEF and higher risk of hospitalization due to heart failure. On the other hand, patients with decreased LVEF are known to have increased risk of SCD. Hypothetically, some of the post-MI subjects with fQRS could benefit from more intensive follow-up of cardiac function and possible evolution of HF.

Before applying fQRS to wide clinical use, more studies are needed. The morphological differences of fQRS should be considered and the classification of fQRS reviewed. For example, identification of high-risk versus low-risk morphologies of fQRS is important from a clinical perspective and should be considered. In most of the studies, the definition of fQRS has followed that presented by Das et al. (Das et al., 2006). This categorization could predispose to intra- and interobserver variability (Haukilahti, Eranti, Kentta, & Huikuri, 2016). As the vast majority of studies of fQRS are performed using selected populations with underlying cardiac conditions, there is an obvious need for future studies involving subjects with healthy hearts. Studies on widespread fQRS in different populations are also needed for further evaluation.

### 6.2 Electrocardiogram to predict cardiac events

The aims were to 1) determine the value of ECG abnormalities in predicting cardiac death (ICD-10 I20-25, ischemic heart diseases) among subjects aged under 65 years without known cardiac condition, and to 2) determine ECG’s ability to predict non-fatal cardiac events (I20-25) and hospitalization. The value of the end points was evaluated after 10 and 30 years of follow-up.
Abnormal ECG was more frequently observed in men, and the subjects with abnormalities were older and more hypertensive compared to those with normal ECG. The incidence of cardiac death was significantly higher among subjects with abnormal ECG than among those with normal ECG. The abnormal ECG increased the risk of cardiac death to approximately 1.5-fold over the 10- and 30-year follow-up periods. During the 10-year period, pathological Q-waves, T-wave inversions, ST-segment depression, prolonged QRS-duration and LBBB were significant independent predictors of mortality. In the complete follow-up of 30 years, pathological Q-waves, T-wave inversions and LVH were the strongest independent predictors of a fatal event. Abnormal ECG did not significantly increase the risk of hospitalization due to non-fatal cardiac causes.

From a methodological point of view, a similar study was conducted in 2014 with subjects free of cardiac disease. (Jorgensen et al., 2014) However, those subjects were considerably older compared to our cohort, and abnormal ECG was present in 30.6% of the subjects, versus 11.6% in our study. Jorgensen and colleagues found that the presence of major ECG abnormalities (Q-waves, ST-depression, T-wave changes, ventricular conduction defects, LVH) increased the risk of fatal CVD event by 30%, which is comparable to our results. Parallel to our findings, they also found that Q-waves, ST-depression and T-wave changes had the highest risk. The C-index showed moderate improvement in risk prediction of cardiac death when ECG abnormalities were added to the model on conventional risk factors (0.705 to 0.719), whereas improvement in our cohort was scarce (10-year analysis from 0.851 to 0.853; 30-year analysis from 0.742 to 0.743). Moreover, evidence from other studies indicates that ECG abnormalities have predictive value for cardiac death, even in the absence of known cardiac disease (Auer et al., 2012).

As a screening tool of future cardiovascular events, the 12-lead ECG is of great interest because of its wide availability, simple interpretation and the high prevalence of cardiovascular disease in the population. The use of 12-lead ECG as a screening tool is an issue under debate. There is some evidence that abnormal ECG in older adults significantly improves risk stratification of CVD events beyond traditional risk factors (Auer et al., 2012); however, there is a lack of evidence from randomized controlled trials for a definite value of resting or exercise ECG versus no screening to prevent these events (Chou et al., 2011). A recent recommendation statement from the US Preventive Services Task Force concluded that it is very unlikely that screening asymptomatic subjects with low risk of CVD events (under 10% during a 10-year period) changes the risk category assessed with traditional risk factors, and screening of these subjects is thus not
recommended (US Preventive Services Task Force et al., 2018). The possibility of harm is present if resting or exercise ECG findings induce subsequent invasive testing. Moreover, there is a lack of evidence as to what extent ECG recordings bring additional value to CVD risk prediction beyond traditional risk factors in asymptomatic subjects with intermediate (10-20%) and high (>20%) risk in 10-year interval (US Preventive Services Task Force et al., 2018).

6.3 Electrocardiographic markers for sudden cardiac death

In the third study, the aim was to evaluate the ability of abnormal ECG to predict sudden cardiac death. Subjects with abnormal ECG were older, more commonly men, and had higher systolic blood pressure and frequency of smoking than those with normal ECG. After 10 years of follow-up, abnormal ECG was associated with the risk of SCD (HR 1.6, P=0.052). Significant independent predictors of SCD were QRS duration >100 ms, QRS-T angle >100°, LVH and T-wave inversions. During the follow-up of 30 years, those with abnormal ECG had 30% (HR 1.3, P=0.007) higher risk of SCD than those with normal ECG. When observed separately, QRS-T angle, LVH and ER were the strongest predictors of SCD in long-term follow-up. Subjects with ≥2 ECG abnormalities had an approximately 3-fold risk for SCD in both short- and long-term follow-ups.

