Antti Eranti

THE ROLE OF ELECTROCARDIOGRAPHIC ABNORMALITIES, OBESITY, AND DIABETES IN RISK STRATIFICATION FOR SUDDEN CARDIAC DEATH IN THE GENERAL 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 1, Haartman Institute (Haartmaninkatu 3, 00290 Helsinki), on 16 December 2016, at 12 noon

UNIVERSITY OF OULU, OULU 2016
Eranti, Antti, The role of electrocardiographic abnormalities, obesity, and diabetes in risk stratification for sudden cardiac death in the general population.
University of Oulu Graduate School; University of Oulu, Faculty of Medicine

Abstract
The incidence of sudden cardiac death (SCDs) in the western countries is 50 – 100 in a population of 100,000. The most common disease causing SCDs is coronary heart disease. A large proportion of the victims are unaware of the underlying cardiac disease or only mildly symptomatic. Many SCDs could be prevented with therapies targeted to the underlying cardiac disease and with implantable cardioverter defibrillators. However, current protocols identify only patients at highest risk and only a minority of SCDs occur in this group. Thus, markers for identifying subjects at risk for SCD are needed.

The aim of this thesis was to study the roles of abnormalities in the electrocardiogram (ECG), obesity, and diabetes in SCD risk stratification. The prevalence and prognostic significance of the location of QRS transition zone (the chest lead in the ECG in which R wave amplitude ≥ S wave amplitude) and abnormal P terminal force in lead V1 of the ECG were assessed. In addition, the value of ECG abnormalities in SCD risk stratification in subjects with different relative weights were studied. These topics were assessed in a cohort of 10,000 middle-aged Finnish subjects followed over 30 years from national registers.

Delayed QRS transition (occurring at V4 or leftwards) occurred in 16.4% of subjects and a markedly delayed QRS transition (at V5 or leftwards) occurred in 1.3% of subjects. Delayed QRS transition was associated with an increased risk of death and SCD and the risk of SCD was over 1.5-fold among those with markedly delayed QRS transition. An abnormal PTF (≥ 0.04mm·s) was present in 4.8% of subjects and a markedly abnormal PTF (≥ 0.06mm·s) in 1.2% of subjects. A markedly abnormal PTF was associated with an almost 2-fold risk of death and atrial fibrillation, but it did not predict SCDs. Both obesity and diabetes were associated with an increased risk of SCD, but the proportion of SCDs of all cardiac deaths did not increase in subjects with either of these conditions. ECG abnormalities provided most value in SCD risk stratification among normal weight subjects with a low level of risk factors. Overall, these studies provide information on the predictive value of some ECG risk markers and cardiovascular risk factors. However, the definite role of these risk markers in predicting the risk of SCD in general population at an individual level remains indecisive.

Keywords: arrhythmias - cardiac, atrial fibrillation, death - sudden - cardiac, diabetes mellitus, electrocardiography, mortality, obesity
Eranti, Antti, EKG-muutosten, lihavuuden ja diabeteksen rooli sydänperäisen äkkikuolemman riskiarvioissa.
Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta
Oulun yliopisto, PL 8000, 90014 Oulun yliopisto

Tiivistelmä


QRS-transitio tapahtui myöhään (V4:ssä tai sitä vasemmalle) 16.4 %:lla tutkituista ja huomattavasti myöhään (V5:ssä tai sitä vasemmalle) 1.3 %:lla tutkituista. Myöhäinen QRS-transitio liittyi kuoleman ja sydänperäisen äkkikuolemen riskiin. Sydänperäisen äkkikuolemen riski oli yli 1.5-kertainen henkilöillä, joilla oli huomattavan myöhäinen QRS-transitio. Poikkeava PTF (≥ 0.04 mm·s) todettiin 4.8 %:lla väestössä ja huomattavan poikkeava PTF (≥ 0.06 mm·s) 1.2 %:lla väestöstä. Huomattavan poikkeavasta PTF:stä liittyi lähisaksinkertainen kuoleman ja eteisvärien riski, mutta ei äkkikuolemariskiä. Lihavuuteen ja diabetekseen liittyvissä suorittu sydänperäisen äkkikuoelman riski. Toisaalta lihavilla ja diabeetikoilla myös ei-äkkilisten sydänkuolemien riski oli suurentunut, eikä äkkilisten kuolemien osuus sydänkuolemista korostunut. Sydänperäisen äkkikuolemen riskiin liitetty EKG-muutokset paransivat riskiarviota eniten normaalipainoisilla henkilöillä, joilla oli vähemmän sydän- ja verisuonitautien riskitekijöitä. Kokonaisuutena nämä tutkimukset luovat uutta tietoa EKG-riskimarkkereista, lihavuudesta ja diabeteksesta sydänperäisen äkkikuoelman riskiarviossa. Näiden biomarkkereiden lopullinen rooli yksilöitäisi vielä lisätutkimuksia.

Asiastat: diabetes, elektrokardiografia, eteisväriinä, kuolevuus, lihavuus, sydämen rytmihäiriöt, sydänperäinen äkkikuoelma
To my family
Acknowledgements

This study was carried out in Medical Research Center Oulu, University Hospital and University of Oulu and Department of Internal Medicine, Päijät-Häme Central Hospital, in close collaboration with Department of Health, Functional Capacity, and Welfare, National Institute of Health and Welfare during the years 2012–2016. It was supported by grants from Paavo Nurmi’s Foundation, Onni and Hilja Tuovinen’s Foundation, Finnish Cardiac Society, Finnish Medical Foundation, and by a special federal grant (EVO) to Päijät-Häme Central Hospital all of which I gratefully acknowledge.

I am most grateful to my principal supervisor Professor Heikki Huikuri whose world-class expertise, vision, and innovativeness in the field of cardiac electrophysiology and sudden cardiac death have enabled the use of novel viewpoints and thus increased the impact and timeliness of this research vastly. His ability to find directions and answers without delays despite his vast amount of responsibilities has been of key importance for the progress of this study.

I am also deeply grateful to my co-supervisors Docent Tuomas Kerola and Dr. Aapo Aro for their dedication in tutoring me throughout this project. Despite occasional geographical challenges, they have been able to discuss timely problems, prohibit their gain in magnitude in my mind, and find solutions. Their advice in practical matters has made this path a lot less rocky and their substantial contributions in our research articles have been invaluable.

I owe my gratitude to Docent Jani Tikkanen for his enormous effort in collecting most of the electrocardiographic data used in this project. I am very grateful to M.Sc. Harri Rissanen for his deep knowledge of the cohort studied, as well as for his help with the practical problems encountered with the data. I wish to express my gratitude also to my other co-authors Docent Juhani Junttila, Docent Olli Anttonen, Dr. Tuomas Kenttä, Professor Paul Knekt, and Dr. Kimmo Porthan for their contributions.

I also wish to thank the younger members of our research group, Arttu and Anette, as well as the people at the Department of Health, Functional Capacity, and Welfare, for being my workmates and bringing some human interaction around the more solitary research tasks. I thank Seamus Morley and Pertti Väyrynen for their help with English grammar and Juha Lehto for his help in statistical computing with R.
Docent Antti Hedman and Docent Vesa Virtanen are sincerely acknowledged for their constructive and well-grounded comments and expert review of this thesis. I wish to thank my dear friends for counterbalancing the sometimes heavy workload by providing me with great experiences in superb company on skis, mountain bikes, tennis courts, rock climbing cliffs, golf courses, and parties. Your presence and support also in everyday encounters has indeed been a crucial source of energy and joy for me.

Finally, I would like to thank my family Leena, Esa, and Katri, as well as Mummo and Heikki for all their love, caring, and support, which has been most essential to me.

29.10.2016 Antti Eranti
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>CAN</td>
<td>cardiac autonomic neuropathy</td>
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<tr>
<td>CHD</td>
<td>coronary heart disease</td>
</tr>
<tr>
<td>CHD study</td>
<td>Social Insurance Insitution’s Coronary Heart Disease study</td>
</tr>
<tr>
<td>CHF</td>
<td>congestive heart failure</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CKD</td>
<td>chronic kidney disease</td>
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<tr>
<td>ECG</td>
<td>electrocardiogram</td>
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<td>ER</td>
<td>early repolarization</td>
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<td>fQRS</td>
<td>fragmented QRS complex</td>
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<td>HR</td>
<td>hazard ratio</td>
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<tr>
<td>IAB</td>
<td>interatrial block</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 improvement</td>
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<tr>
<td>IGT</td>
<td>impaired glucose tolerance</td>
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<td>IVCD</td>
<td>intraventricular conduction delay</td>
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<td>MC</td>
<td>Minnesota code</td>
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<tr>
<td>mm</td>
<td>millimeter</td>
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<tr>
<td>mV</td>
<td>millivolt</td>
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<tr>
<td>cNRI</td>
<td>continuous net reclassification index</td>
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<tr>
<td>LBBB</td>
<td>left bundle branch block</td>
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<tr>
<td>LQTS</td>
<td>long QT syndrome</td>
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<tr>
<td>LVH</td>
<td>left ventricular hypertrophy</td>
</tr>
<tr>
<td>OGTT</td>
<td>oral glucose tolerance test</td>
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<tr>
<td>PEA</td>
<td>pulseless electrical activity</td>
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<tr>
<td>PTF</td>
<td>p terminal force</td>
</tr>
<tr>
<td>QTc</td>
<td>QT interval corrected for heart rate according to Bazett’s formula</td>
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<tr>
<td>ROC</td>
<td>receiver operating characteristics</td>
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<tr>
<td>RBBB</td>
<td>right bundle branch block</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
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<tr>
<td>USA</td>
<td>the United States of America</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>
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List of original publications

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

Sudden cardiac death (SCD) is a devastating event to the families and relatives of the victim, and unfortunately, such a frequent event that it is a major global health problem. Recent estimates of the incidence of SCD in the western countries range from 50 to 100 cases in a population of 100,000 subjects (Chugh et al. 2008). Approximately half of the SCD victims have not been diagnosed with heart disease or are only mildly symptomatic (Fox et al. 2004, Marijon et al. 2016). Many SCDs could be prevented with treatments and lifestyle interventions targeted on the underlying heart disease, as well as with implantable cardioverter defibrillators (ICDs) that abort the possibly terminal ventricular arrhythmia (Chugh et al. 2008). Despite the advancements in the field of estimating cardiovascular risk at the population level, SCD risk stratification at individual level remains is a challenge. Current guidelines recommend primary prevention ICDs for subjects with severely depressed left ventricular ejection fraction. Primary prevention ICDs are also recommended for subjects with rare cardiomyopathies or inherited arrhythmia syndromes if the risk of ventricular arrhythmias is high based on an individual risk assessment. However, no SCD risk screening is performed in the general population or among mildly symptomatic coronary heart disease (CHD) patients who form the vast majority of SCD victims. (Priori et al. 2015).

Recent research has studied the role of electrocardiographic abnormalities, measures of cardiac function, parameters indicating the tone of the autonomic nervous system, cardiac imaging modalities, biomarkers, and genetic risk markers in SCD risk stratification. A great deal of this research has been conducted on cardiac patients, whereas less focus has been on the general population. Despite the identification of single promising markers, more research is needed before protocols accurate enough to identify high risk individuals can be utilized in the clinical practice. (Deyell et al. 2015, Wellens et al. 2014).

The standard 12-lead electrocardiogram reflects the electrical activity of the heart. It is an attractive tool for SCD risk stratification due to its wide availability, non-invasiveness, and affordable price. Indeed, multiple electrocardiographic abnormalities associated with an increased risk of have been identified. However, there is still room for more accurate and specific risk markers. (Wellens et al. 2014). The prognostic significance of an abnormal QRS transition zone had not been studied previously with regard to SCD risk. Another long-known electrocardiographic abnormality which had been neglected with regard to SCD
risk was P Terminal Force (PTF). PTF was originally introduced as a marker of the severity of left-sided valvular insufficiency in the heart, but it was later shown that it is also related to increased left heart filling pressures, and degeneration of the interatrial conduction pathways (Heikkilä et al. 1973, Morris et al. 1964, Platonov 2012).

The traditional cardiovascular risk factors are generally associated with SCD risk as they promote the progression of CHD which is the cause behind the majority of SCDs. However, recent research has identified potentially arrhythmogenic alterations in cardiac structure and function beyond coronary atherosclerosis related to obesity and diabetes (Bergner and Goldberger 2010, Plourde et al. 2014). However, no consensus has been reached as to whether the proportion of SCD of all cardiac deaths pronounces in these conditions. Also the relationship of impaired glucose tolerance and SCD is scarcely documented. Beyond its physiologic effects, obesity also affects the electrocardiogram (Fraley et al. 2005). Thus, it is uncertain whether the established electrocardiographic SCD risk markers perform similarly in subjects with different relative weights.

The aims of this study were to assess the prevalence and prognostic significance of delayed QRS transition zone and PTF in middle-aged general population. In addition, the roles of obesity and diabetes as SCD risk factors were studied and special attention is paid to whether the risk of SCD exceeds the risk of non-sudden cardiac death in these conditions. The performance of electrocardiographic risk markers of SCD in subjects with different relative weights was tested.
2 Review of the literature

2.1 Sudden cardiac death – scope of the problem

Cardiovascular diseases are estimated to account for 31% of deaths, globally coronary heart disease (CHD) being the most common cause for these deaths (Mendis et al. 2011). Approximately half of CHD deaths have been estimated to be sudden, the percentages in individual studies ranging from 33 to 48 making SCD a major global problem (Deo and Albert 2012, Escobedo and Zack 1996, Fox et al. 2004, Ni et al. 2009). The burden of premature death assessed by estimating potential life lost has been estimated to be greater for SCD than for all individual cancers and most other leading causes of death in the USA (Stecker et al. 2014).

Numerous estimates of the incidence of SCD have been presented in the literature, but large differences exist in the estimates between studies. For example, the estimates of the total number of SCDs in the USA range from 180,000 to > 450,000. The large differences arise from different definitions of SCD, different sources of data, case ascertainment criteria, and data being from different decades. (Kong et al. 2011). The main reason for the differences probably lies in the SCD definitions. It has been shown that using deaths caused by CHD occurring outside of hospital as a proxy for SCD overestimates the SCD incidence compared to studies trying to estimate the rate of arrhythmic deaths using a physician panel assessment taking into account medical reports, autopsy report, and next-of-kin interviews (Chugh et al. 2004, Fox et al. 2005). However, even when careful case ascertainment has been performed, the estimates for USA have been between 180,000–250,000 or 53/100,000 residents translating to 5.6% of total mortality (Chugh et al. 2008). Similar incidence rates have been demonstrated in the West of Ireland (51/100,000) (Byrne et al. 2008). In a study conducted a decade earlier in the Netherlands an incidence rate of 97/100,000 was demonstrated translating to 18.5% of total mortality in a population consisting of residents 20–75 years old (Dubois-Arbouw and van Ree 1997). It has been estimated that approximately half of out-of-hospital cardiac arrests are caused by arrhythmias (ventricular tachycardia [VT] or ventricular fibrillation [VF]) and half by pulseless electrical activity (PEA) or asystole (Ilkhanoff and Goldberger 2012).

The difference in the incidence rates in the above cited studies is also partly explained by the declining SCD incidence rates during the last decades, both in the USA and the Netherlands (Ni et al. 2009, Niemeijer et al. 2015). The observed
decline in SCD incidence rates is in line with decline in overall cardiovascular mortality in high-income countries, which is at least partly related to favorable trends in cardiovascular risk factors and improvements in prevention and treatment of cardiovascular events (Ezzati et al. 2015, Kuulasmaa et al. 2000, Moran et al. 2014). However, the proportion of SCD of all cardiac deaths has remained stable or slightly increased (Fox et al. 2004, Ni et al. 2009, Zheng et al. 2001).

A remarkable concern in SCD is that it is often the first manifestation of heart disease. In large prospective surveys, between 48% and 63% of SCD victims had not been diagnosed with heart disease (Ni et al. 2009, Niemeijer et al. 2015). Therefore, most of these subjects had not been identified as being at high risk for SCD and therefore the most effective preventive measures had not been targeted on them. Given that the prognosis of cardiac arrest is poor despite the developments in resuscitation and intensive care, it would be important to identify the subjects at risk for SCD to prevent the fatal event (Sasson et al. 2009).

2.2 Normal cardiac activation and mechanisms of arrhythmias

The normal cardiac activation originates in the sinus node which is located in the right atrium in the proximity superior vena cava. From the sinus node, the action potential propagates through the atria and to the atrioventricular node, which is the only site for conduction of the action potential from the atria to the ventricles in the normal heart. After a phase of slower conduction through the atrioventricular node, the action potential spreads to the ventricles via the bundle of His to the bundle branches and Purkinje fibers, which penetrate to the myocardium from the endocardial surface.

In the His-Purkinje system and the myocardial cells, the action potential propagates from cell to cell via gap junctions consisting of connexins which allow the movement of ions and small molecules from cell to cell. There are different amounts of subtypes of connexins with different conduction properties, voltage sensitivities and permeabilities in different parts of the heart. The spatial distribution of connexins in the myocardial cells may be altered in cardiac disease. In a canine model of dilated cardiomyopathy, the hypophosphorylation and redistribution of connexin 43 from the end of cardiomyocytes to the lateral border of cardiomyocytes was associated with conduction slowing and arrhythmogenesis. (Akar 2004, Rubart and Zipes 2012). Altered connexin 43 distribution and upregulation of dephosphorylated connexin 43 have also been documented in humans with end-stage dilated cardiomyopathy and discordant conduction
velocities in the presence of increased fibrosis were documented in these hearts (Glukhov et al., 2012).

In the resting cardiomyocyte, the cell membrane potential is normally between -80 to -95 mV. The concentration of Na⁺ is 15 mmol/l inside the cardiomyocyte (145 mmol/l outside), the concentration of K⁺ is 150 mmol/l (4 mmol/l outside), the concentration of Cl⁻ is 5–30 mmol/l (120 mmol/l outside) and the concentration of Ca²⁺ is 10⁻⁷ mmol/l (2 mmol/l outside). The Na-K-ATPase (an energy-dependent ion pump which transfers three ions of Na⁺ out of the cell and two K⁺ ions in the cell at a time) is the main factor maintaining the resting membrane potential. As the action potential first generated in the sinus node (with lesser membrane potential, as a result of Iᵢ current through hyperpolarization-activated cyclic nucleotide-gated ion channels) approaches the cardiomyocyte, the membrane potential in the cardiomyocyte reduces leading to the opening of voltage-gated sodium (Iₙa) and calcium (I_Ca,L) channels and a rapid influx of Na⁺ and Ca²⁺ accompanied with the loss of membrane potential (“rapid depolarization”, Phase 0). This loss of membrane potential and the increased intracellular Ca²⁺ concentration then leads to the inactivation of the Iₙa channel (and I_Ca,L channel which inactivates markedly slower). The increased intracellular Ca²⁺ concentration also triggers the release of Ca²⁺ from the sarcoplasmic reticulum which leads to excitation-contraction coupling (contraction of the heart muscle). (Rubart and Zipes 2012).

This rapid depolarization is followed by early rapid repolarization (Phase 1) which is caused by several outward currents. The rapid depolarization opens the Iₒ channel resulting in a transient outward sodium current. Also the I_ClCa (Ca²⁺ activated chloride channel) and Na⁺/Ca²⁺ exchanger contribute to the early rapid repolarization. (Rubart and Zipes 2012).