The increasing information and knowledge provided by clinical trials and genetic testing has led to better understanding of risk factors predisposing to ventricular arrhythmias and SCD, such as CAD, channelopathies and cardiomyopathies (US Preventive Services Task Force et al., 2018). However, the predictability of SCD has proven to be difficult since the majority of these events occur in low-risk populations free of underlying cardiac disease (Huikuri et al., 2001; US Preventive Services Task Force et al., 2018). The LVEF is widely used to identify those at high risk for SCD (Maggioni et al., 2013) even though evidence of a direct association to arrhythmia mechanisms is lacking (Wellens et al., 2014). Evaluating the risk of SCD with ventricular function is suggested to be insufficient and suggested to identify approximately one third of subjects at high risk for SCD; the majority of the victims would thus not have met the criteria for appropriate ICD implantation (Stecker et al., 2006). Therefore, there is an obvious need for better prediction methods for the group of low-risk subjects with preserved ventricular function. A study in 2017 aimed to evaluate the power of cumulative ECG risk score beyond LVEF (Aro et al., 2017). They noticed that in subjects with preserved LVEF (>35%) the risk of SCD progressively increased according to the number of
abnormalities present. Subjects with 2 abnormal ECG findings had over 4-fold risk (OR 4.5, P<0.001) of SCD, and the risk increased substantially when 3 or 4 abnormalities were present (OR 10.4 and 26.1, respectively). In addition, this cumulative ECG risk score markedly improved the risk prediction in C-statistics and IDI analyses. The cumulative effect of ECG risk markers for predicting SCD has also been observed in other studies (Reinier et al., 2015).

6.4 Future aspects of electrocardiogram to prevent cardiac events

In the 1970s, a group of physicians introduced a general cardiovascular risk profile, generally known as the Framingham Risk Score (Kannel, McGee, & Gordon, 1976), which is still widely used with some modifications. The aim was to identify subjects at high risk of cardiovascular events by utilizing information about age, gender, systolic blood pressure, serum cholesterol, smoking and glucose intolerance, and since then, this has proven a valid approach to prevent future CVD events (D'Agostino RB et al., 2008). A recent study suggested obvious benefits from physical exercise to prevent CVDs (Winzer et al., 2018).

The 12-lead ECG is a valuable tool in certain populations to identify those at high risk of cardiac events. For example, ECG may identify certain channelopathies and cardiomyopathies, and certain ECG abnormalities may refer to other cardiac diseases such as HF, hypertension and CAD. Therefore, ECG can be regarded as a valuable part of the clinical evaluation. One of the major benefits of ECG is the global availability and wide ability of interpretation. Despite these obvious strengths, it is thought to be unlikely that any single ECG abnormality demonstrates adequate discriminative power for cardiac events, and development of a novel electrical risk score would therefore be useful for better risk assessment in different populations (Narayanan & Chugh, 2015). Electrocardiographic screening, in addition to physical examination and history of young healthy athletes, is systematically executed in some countries, for example Israel, Italy and the United States (Maron et al., 2015) despite the emerging evidence that ECG screening lacks the ability to reduce mortality in this population (Maron, Haas, Doerer, Thompson, & Hodges, 2009; Steinvil et al., 2011).

At present, screening low-risk asymptomatic subjects with resting or exercise ECG to detect those at high risk for cardiac events is not recommended because of insufficient evidence of benefits over harms (US Preventive Services Task Force et al., 2018). The development of automated ECG recordings alongside novel electrical risk score algorithms will probably improve the accuracy of ECG to
identify subjects in need of further clinical evaluation. The GWAs have added fascinating knowledge of the genetic factors predisposing to coronary artery disease, thus improving the ability of early intervention in such individuals (Ripatti et al., 2010; van der Harst & Verweij, 2018).

6.5 Limitations and strengths of the study

The extensive cohort used in this thesis was drawn from different geographical areas, thus representing a good national cross-section of the Finnish population at that time. The demographic information included important clinical variables, and validated questionnaires were used by trained professionals. The death certificates were read by clinical cardiologists to conclude death as arrhythmic or non-arrhythmic and data was collected using reliable national registries.