A plateau phase (Phase 2) lasting up to several hundred milliseconds follows after the early rapid repolarization and is characterized by relatively low membrane conductance for all ions. An outward current of K⁺ and Cl⁻ ions is coupled by Ca²⁺ moving inwards through open I_Ca,L channels and Na⁺ being exchanged to intracellular Ca²⁺. The low membrane potential leads to closing of voltage dependent I_Kc, channels, thus preventing potassium efflux. (Rubart and Zipes 2012).

The final repolarization (Phase 3) is characterized by the decrease in inwards positive currents (time-dependent inactivation of I_Ca,L channel) and activation of the slow and rapid components of K⁺ currents through I_Kc and I_Kr channels and inwardly rectifying I_K1 channel. After the final repolarization, the membrane potential remains steady, but in certain parts of the heart with cells with pacing
potential (sinus node, Purkinje fibers and in the sinoatrial node) gradually depolarizes leading to cardiac activation in case of a failure in the sinus node. An important feature in multiple ion channels in the heart is refractoriness which means that they can not reactivate until a certain time has elapsed from their inactivation. (Rubart and Zipes 2012). The timing of the ion currents during a cardiac action potential is presented in Figure 1.

Multiple physiologic stimuli (including input from sympathetic and parasympathetic nerves) and pathologic conditions, including ischemia and electrolyte disturbances affect the function of the ion channels responsible for myocardial activation. For example, the I_{Na} channel is partially inactivated by membrane potentials lesser than the normal resting potential (for example, during ischemia and in cases of prolonged action potential or early afterdepolarizations in the long QT syndrome), which leads to the slowing of conduction velocity. (Qu and Weiss 2015). A decrease in I_{K1} activation has been documented in failing cardiomyocytes. It causes slowing of repolarization and predisposes to delayed afterdepolarizations and is believed to have a major role in arrhythmogenesis in heart failure. Also mutations in the genes coding these ion channels have been linked to various arrhythmogenic cardiac conditions such as the Brugada syndrome and different types of long QT syndrome. (Rubart and Zipes 2012).

The two main mechanisms initiating and preserving ventricular arrhythmias are spontaneous depolarizations, either by automaticity or triggered activity (early afterdepolarizations occurring spontaneously during the plateau phase of the action potential or the final repolarization and delayed afterdepolarizations during the diastole) and re-entry. One central mechanism of delayed afterdepolarizations is the rapid mobilization Ca^{2+} from the sarcoplasmic reticulum through the ryanodine-sensitive Ca^{2+} channels which normally open triggered by Ca^{2+} influx to the cell during rapid depolarization. Mutations in the gene coding this ion channel and proteins regulating it have been linked to the catecholaminergic polymorphic ventricular tachycardia. Also the IP_3 receptor Ca^{2+} channel has been documented to be implicated in generation of afterdepolarizations related to ischemia and reperfusion injury, inflammatory processes, and heart failure. (Rubart and Zipes 2012).
Late Na\(^+\) influx through the \(I_{\text{Na}}\) channel can be initiated by the activation of Ca\(^{2+}\)/calmodulin-dependent protein kinase pathway (which is activated in heart failure) and thus lead to increase in intracellular Ca\(^{2+}\) as a product of activation of Na\(^+\)/Ca\(^{2+}\) exchangers (Qu and Weiss 2015).

In re-entry, the depolarization wave propagates continuously in a circular path returning to its site of origin to reactivate it. Typically, a group of cells does not get activated during the initial impulse due to a longer refractory period but regains excitability before the activation diminishes and then may re-excite areas that have
recovered from the initial activation. A macroscopic re-entry loop may form around an infarct scar or in a damaged bundle branch but also microanatomic re-entry has been proposed possible, especially in a fibrotic myocardium but it is difficult to separate from automaticity with current techniques. (Rubart and Zipes 2012).

The presence of some of the mechanisms linked to the initiation and preservation of ventricular arrhythmias may be reflected to the standard 12-lead surface electrocardiogram. These include general or local conduction slowing and abnormalities in repolarization. However, due to the changes in cardiac conduction properties and the function of ion channels as the result of conditions such as heart failure and myocardial ischemia, it is evident that the vulnerability to fatal arrhythmias might not be detectable from an electrocardiogram recorded in the healthy state.

2.3 Underlying aetiologies of sudden cardiac deaths

Sudden cardiac death is not an independent disease, but the possible terminal complication of numerous cardiac diseases. The aetiologies behind sudden cardiac death vary greatly by age of the victim. In young populations, a wide group of cardiomyopathies (dilated, hypertrophic, and arrhythmogenic right ventricular cardiomyopathy), primary electric disorders (for example, long QT syndrome and Brugada syndrome among others), congenital cardiac abnormalities, and myocarditis together are the dominant cardiac conditions behind SCDs. After the age of 30–35 years, CHD becomes the most common underlying cardiac condition. (Eckart et al. 2011, Risgaard et al. 2014). Despite vigorous efforts to identify the underlying cause, including autopsies and genetic screening, also a large proportion of sudden cardiac deaths still remain unexplained (Eckart et al. 2011, Risgaard et al. 2014, Tan et al. 2005). The proportion and number of SCDs caused by CHD greatly increases with advancing age, but the proportion of CHD deaths that are sudden seems to decrease among the elderly (Tung and Albert 2013). Overall, it has been estimated that CHD accounts for 75% of SCD being more common in males (Deo and Albert 2012).

2.4 Risk factors and indicators of increased risk of sudden cardiac death

A plethora of different markers indicating increased risk of SCD both in healthy subjects and patients with CHD or CHF (congestive heart failure) have been
identified (Goldberger et al. 2008, Huikuri et al. 2001). As CHD is the most common disease causing SCDs, consequently traditional CHD risk factors such as smoking, hypertension, elevated blood cholesterol, diabetes, obesity, and family history of CHD are also SCD risk factors (Huikuri et al. 2001). Measures of cardiac function, including both pump function and electrical function, measures of the function of the autonomic nervous system, tests to assess the severity of myocardial ischemia, and markers of cardiac fibrosis obtained by advanced imaging techniques can also be used. (Ambale-Venkatesh and Lima 2014, Goldberger et al. 2008, Huikuri et al. 2001). Some of these risk markers are associated with cardiac pathology in general, whereas others are more related to susceptibility to arrhythmias.

2.4.1 Risk factors of coronary heart disease

It has indeed been confirmed in multiple population-based studies that elevated blood cholesterol, elevated blood pressure, smoking, obesity, family history of CHD, and diabetes increase the risk of SCD (Bertoia et al. 2012, Jouven et al. 1999, Kannel and Thomas 1982, Soliman et al. 2011). Also prediabetic dysglycemic states – impaired glucose tolerance and impaired fasting plasma glucose – which are generally associated with adverse cardiovascular events have been shown to be associated with SCD risk (Curb et al. 1995, Ford et al. 2010, Laukkanen et al. 2012). However, only a few epidemiologic studies have assessed whether these risk factors increase the risk of SCD more than the risk of non-sudden cardiac deaths or non-fatal cardiac events. In early reports from the Framingham study, a greater proportion of cardiac deaths were sudden among obese subjects and smokers (Doyle et al. 1976, Kannel and Thomas 1982). Also in a more recent study, the risk of SCD was more pronounced among the obese than the risk of other manifestations of CHD and also hypertension was a stronger predictor of SCD than other cardiac events in that study (Soliman et al. 2011). The results regarding the proportion of deaths being sudden among diabetes patients are somewhat mixed. Diabetes is a well-established SCD risk factor (Zaccardi et al. 2014). Generally, diabetes has been a similar predictor of both SCD and other cardiac events (Kucharska-Newton et al. 2009, Siscovick et al. 2010). However, in one study, diabetes predicted SCD, but not non-fatal myocardial infarction, and in other study diabetes did not predict SCD (Balkau et al. 1999, Wannamethee et al. 1995). In studies conducted on post-MI patients, it seems that the incidence of SCD is markedly higher in diabetes
patients (Junttila et al. 2010, Yeung et al. 2012). Diabetes, obesity, and hypertension are interesting risk factors of SCD as they independently increase the risk of CHF, which is another important risk factor of SCD, in addition to the CHD risk (Bastien et al. 2014, Falcão-Pires and Leite-Moreira 2011, Kenchaiah et al. 2002, Rydén et al. 2013). There are also data that they might have independent arrhythmogenic properties (Falcão-Pires and Leite-Moreira 2011, Plourde et al. 2014).

Changes in the heart caused by obesity

Obesity affects the structure and function of the heart with multiple mechanisms and is often accompanied by a burden of other cardiovascular risk factors as well (Bastien et al. 2014). These changes include increases in left ventricular cavity size and wall thickness, hypertrophy of cardiomyocytes, pericardial and extra- and intracellular fat accumulation. Subclinical left ventricular contractile abnormalities and impaired diastolic function are often documented among the obese. The processes behind these changes are assumed to be related to increased blood volume and cardiac output among the obese, decreased adiponectin concentrations, excretion of different cytokines, and renin-angiotensin-aldosterone axis activation. Also frequent comorbidities of obesity, hypertension and obstructive sleep apnea, have been suggested to play a role in these findings. (Abel et al. 2008, Iozzo 2011, Plourde et al. 2014). In subjects with morbid degrees of obesity, increased incidence of dilated cardiomyopathy has been observed (Wong and Marwick 2007). Obesity also alters the electrical properties of the heart: QT interval lengthening, increased QT dispersion, decreased heart rate variability and abnormal late potentials in the signal-averaged electrocardiogram have been documented (Plourde et al. 2014).

Interestingly, during the last years, in multiple epidemiologic studies, both in general population samples and among cardiac patients, mild degrees of obesity have been associated with improved outcomes. However, it has been discussed that lower prevalence of smoking, younger age at presentation, and greater prevalence of hypertension allowing for more cardiac medications, and on the other hand, the possibility of pre-existing illnesses as the cause of low weight among the lean might have a confounding role in these findings. (Lavie et al. 2014). Anyhow, the relationship of BMI and both all-cause and cardiac mortalities seems J-shaped (De Gonzalez et al. 2010). The body composition greatly influences the effect of obesity on mortality. Measures of abdominal obesity such as waist circumference and waist
to hip ratio are stronger predictors of mortality and SCD than BMI alone (Adabag et al. 2014, Pischon et al. 2008). Also the lifetime burden of obesity affects the SCD risk. In a recent study conducted in a large cohort of females, elevated BMI at the age 18 predicted SCD - even after adjusting for a more recent BMI (Chiuve et al. 2015). Interestingly, obstructive sleep apnea, a frequent complication of obesity, is also associated with SCD risk (Gami et al. 2013).

**Cardiac pathology caused by diabetes**

Diabetes causes a heavy burden of heart disease due to accelerated coronary atherosclerosis at least partly due to atherogenic dyslipidemia that often accompanies it (Ryden et al. 2013). However, it affects the heart with multiple other mechanisms as well. Hyperglycemia leads to reduced levels of insulin-like growth factor-1, which is a growth factor with multiple targets one of which is suppressing apoptosis of cardiomyocytes. Paradoxically in hyperglycemic states, also the amount of circulating free fatty acids is increased and cardiomyocytes employ more free fatty acids as an energy source. This in turn may lead to intracellular accumulation of toxic intermediates of free fatty acids (lipotoxicity) and an increase in the oxygen demand of cardiomyocytes. Also increased production of reactive oxygen species leads to harmful effects causing cellular damage and disrupting vascular homeostasis. The activity of renin-angiotensin-aldosterone-axis is also locally enhanced. Increased amounts of cardiomyocyte apoptosis and necrosis are thus seen in histologic samples of diabetic hearts, in addition to interstitial and perivascular fibrosis, and myocyte hypertrophy. Based on animal models of diabetic hearts, Ca$^{2+}$ homeostasis in the cardiomyocyte is altered leading to increased Ca$^{2+}$ concentration in the cytosol, which correlates with impaired relaxation and thus diastolic dysfunction. Also systolic dysfunction may develop later in the course of the disease. The aforementioned mechanisms together form the basis for the development of diabetic cardiomyopathy. (Falcão-Pires and Leite-Moreira 2011). Some of these mechanisms are also present in prediabetic dysglycemic states. However, it is generally thought that accelerated atherosclerosis leading to CHD and ischemic events is the predominant mechanism leading to cardiac pathology in prediabetic dysglycemic states. (Ryden et al. 2013).

Cardiac autonomic neuropathy (CAN) is a complication of diabetes arousing growing interest. The altered metabolic milieu and neuronal malperfusion lead to neuronal damage also affecting the autonomous innervation of the heart in diabetes.
Longer nerves are more vulnerable to damage, including the vagus nerve, through which parasympathetic activity is transmitted to the heart. Thus, parasympathetic activity in the heart is first reduced in the course of the disease. This leads to increased sympathetic tone in the heart, but over time, also sympathetic denervation occurs. The most obvious signs of CAN include an elevated resting heart rate and decreased baroreflex sensitivity, as well as heart rate variability. The increased sympathetic tone in the heart induces insulin resistance and promotes the use of free fatty acids as a source of energy. Both the increased fatty acid utilization and the increased sympathetic tone increase the oxygen demand in the heart and also lead to increased production of reactive oxygen species. It has been proposed that this increased oxygen demands makes the diabetic heart especially vulnerable to increased workloads and ischemia. Damage to the autonomic nerve fibers disrupts also the regulation of microvasculature in the heart further worsening the oxygen supply. Expectedly, the presence of CAN has been associated with increased cardiovascular mortality with a high proportion of deaths attributed to sudden cardiac death. (Kuehl and Stevens 2012). The mechanisms behind the increased risk of SCD in diabetes patients have been discussed. In addition to the extent of coronary atherosclerosis and heart failure, autonomic imbalance, silent ischemia, and QT interval prolongation, a frequent finding in diabetes patients, and especially subjects with CAN, have been proposed (Bergner and Goldberger 2010). An important remark that might explain the conflicting data regarding the proportion of cardiac deaths being sudden in diabetes in epidemiological studies and in studies following post-MI patients is that in type 2 diabetes, coronary atherosclerosis begins to develop already in the prediabetic state, whereas the possible arrhythmogenic complications of diabetes, heart failure and CAN, develop late in the course of the disease (Rydén et al. 2013).

Other risk factors of CHD

Hypertension causes left ventricular pressure overload and is accompanied by increased sympathetic activation and altered concentrations of multiple hormones, growth factors, and cytokines. These conditions lead to an increase in cardiomyocyte size, alterations in the composition of extracellular matrix, and accumulation of fibrosis in the heart and in the course of time left ventricular hypertrophy (LVH) develops and may eventually lead to heart failure. (Drazner 2011). Expectedly, LVH has been shown to be associated with reduced survival and an increased risk of SCD (Haider et al. 1998, Levy et al. 1990). The mechanisms
behind the SCD risk in LVH change during the course of the disease. Action potential duration and refractoriness prolongs in mild to moderate hypertrophy and an increased predisposition to early afterdepolarizations have been documented as well. Also changes in Na-Ca exchange have been documented. In severe hypertrophy connexin43 expression and the amount of gap junctions are reduced and alterations in the potassium homeostasis of cardiomyocytes are observed. Fibrosis, increased sympathetic tone, and myocardial ischemia which is often present in subjects with a long course of hypertension together contribute to the arrhythmia risk in the presence of the foremost mentioned electrical alterations. (Wolk 2000).

Age and sex substantially influence one's risk of adverse cardiac events. The risk increases with advancing age as the cumulative exposure to cardiovascular risk factors increases. Cardiovascular diseases are a major cause of mortality also in women, but their risk is postponed compared to men. (Perk et al. 2012). The impact of cardiovascular risk factors seems somewhat different in men and women as it has been shown that diabetes is a stronger risk factor among women and gender differences exist in the impact of high-density lipoproteins, lipoprotein (a) and triglycerides (Van Lennep et al. 2002). SCD incidence also increases with advancing age, but a smaller proportion of cardiac deaths are sudden in the oldest age groups. Among women, a smaller proportion of SCD are attributed to CHD and the increase in SCD incidence observed with advancing age presents later than among men. (Chugh et al. 2008, Deo and Albert 2012). Traditional cardiovascular risk factors and previous myocardial infarction or heart failure are strongly predictive of SCD also in women (Bertoia et al. 2012). The gender- and age-based composition of a population-based SCD register is presented in Figure 2.
Fig. 2. Gender- and age-based composition of a population-based SCD register. Adopted from Chugh et al. 2004 with permission of the publisher. Copyright © 2004 American College of Cardiology Foundation.

One more cardiovascular risk factor worth mentioning regarding the SCD risk is chronic kidney disease (CKD). Even though subjects with CKD often present with diabetes and hypertension, CKD is an independent risk factor of CHD. It has been estimated that 20–25% of deaths among hemodialysis or peritoneal dialysis patients are SCDs. Measures of kidney function predict adverse cardiac outcomes, but also albuminuria is associated with worse prognosis independent of kidney function. Mechanisms leading to adverse events among CKD patients include uremia-related protein carbamylation leading to endothelial dysfunction and increasingly atherogenic forms of low density lipoprotein. Also indicators of oxidative stress are elevated in CKD. Altered vitamin D metabolism may contribute to cardiac hypertrophy and increased levels of cardiotoxic steroids may induce myocardial dysfunction and fibrosis. (Tonelli et al. 2016). In hemodialysis patients, also alterations in electrolyte concentrations, acid-base-balance, and various metabolite concentrations contribute to the arrhythmia risk (Franczyk-Skóra et al. 2012).

2.4.2 Role of established cardiac disease

As myocardial ischemia, myocardial scarring, and myocardial fibrosis are important pathophysiologic components in arrhythmogenesis, cardiac disease is expectedly an important risk factor of SCD. This conception was confirmed already
in early reports. In the Framingham Study, the incidence of SCD varied from 2.3-fold to 12-fold in different age and sex categories in subjects with CHD compared to subjects free of CHD and the risk was generally more pronounced in males and younger subjects (Kannel and Schatzkin 1985). In a community-based study from the Netherlands, subjects with known cardiac disease were at 11-fold risk of SCD. In this study, only 20% of the SCD victims with previous myocardial infarction who had echocardiographic data available had left ventricular ejection fraction (LVEF) > 50% and over 40% had LVEF ≤ 30% (Dubois-Arbouw and van Ree 1997). Later, in another study from the same area, it was shown that within the heart failure population, the incidence of SCD increases with worsening pump function (Gorgels et al. 2003). In a population based study in Oregon, similar trends were observed, but only in 30% of SCD victims who had had an echocardiography before SCD the LVEF was ≤ 35% (Stecker et al. 2006). It has also been shown in subjects with previous myocardial infarction that heart failure increases the risk of SCD 4-fold (Adabag et al. 2008). Also in a study following subjects after myocardial infarction with LVEF ≤ 40% or clinical or radiological evidence of heart failure, it was documented that the incidence of SCD increases with worsening LVEF. In this study (Solomon et al. 2005), 26% of patients had LVEF ≤ 30%, but 49% of SCDs occurred in this group.