The cohort used in this thesis represented Finnish population in the 1960s and 1970s. The knowledge of pathophysiology and treatment of cardiac diseases has improved significantly since the era 50 years ago. As the definition of cardiac disease was based on clinical history and/or symptoms referring to cardiac disease, we cannot rule out the possibility of subclinical cardiovascular disease at baseline or evolving of cardiac disease during the long follow-up. The baseline measurements did not include echocardiographic measurements such as LVEF, which is an apparent limitation to determine those with normal cardiac function. Our data involved only few subjects with widespread fQRS; consequently, we were unable to draw any conclusions of this finding. Interactions of fQRS with Q-waves and ST-abnormalities could not be ruled out in subjects with ECG signs of infarction and CAD. Our study followed the definition of fQRS presented in 2006 (Das et al., 2006) and different morphologies of fQRS were therefore not evaluated.

The definition of cardiac disease was based on self-reported symptoms and history (for example, medications, angina pectoris symptoms, smoking, shortness of breath, socioeconomic status), and is thus vulnerable to bias. However, this was a valid method at that time of pre-digitalization. Only total cholesterol was available in our cohort. The study population consisted of middle-aged subjects, which is why the results cannot be adapted to other age groups per se. Furthermore, the population included only inhabitants from Northern Europe; therefore, other ethnic groups should be further studied before drawing any definitive conclusions. The definition of sudden death in this cohort followed that reported in the arrhythmia cardiac pilot study (Greene et al., 1989). However, this definition of
SCD is not free of error since other non-cardiac conditions may lead to sudden death.
7 Conclusion

This thesis studied the value of the electrocardiogram to predict adverse cardiac events in middle-aged general population with and without known cardiac disease. Our study (I) was among the first to evaluate fQRS in the general population, thus adding value to this field of research. Our results indicated that fQRS on lateral leads is associated with cardiac events in subjects with coronary artery disease. Other ECG abnormalities were evaluated using both traditional and novel statistical methods to obtain knowledge on independent and cumulative risk factors observed on ECG. The ECG abnormalities had prognostic value for predicting mortality due to ischemic events (II). However, C-index and IDI analysis showed only marginal improvement in risk prediction beyond the traditional risk factors. Results of study III implied that a 12-lead ECG has a role in predicting SCD, but novel statistical methods failed to demonstrate that ECG abnormalities would have significant value beyond traditional risk markers in categorizing subjects into higher risk class for fatal arrhythmic events. The association of abnormal ECG and SCD was more obvious when $\geq 2$ ECG abnormalities were present.

As a summary, fQRS on 12-lead ECG in subjects with cardiac disease could be a sign of underlying cardiac disease, decreased left ventricular function and increased risk of mortality in selected populations. In asymptomatic middle-aged subjects free of cardiovascular disease, the fQRS is probably a benign variant and quite frequently observed. Future studies should focus on morphological and territorial differences of fQRS among various populations to gain more precise knowledge and value for clinical practice. For the risk prediction value of the selected ECG abnormalities in subjects with no history of underlying cardiac disease, pathological Q-waves, T-wave inversions, ST-depression, QRS-duration $\geq 100$ ms and LBBB were associated with increased risk of cardiac death in short-term follow-up. In addition, pathological Q-waves, T-wave inversions and QRS duration $\geq 100$ ms were associated with death due to ischemic heart disease in long-term follow-up. In the same population, frontal QRS-T angle $\geq 100^\circ$, QRS duration $\geq 100$ ms, LVH, ER and T-wave inversions were associated with the risk of SCD, and the risk increased markedly when $\geq 2$ abnormalities were present.

Future risk prediction algorithms are needed to evaluate short- and long-term prognostic value of the ECG beyond traditional risk factors. Cumulative effect of ECG abnormalities should be regarded in risk prediction, and a combination of high-risk ECG markers for cardiac events should be resolved in future studies. Numerous studies have tried to demonstrate the value of single ECG abnormalities
using varying statistical methods. Before any definite conclusions can be drawn, the association with and the absolute risk of a single ECG abnormality for certain outcomes should be confirmed in studies using novel statistical methods (IDI, C-statistics), different populations, adequate clinical information and uniform definition of ECG findings. Automated ECG interpretation should be developed to decrease intra- and interobserver variability in the assessment of new ECG risk markers.
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List of original articles

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:


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1523. Mälinen, Jari (2019) Studies on acute appendicitis with a special reference to appendicoliths and periappendicular abscesses

1524. Paavola, Timo (2019) Associations of low HDL cholesterol level and premature coronary heart disease with functionality and phospholipid composition of HDL and with plasma oxLDL antibody levels


1526. Szabo, Zoltan (2019) Modulation of connective tissue growth factor and activin receptor 2b function in cardiac hypertrophy and fibrosis

1527. Marttunen, Markus (2019) Lääkkeiden turvallinen toteuttaminen ikääntyneiden hoitohenkilöstön arvioimana


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