Of all risk markers related with SCD, LVEF is the most important by far guiding the selection of patients with heart failure to receive therapy with ICDs (Priori et al. 2015). These devices have been used in prevention of SCD in the heart failure population after their efficacy was shown in randomized controlled trials (Bardy et al. 2005, Moss et al. 2002). Current guidelines suggest the implantation of an ICD to symptomatic heart failure patients with LVEF ≤ 35% after three months of optimal medical therapy both in ischemic and non-ischemic aetiologies. They are also used for secondary prevention in subjects with documented VF or hemodynamically non-tolerated VT in the absence of a reversible cause, and also in selected patients inherited primary arrhythmia syndromes. (Priori et al. 2015).

2.4.3 Electrocardiographic markers of risk of SCD and adverse prognosis

The electrocardiogram has been one of the most important diagnostic tools in cardiology for over a century. The standard 12-lead electrocardiogram shows the rhythm of the heart and provides information of the impulse propagation properties
of the cardiac structures. Multiple pathologic conditions such as ischemia, hypertrophy, scarring, abnormal impulse conduction, and infiltrative cardiac disease can be either diagnosed or suspected based on the interpretation of the electrocardiogram. During the recent decades, increasing interest has aroused in the field of the use of the electrocardiogram as a risk stratification tool, and the assessment of the risk of SCD has been of particular interest. Markers of increased SCD risk in the general population that can be observed from the standard 12-lead electrocardiogram are reviewed in the following sections. Most of these markers reflect the presence of cardiac pathology and are markers of adverse prognosis and not specifically related to increased risk of SCD.

**Abnormalities in the rhythm of the heart**

Elevated resting heart rate has been shown to be associated with all-cause mortality, cardiac mortality, and SCD in the general population. The risk seems to be especially pronounced in subjects with resting heart rate \( \geq 90 \text{ bpm} \). The proposed mechanisms behind this association include autonomic dysfunction or sympathetic overactivity, but also associations with atherosclerosis and myocardial energetics have been proposed. (Ho *et al.* 2014, Jouven *et al.* 1999, Shaper *et al.* 1993). Atrial fibrillation, a common arrhythmia among the elderly and subjects with cardiac disease, is associated with a 2-fold risk of death and 3-fold risk of heart failure in the general population (Benjamin *et al.* 1998, Stewart *et al.* 2002). It generally predicts SCD and non-sudden cardiac death similarly in the general population, but some data exists that it might carry a greater risk for SCD than non-sudden cardiac death. However, as atrial fibrillation often presents with CHD or CHF and multiple other risk factors for heart disease, the individual contribution of atrial fibrillation to prognosis is difficult to separate. (Chen *et al.* 2014, Chen *et al.* 2013). Premature ventricular contractions have been documented to be associated with adverse prognosis in subjects with cardiac disease, but are often documented in subjects without overt heart disease in whom their significance has been less well-established. However, a recent meta-analysis combining data from general population studies suggests that premature ventricular contractions are associated with a 2-fold increased risk of SCD and also with total cardiac mortality. (Ataklte *et al.* 2013). Also the presence of premature atrial contractions is associated with CHD events, but no statistical significance has been reached in studies assessing the SCD risk associated with premature atrial contractions. (Cheriyath *et al.* 2011).
Abnormalities of the P wave and PR interval

The P-wave on the electrocardiogram represents the depolarization of the atria of the heart. Normally, originating from the sinus node near the superior vena cava the depolarization proceeds to the right atrium and via interatrial connection routes to the left atrium. The shape of the P wave is determined by the position of the heart in the thorax, the anatomy of the atria, and interatrial conduction which is also affected by the tone of the autonomous nervous system. The terminal portion of the P-wave represents left atrial activation in sinus rhythm. (Lemery et al. 2007, Platonov 2012). P wave duration is a crude marker of interatrial conduction and durations of ≥110ms are considered abnormal and indicative of interatrial block (IAB) (Chhabra et al. 2014). In the normal heart, the interatrial conduction occurs through multiple routes which include the anteriorly and superiorly located Bachmann’s bundle and the posteriorly located interatrial conduction routes. The posterior fibers near the fossa ovalis are generally thinner and thus potentially more vulnerable to damage than the Bachmann’s bundle. Interatrial conduction through the Bachmann’s bundle is often documented in subjects with paroxysmal atrial fibrillation. More advanced atrial fibrosis interrupts the conduction through the posterior fibers and the Bachmann’s bundle and results in interatrial conduction through inferior routes near the coronary sinus. Conduction over the Bachmann’s bundle results in superior to inferior left atrial activation, which is seen as a terminal negative deflection of the P-wave in lead V1 in the electrocardiogram. Conduction through the inferior conduction routes leads to inferior to superior activation of the left atrium which is seen as a negative terminal portion of the P wave in the inferior leads of the electrocardiogram. (Chhabra et al. 2014, Platonov 2012). The locations of these conduction routes are presented in Figure 3.

Measuring the size of the terminal negative portion of the P wave in lead V1 of the electrocardiogram was first proposed by Morris et al. (1964). They showed that the product of the duration and amplitude of the negative terminal portion of the P wave in lead V1, P Terminal Force (PTF), separates patients with left-sided valvular lesions from normal subjects when exceeding 0.04mm·s and reflects the severity of the disease. The magnitude of PTF has been shown to correlate with the filling pressures of the left side of the heart in various cardiac conditions in both acute and chronic settings (Heikkilä et al. 1973, Kasser and Kennedy 1969, Kölbl et al. 1977). Both PTF and IAB have been shown to be associated with left atrial enlargement detected with echocardiography in early studies conducted on cardiac
patients the sensitivities and specificities varying depending on the cutoff used and the population studied (Hazen et al. 1991, Miller et al. 1983). However, in a more recent study using computed tomography to assess left atrial size, only IAB was associated with left atrial enlargement (Truong et al. 2010). Both IAB and PTF have been associated with increased mortality, but the evidence for PTF has been based on studies on elderly subjects or cardiac patients until recently (Hsieh et al. 2005, Kaykha et al. 2010, Magnani et al. 2010).

Fig. 3. A schematic illustration of the interatrial conduction routes. The three main interatrial conduction routes are the Bachmann’s bundle (BB), posterior routes near the fossa ovalis (FO), and the inferior route near the coronary sinus (CS). SVC is superior vena cava, SN sinus node, IVC inferior vena cava, AV atrioventricular node, LA left atrium, RV right ventricle, and LV left ventricle.
In recent studies, both PTF and IAB (>120ms in this study) have been associated with atrial fibrillation and mortality in general population samples and subjects presenting with PTF were also at increased risk for SCD (Magnani et al. 2014, Tereshchenko et al. 2014). Interestingly, both PTF and P wave duration were associated with left ventricular interstitial fibrosis based on a cardiac magnetic resonance imaging study (Win et al. 2014). The measurement of PTF is demonstrated in Figure 4.

**Fig. 4.** A schematic illustration demonstrating the assessment of a pathological PTF in an electrocardiogram with paper speed 50 mm/s and calibration of 10 mm/mV. PTF is calculated by multiplying the duration of the terminal negative deflection of the P wave (d, in seconds) with its amplitude (a, in millimetres).

The PR interval represents the time from the beginning of atrial depolarization to the beginning of ventricular depolarization. The PR interval is influenced by heart rate and autonomic tone, as well as degeneration of the cardiac conduction system. Prolongation of the PR interval to > 200 ms, also called as first degree atrioventricular block, has been shown to be associated with increased risk of death, pacemaker implantation, and atrial fibrillation in the general population but the increment in risk has been estimated to be only 1.3-fold for atrial fibrillation and 1.4-fold for death (Cheng et al. 2014, Cheng et al. 2009). However, in one big study
with a younger population than in other studies, PR interval prolongation was not associated with adverse outcomes (Aro et al. 2013).

Despite the associations of PTF, IAB, and PR interval with adverse events, one should bear in mind that they are also relatively common findings in presumably healthy subjects. In a multi-ethnic general population cohort in middle-aged subjects who were free of cardiac disease or cardiovascular risk factors, the 95th percentiles between races and sexes ranged from 188–228ms, 114–130ms, and 0.03–0.06mm·s for PR interval, IAB, and PTF, respectively (Soliman et al. 2013).

**Electrocardiographic changes related to altered impulse conduction in the ventricles**

A plethora of electrocardiographic abnormalities reflecting the presence of CHD, impaired conduction, left ventricular hypertrophy, or abnormal repolarization have been linked to increased SCD risk (Wellens et al. 2014). The most specific electrocardiographic signs of CHD include Q-waves and ST-segment depressions. Wide Q waves in leads other than aVR and V1 are often caused by a transmural myocardial infarction and thus associated with the risk of SCD. (Surawicz and Knilans 2008a, Wellens et al. 2014). ST-segment depressions which can be attributed to myocardial ischemia, but also left ventricular hypertrophy have been shown to be associated with an increased risk of SCD (Thorgeirsson et al. 2005, Wellens et al. 2014).

Locally impaired impulse conduction in the heart may produce conditions favourable for the initiation of tachyarrhythmias by re-entry mechanism. Fragmented QRS (fQRS) has been proposed to represent a conduction delay caused from inhomogenous activation of the ventricles due to a myocardial scar (Jain et al. 2014). Originally shown to be a highly sensitive and specific marker of myocardial scar in patients referred to myocardial stress testing, it has been shown to be associated with increased mortality and greater incidence of arrhythmic events in populations of cardiac patients (Das et al. 2006, Jain et al. 2014). However, fQRS has been shown to be a common finding, especially in the inferior leads of the electrocardiogram in general population samples. In one study (Terho et al. 2014) based on a 30-year follow-up of a general population sample of over 10,000, fQRS was present 19.7% of the subjects and did not predict adverse events. However, in subgroup analyses of this study, a lateral fQRS was shown to be predictive of all-cause mortality, cardiac mortality, and a 3-fold risk of SCD in subjects with a known cardiac disease. One detail that may explain the differences between these
studies is that in the later cited study, the paper speed of the electrocardiograms was 50mm/s allowing for detection of lesser fragmentations, whereas in a majority of other studies, it was 25mm/s. However, also in one population based case-control study of obese SCD victims using paper speed of 25mm/s, only lateral fragmentations were associated with an increased risk of SCD (Narayanan et al. 2015). Thus, fQRS seems a useful marker of myocardial scar and adverse prognosis in patients with advanced heart disease, but lacks specificity in general population samples.

Prolongation of the QRS complex may result from bundle branch blocks, nonspecific intraventricular conduction delay (IVCD), or pre-excitation. Prolonged QRS complex is a well-established marker of adverse prognosis in subjects with heart disease (Kashani and Barold 2005). Recently, large general population studies have assessed the prognostic significance of prolonged QRS duration also in general population. Both the presence of left bundle branch block and IVCD (defined as QRS duration ≥ 110 ms) have been consistently associated with over a 2-fold risk of SCD in general population. (Aro et al. 2011a, Kurl et al. 2012). Increases in mortality have been documented also in subjects with QRS duration ≥ 100 ms in the absence of bundle branch blocks (Zhang et al. 2016a). The prognostic significance of right bundle branch block is less well established as it has been associated with adverse prognosis in some studies (Badheka et al. 2013, Bussink et al. 2012), but in other studies, it has seemed to be a benign finding, at least in the absence of heart disease (Aro et al. 2011a, Zhang et al. 2016a).

Abnormalities of the electrical axes of the QRS complex and T wave

The normal electrical axis of the QRS complex in the frontal plane in adults ranges from -30 to 90 degrees and is affected by age and body composition. Leftward shifts of the frontal QRS axis are often documented with advancing age and increasing degrees of obesity (Fraley et al. 2005, Surawicz et al. 2009). They may also be associated with left ventricular hypertrophy (Hancock et al. 2009). Thus, in univariate models, a leftward electrical axis of the heart has been associated with adverse prognosis in general population samples, but this association has diminished after a comprehensive multivariate adjustment (Aro et al. 2011b, Estes et al. 2015, Tan et al. 2009). Also right axis deviation has been univariately associated with increased cardiac mortality, but in another study after adjustments, it did not predict SCD or other adverse outcomes (Aro et al. 2011b, Tan et al. 2009).
QRS transition zone is defined as the chest lead of the electrocardiogram in which rS pattern turns to Rs, or in which an isoelectric RS pattern is present. It is related to the electrical axis of the heart in the horizontal plane and occurs normally between leads V3 and V4. Thus, QRS transition occurring at < V3 is early and ≥ V4 is delayed. Also terms counterclockwise (rightward) and clockwise (leftward) rotation of the heart have been used. (Rose and Blackburn 1968). An electrocardiogram of a subject with markedly delayed QRS transition is presented in Figure 5. Interestingly, only in two thirds of 102 subjects studied with computed tomography, abnormal QRS transition could be explained by anatomical rotation of the heart (Tahara et al. 1991). In a recent report assessing the correlates of delayed QRS transition zone in a population-based SCD-victim case-control study, delayed QRS transition was independently associated with prior myocardial infarction, reduced left ventricular ejection fraction, and LVH (Aro et al. 2016). In this study, delayed QRS transition was associated with SCD and the relationship was independent of left ventricular ejection fraction. Despite being defined decades ago, QRS transition zone has received only little attention regarding its prognostic significance, excluding the aforementioned study. In one study (Nakamura et al. 2012) based on Japanese population, early QRS transition was associated with favourable outcome and delayed transition was associated with total mortality, cardiac mortality and CHF. In that study, delayed transition was more prevalent in older age groups and often also other abnormal electrocardiographic changes were present in subjects with delayed QRS transition, but the association with adverse outcomes remained significant after multivariate adjustment. In a recent study, largely similar results regarding all-cause and cardiovascular mortality were observed in a multi-ethnic population free of cardiovascular disease at baseline (Bradford et al. 2014). Also a related electrocardiographic phenomenon, poor R wave progression (defined as R wave amplitude in lead V3 ≤ 0.3 mV and ≥ R wave amplitude in lead V2), was associated with all-cause mortality and cardiovascular mortality in a Finnish general population cohort (Anttila et al. 2010).

QRS-T angle is the angle between the QRS axis and T wave axis and it is considered to represent either primary or secondary repolarization abnormality. It can be assessed spatially either by vectorcardiography or by calculating an estimate of the vectorcardiogram from the standard 12-lead electrocardiogram. As this approach requires digital ECG tracings and is not readily available in all commercial ECG recording devices, also QRS-T angle in the frontal plane has been studied.
Fig. 5. An ECG of a 49-year old female with markedly delayed QRS transition at lead V5. Paper speed is 50 mm/s and calibration 10mm /mV. Adapted from Aro et al. 2014 with permission from publisher. Copyright © 2014, Elsevier.

An abnormal QRS-T angle (no consensus of cutoffs have been established, but generally cutoff from 90 to 135 degrees have been used for both spatial and frontal QRS-T angle) has been shown to predict SCD, cardiac mortality and all-cause mortality, both in general population and heterogenous populations of cardiac patients (Oehler et al. 2014). Interestingly, in studies which reported hazard ratios
for SCD and total mortality in subjects with abnormal QRS-T angle, the hazard ratios for SCD were greater, both in general population and non-ischemic cardiomyopathy patients (Aro et al. 2011a, Laukkanen et al. 2014, Pavri et al. 2008).

Abnormal T-wave inversions predict adverse prognosis, also when the QRS axis is not accounted for in the analysis. They are most commonly related to repolarization abnormalities caused by ventricular hypertrophy or ischemia. In adults, a T wave inversion is normal in lead aVR and also commonly seen in leads aVL, III, and V1. Normally, upright T waves are seen in leads I, II, and V3–V6. (Rautaharju et al. 2009). In a study based on a general population sample of over 10,000 subjects followed over 30 years, T wave inversions in leads V1–V3 were not associated with adverse prognosis. In this study, the presence of T wave inversions with an amplitude of 0.1mV or deeper in leads I, II, aVF, or V4–V6 was associated with 3-fold risk of SCD and 1.6-fold risk of death. (Aro et al. 2012). Similar results were seen in another study in which a population of middle-aged men was followed (Laukkanen et al. 2014).

**Early repolarization and other repolarization abnormalities**

The term early repolarization has traditionally referred to upsloping ST segments commonly seen in the precordial leads of young subjects and athletes. However, during the last decade, it has been under vigorous research after the elevation of the J point (QRS-ST-junction) in inferior or lateral leads was shown to be a prevalent finding in subjects with idiopathic ventricular fibrillation predicting arrhythmia recurrence. (Haissaguerre et al. 2008). Epidemiological studies have shown that an early repolarization pattern, especially in inferior/lateral leads accompanied with horizontal/downsloping ST segment, predicts SCD also in the general population (Tikkanen and Huikuri 2015, Tikkanen et al. 2011). In a recent meta-analysis, subjects with early repolarization pattern were at 1.7-fold risk of SCD, but no stratification for ST segment morphology was performed in this study (Wu et al. 2013). During the last years, different phenotypes of the ER pattern have been identified of which some are more benign and some are related with worse prognosis (Tikkanen and Huikuri 2015). One thing that has led to differences in results between studies assessing the prognostic significance of different early repolarization patterns has been the heterogeneity of definitions of early repolarization pattern. Due to recent efforts to standardize the definitions, more generalizable results are expected in the future (Macfarlane et al. 2015). However,
at the moment, it is recommended that the term early repolarization syndrome should be used only in subjects with idiopathic ventricular fibrillation and that the presence of an early repolarization pattern in an asymptomatic subject should not lead to treatment interventions before more knowledge accumulates (Priori et al. 2015).

T peak to T end interval measured from the lead V5 correlates with the dispersion of ventricular repolarization (Kors et al. 2008). Increased dispersion is associated with ventricular arrhythmias and prolongation of T peak to T end interval has indeed been associated with SCD, both in a general population case-control study and subjects with systolic heart failure (Panikkath et al. 2011, Rosenthal et al. 2015). However, in another general population study, prolongation of T peak to T end interval was not associated with SCD (Porthan et al. 2013). With recent advances in technology automated assessment of several T wave morphology parameters associated with abnormally heterogeneous repolarization such as parameters assessed with principal component analysis, T wave morphology dispersion, and T wave residuum have become available and these markers have been shown to predict SCD (Porthan et al. 2013). Also a measure of T wave heterogeneity in leads V4–V6 based on second central moment analysis was shown to be associated with an increased risk of SCD and this result was based on an automated screening of a digital ECG archive (Kenttä et al. 2015). Thus, in the future, automated ECG archive based screening techniques may be used to identify subjects with an elevated risk of SCD. The most recent advancement in the field of digital ECG signal processing was the development of an electric heterogeneity risk score combining five measures automatically calculated from digital 12-lead ECG tracings (Waks et al. 2016). This risk score was independently associated with SCDs in general population and also improved risk stratification based on reclassification measures.

**QT interval**

QT interval represents the time from the earliest ventricular activation to the end of repolarization. QT interval shortens with increasing heart rate and is therefore corrected for heart rate to make the measurements comparable. The most commonly used formula for correction of QT interval for heart rate is the one established by Bazett, but due to its limitations, other formulas are also available. In addition to heart rate, also gender, multiple drugs, and disorders of calcium
homeostasis affect the QT interval. Generally, heart rate corrected QT interval (with Bazett’s formula, QTc) $\geq 450$ ms for males and $\geq 460$ ms for females are considered abnormal in the general population. (Rautaharju et al. 2009). In the extremes of the spectrum of QT interval, lie heritable primary arrhythmia disorders long QT syndrome and short QT syndrome. QTc $\geq 480$ ms is generally suggestive of long QT syndrome, but it may be diagnosed also in subjects with shorter QTc if additional criteria are met or a pathologic mutation is detected. Short QT syndrome is characterized by QTc $\leq 340$ ms or $\leq 360$ ms if additional criteria are met. (Priori et al. 2015). Modest increases in QTc in the absence of the aforementioned inheritable arrhythmia syndromes are associated with increased mortality at population level (Zhang et al. 2011). In a recent study with a population of 170,000 subjects, the women who presented with the shortest QTc intervals were at an increased risk for death in addition to subjects with QTc in the longer end of the spectrum (Nielsen et al. 2014). Prolongation of QTc interval has been strongly associated with SCD in general population and the risk seems to increase gradually as the QTc interval lengthens (Chugh et al. 2009, Straus et al. 2006).

**Electrocardiographic changes in left ventricular hypertrophy**

Left ventricular hypertrophy leads to changes in the electrical axis of the QRS complex, increases in voltages, delayed intrinsicoid deflection (time from QRS onset to R peak $\geq 0.05$ s in lead V5 or V6), and the presence of repolarization abnormalities in the electrocardiogram. Multiple electrocardiographic criteria for the diagnosis of LVH with varying sensitivities and specificities in different populations have been established. Of these, the Sokolow-Lyon’s voltage, Cornell’s voltage-duration product, and the Romhilt-Estes point score system are among the most used. (Surawicz and Knilans 2008b). Given the functional, histological, and electrical changes in the heart occurring with LVH reviewed previously, expectedly also electrocardiographically detected LVH has been long known to be associated with SCD (Kannel et al. 1975). Electrocardiographic LVH is also associated with all-cause mortality and the risk of death increases with an increasing number of signs of LVH on the electrocardiogram (Estes et al. 2015). Interestingly, recent data suggests that echocardiographic and electrocardiographic LVH are somewhat distinct entities. The former reflects more anatomical remodelling and the latter electrical remodelling and both of these findings independently contribute to the SCD risk. (Narayanan et al. 2014). Also delayed intrinsicoid deflection in leads V5 and V6, which is a part of the Romhilt-Estes point score system and is often seen
in LVH, has been shown to predict SCD independently of echocardiographically detected LVH and various other important confounders (Darouian et al. 2016). Regression of both Cornell’s voltage-duration product and Sokolow-Lyon voltage during antihypertensive treatment has been shown to reduce the risk of SCD (Wachtell et al. 2007).

**Overall usefulness of the electrocardiogram in SCD risk stratification**

The electrocardiogram has numerous benefits as a risk stratification tool. It is cheap, non-invasive and widely available through healthcare systems. It is also routinely recorded if a patient presents with symptoms attributable to heart disease and also during yearly control visits to the practitioner in a wide range of conditions. This is important because almost half of myocardial infarctions defined by the occurrence of a new Q wave to the electrocardiogram are silent (not diagnosed during the acute phase) and these infarctions are associated with adverse prognosis as well (Zhang et al. 2016b).

Modern digital ECG archives enable automatic screening procedures and the screening may be repeated if new risk markers emerge. However, in a population at low risk, the predictive value of an electrocardiogram as a single test is low. In addition, the prevalence of electrocardiographic abnormalities, which have had the highest relative risks for SCD in population based studies, such as IVCD and high-amplitude inferior early repolarization pattern, have been relatively low. Also the optimal combination of electrocardiographic parameters to be used in risk stratification remains to be established. (Deyell et al. 2015, Wellens et al. 2014).

One area which has received only little attention previously is the prognostic significance of the presence of multiple electrocardiographic abnormalities simultaneously. For example, it was recently shown that subjects with delayed intrinsicoid deflection are at higher risk of SCD if they are at the highest quartile of JTc interval duration (Darouian et al. 2016). Thus, it is likely that the full potential of the ECG still remains to be established.

**2.4.4 Genetic abnormalities as indicators of SCD risk**

Family history of SCD has been regarded as an established risk factor for SCD for years. In a 23-year follow-up of 7,746 middle-aged French men, a multivariate-adjusted hazard ratio of 1.80 (95% confidence interval [CI] 1.11–2.88) for SCD
was demonstrated for subjects with parental SCD (Jouven et al. 1999). This finding has been confirmed with case-control studies, of which one compared ST-elevation myocardial infarction patients with or without primary VF and another SCD victims, acute myocardial infarction patients and controls (Bezzina et al. 2006, Kaikkonen et al. 2006).

Although a strong hereditary component has been documented in SCD risk in epidemiological studies, the efforts to discover genes explaining this association in the general population have been disappointing. A handful of candidate-genes also present in primary electrical disorders have been shown to be associated with SCD risk in the general population, but most of these findings remain to be independently replicated. In a study using a custom single nucleotide polymorphism (SNP) array of almost 120,000 SNPs, two SNPs associated with SCD were found. These findings also remain to be replicated. (Marsman et al. 2013). In genome-wide association studies, two candidate-genes associated with SCD risk have been proposed. One of these is located near the gene coding coxsackievirus and adenovirus receptor. This receptor is located in the intercalated disc which is a part of the gap junction. The receptor has a role in viral myocarditis and, based on mice studies, has also seemed to have a role in electrical impulse conduction in the heart. (Bezzina et al. 2010, Marsman et al. 2013). The other is related to BAZ2B gene, which is expressed in the heart but no exact molecular mechanism related to cardiac electrical properties has been documented yet (Arking et al. 2011, Marsman et al. 2013). What is more, efforts to replicate these findings have also yielded inconsistent results. It should be also noted that most of the studies conducted have had small sample sizes. Also the nature of CHD as a disease in which lifestyle factors largely modify the course of the disease weaken the relative contribution of genetic factors compared to the Mendelian diseases. New sequencing technologies and better understanding of genetic modifiers and epigenetics might allow for breakthroughs in this field in the future. (Marsman et al. 2013).

Even though genetics provide only little help for the clinician in SCD risk stratification in the general population, they have nevertheless got a central role in diagnostics, predicting prognosis, screening of family members, and responses to medications in multiple inherited electrical disorders of the heart. For example, in the LQTS, certain mutations predict a good response to sodium channel blockers. The identification of the genes behind these diseases has also allowed for the research of the exact molecular mechanisms behind the susceptibility to arrhythmias. (Marsman et al. 2013, Priori et al. 2015).
2.4.5 Other markers of increased SCD risk

A plethora of other methods for SCD risk stratification have been studied in addition to traditional cardiovascular risk factors and risk markers in standard 12-lead electrocardiogram. Most of the knowledge of these methods in risk stratification has accumulated from populations of patients with heart failure or myocardial infarction. The most promising methods include imaging of myocardial scar, markers of abnormal autonomic tone, minor beat-to-beat alternations in T wave morphology (T wave alternans), abnormalities in the signal-averaged electrocardiogram, natriuretic hormones, and invasive electrophysiology testing. (Deyell et al. 2015).

Myocardial scar is often the substrate for ventricular arrhythmias and left ventricular systolic function serves as a crude marker for overall scar burden, especially after myocardial infarction (Deyell et al. 2015). In a recent study using speckle-tracking echocardiography in myocardial infarction patients mechanical dispersion, an indicator of heterogeneity in myocardial contractility, was predictive of arrhythmic events, even after adjusting for left ventricular ejection fraction (Haugaa et al. 2013). Also quantification of myocardial scar with magnetic resonance imaging has proven to be a better measure of ventricular tachyarrhythmia risk than left ventricular ejection fraction and especially the amount of regions with scarring, but also functional cardiomyocytes seem to be associated with arrhythmia risk (Schmidt et al. 2007).

The balance of autonomic nervous system may be disrupted in heart failure and myocardial infarction. Increases in sympathetic tone and decreases in parasympathetic tone increase susceptibility to ventricular arrhythmias. Decreases in parasympathetic tone manifest as decreased spontaneous variation of heart rate and low heart rate variability has been associated with both SCD and non-sudden cardiac deaths. (Deyell et al. 2015, Huikuri et al. 2009, La Rovere et al. 2003). Heart rate turbulence is a measure of short-term variation of heart rate after a ventricular premature beat which is closely related to baroreflex sensitivity, which measures the deceleration of heart rate after administration of blood pressure increasing drug. Decreases in both of these measures have been shown to be associated with SCD. (Deyell et al. 2015, Exner et al. 2007).

T wave alternans measures small beat-to-beat differences in T wave morphology which represent heterogeneity in repolarization. The phenomenon is heart rate dependent and it can be observed in normal human hearts at heart rates >
120 beats/minute. In most studies, T wave alternans is assessed in an exercise stress test setting and the presence on the phenomenon at heart rate 105–110 beats/minute is considered abnormal but it can also be measured from ambulatory ECG monitoring. Abnormal T wave alternans has been linked to increased mortality and SCD in a wide range of cardiac patient populations, and on the other hand, negative T wave alternans test results have been associated with favourable prognosis. (Verrier et al. 2011).

The signal-averaged electrocardiogram enables accurate assessment of QRS duration and the detection of late potentials associated with slowly activating regions in the heart. Both QRS duration prolongation and the presence of late potentials in the signal-averaged electrocardiogram have been associated with arrhythmic events in cardiac patients. (Goldberger et al. 2008).

Natriuretic peptides are released to bloodstream as a result of ventricular stretching and are mainly used in diagnosis of heart failure. They have been shown to be predictors of SCD in a wide range of cardiac patient populations (Scott et al. 2009). Recently, high levels of natriuretic peptides were also shown to be associated with SCD in an elderly general population cohort (Patton et al. 2010).

Programmed ventricular stimulation is a method in which ventricular extrastimuli are delivered to induce ventricular tachyarrhythmia during an electrophysiology study. In addition to being used to diagnostic evaluation of patients with suspected ventricular arrhythmias, initiation of ventricular tachyarrhythmia during the test has been shown to be associated with increased risk of fatal or near-fatal arrhythmias (Deyell et al. 2015, Huikuri et al. 2009, Priori et al. 2015).

2.4.6 Substance abuse and drugs

Excessive alcohol consumption and the use of certain illicit drugs is associated with an increased risk of SCD. Heavy intake of alcohol acutely causes an increase of the release of catecholamines, decreases cardiac contractility, and causes both supraventricular and ventricular arrhythmias (Fernández-Solà 2015, George and Figueredo 2010). Chronic heavy alcohol misuse first leads to subclinical diastolic dysfunction and later subclinical left ventricular dysfunction, and finally it may lead to dilated cardiomyopathy. In autopsy studies, alcoholic cardiomyopathy has been characterized by increased heart weight, chamber enlargement, patches of thick endocardium, ventricular scars, and interstitial fibrosis is frequently seen in histologic examination. (Fernández-Solà 2015). Therefore, chronic heavy alcohol
intake has expectedly shown to be associated with an increased SCD risk (Wannamethee and Shaper 1992). Of note, in a large population-based autopsy series of SCD victims from Northern Finland, 38% of SCD victims had at least some alcohol in blood, and 11% of the SCD victims were documented to have a blood ethanol concentration as high as $\geq 1.5\%$ (Perkiömäki et al. 2015).

The use of illicit drugs has been identified as the cause of SCD among young competitive athletes in 2% of deaths (Maron et al. 2009). Cocaine can cause myocardial ischemia and even infarction both by causing coronary vasoconstriction and by accelerating atherosclerosis and increasing platelet aggregation. It increases the sympathetic tone by blocking catecholamine reuptake. It has also been documented that cocaine affects multiple ion channels in the cardiomyocytes, including increased calcium flow through the L-type calcium channels, blockage of sodium channels and inhibition of $I_{Kr}$ potassium channels, thus leading to susceptibility to fatal arrhythmias. (Phillips et al. 2009). Amphetamine and its derivatives also increase the sympathetic tone and amphetamine also blocks the transient outward sodium current ($I_{to}$ current) (Casis et al. 2000, Frishman et al. 2002). Opiate overdoses may cause bradyarrhythmias or asystole, and methadone is known for its QT-interval prolonging properties (Frishman et al. 2002). Thus, a conversant clinician should ask about the use of alcohol and illicit drug when a subject presents with symptoms attributable to arrhythmias.

Also the use of different prescription drugs may modify one’s risk of SCD. Multiple drugs, including antibiotics, antiarrhythmic drugs, antipsychotic drugs, antidepressants, and antihistamines may prolong the QT interval, thus increase one’s susceptibility to arrhythmias especially in case of long QT syndrome. (Priori et al. 2015). The use of epilepsy drugs have been shown to be associated with an increased risk of SCD as a manifestation of acute coronary event, also when used for other indications than epilepsy and especially when used together with other psychotropic medications (Hookana et al. 2016). Multiple antiarrhythmic drugs have got pro-arrhythmic properties (Priori et al. 2015). The use of flecainide, encainide, and other sodium channel blocking agents has been associated with an increased risk of VT in patients with previous myocardial infarction (Echt et al. 1991, Priori et al. 2015).
2.5 Interventions to reduce SCD burden in the population

The targeted therapy to prevent SCD is implantable cardioverter-defibrillator. However, due to the risk of device-related complications, the use of implantable cardioverter defibrillator is limited to subjects at highest risk. Current guidelines (Priori et al. 2015) recommend the prophylactic use of implantable cardioverter defibrillator in patients with symptomatic heart failure and left ventricular ejection fraction $\leq 35\%$ after three months of optimal medical therapy who are expected to survive for at least one year in good functional status. In addition to this group of patients, implantable cardioverter defibrillators are used in subjects with documented VF or hemodynamically not tolerated VT in the absence of reversible causes, and with specific indications in cardiomyopathies and primary arrhythmia syndromes. Antiarrhythmic drugs (amiodarone and $\beta$-blockers), and catheter ablation treatment to modify the arrhythmia substrate, can be used in prevention of ventricular arrhythmias in selected subjects at high risk. However, despite decreasing the rate of SCD, the effect of amiodarone on total mortality seems neutral (Bardy et al. 2005, Piccini et al. 2009).

Due to the lack of protocols to identify subjects at high risk of SCD from general population or CHD or CHF patients with preserved systolic function, most of SCD victims would not have qualified for the aforementioned treatments. At the population level, the cornerstone of SCD prevention is the prevention of development and progression of CHD and CHF. This prevention includes interventions to promote healthy lifestyle, including healthy diet, sufficient level of physical activity, and smoking cessation. Optimal medical therapy of dyslipidemia, elevated blood pressure, and diabetes are recommended to prevent the progression of CHD and the development of CHF. In CHD, medical therapy, including renin-angiotensin-aldosterone axis blocking drugs, aspirin, $\beta$-blockers especially in post-myocardial infarction patients and subjects with reduced LVEF, and statins (or other low density lipoprotein concentration lowering drugs) is the cornerstone of treatment to reduce future ischemic events and pathologic remodelling of the myocardium. Also invasive interventions to prohibit myocardial damage in acute myocardial infarction and interventions to reduce ischemic burden in stable coronary artery disease are used. In CHF, the cornerstones of the treatment are therapies targeted to the underlying cause of CHF and renin-angiotensin-aldosterone axis blocking drugs and $\beta$-blockers are the keys in medical therapy. (Priori et al. 2015). However, if methods to identify subjects at high risk for SCD
beyond the LVEF would arise more, subjects could be included to receive personalized targeted therapies.
3 Aims of the study

The aim of this study was to assess the risk of adverse cardiac events and especially the risk of sudden cardiac death associated with certain electrocardiographic parameters, obesity, glucose tolerance, and diabetes in general population. The specific aims of the study were as follows:

1. To assess the prevalence of delayed QRS transition in the precordial leads of an electrocardiogram and to evaluate the risk of death, coronary death, and sudden cardiac death associated with this electrocardiographic parameter.

2. To study the prevalence of abnormal P terminal force in lead V1 of the electrocardiogram and assess the risk of atrial fibrillation, congestive heart failure, death, and sudden cardiac death related to this electrocardiographic measure.

3. To assess the risk of sudden cardiac death associated with obesity and to test how electrocardiographic parameters related with an increased risk of sudden cardiac death perform in subjects with different relative weights.

4. To evaluate the risk of sudden cardiac death associated with diabetes and abnormal glucose tolerance and to test how electrocardiographic markers of cardiac autonomic neuropathy discriminate diabetes patients regarding suddenness of death.
4 Methods

4.1 Study participants

The population studied in this thesis consists of participants of the Social Insurance Institution’s Coronary Heart Disease Study (CHD study). In the CHD study, 10,962 subjects (52.3% male) aged 30–59 years from twelve populations in four different regions in Finland were examined by the Mobile Clinic in 1966–72. 89% of invited subjects took part in the study (total 12,310 invited subjects) and the sample represented the Finnish middle-aged population well.

The study rationale and procedures performed at the baseline examinations have been described in detail previously (Reunanen et al. 1983). Briefly, before the examination, subjects completed a questionnaire regarding their health habits, history of previous diseases, drug therapies, smoking habits, and symptoms of cardiovascular disease. During the examinations, the answers to the questionnaire were checked and completed, if necessary, by a specifically trained nurse. A standard 12-lead ECG was recorded and blood pressure, weight, and height were measured. An oral glucose tolerance test (OGTT) was performed among subjects who had not been diagnosed with diabetes, but for practical reasons, a venous blood sample was only once at 1 hour after the glucose load. The glucose load as a 20% solution was intended to be 40g/m2 body surface area but for practical reasons fixed doses of 60, 75, or 90 g were used the 75 g dose being the most frequently administered. A venous blood sample was drawn also from subjects who did not have an oral glucose tolerance test and blood cholesterol was measured from all blood samples. The type of diabetes was not specifically documented during the baseline examinations.

4.2 Electrocardiographic measurements

During the baseline examinations, a standard 12-lead electrocardiogram was recorded on a 4-channel Mingograf 34 recorder (Elema Schönander) at paper speed of 50mm/s and calibration of 10mm/mV with the subject resting in supine position. The electrocardiogram was recorded by specifically trained personnel and attention was paid to the correct position of the electrodes. After the baseline examinations, the changes on the electrocardiograms were coded according to the revised Minnesota code (MC) (Rose and Blackburn 1968) by six technicians working in
pairs trained and supervised by two cardiologists. In repeated measurements, the repeatability of coding was assessed to be reasonably good. (Reunanen et al. 1983). In this phase of the study, also the presence of P terminal force (PTF) in lead V1 of the electrocardiogram, left ventricular hypertrophy (according to the Sokolow-Lyon criteria and the Romhilt-Estes point score), heart rate, QT interval, and corrected QT interval (QTc, according to the Bazett’s formula) were assessed. Also QRS transition zone in the precordial leads and QRS axis, T wave axis, and QRS/T angle were assessed in the frontal plane. The QRS transition zone in the precordial leads was defined by determining where the QRS pattern changed from an rS to Rs configuration, or in which lead the dimensions of the R and S waves equalled. An intraclass correlation coefficient of 0.91 was demonstrated between all readers and reference values for a separate test ECG material for determining QRS transition zone (Ristola 1983). The PTF was calculated as the product of the duration (in seconds) and amplitude (in millimeters) of the negative terminal deflection of the P-wave in lead V1 by a single reader. The repeatability of the PTF measurements was good, the correlation coefficient of repeated measurements being 0.97 (Ristola 1983).

The electrocardiograms were re-evaluated later by five physicians for the presence of early repolarization patterns (ER), bundle branch blocks and intraventricular conduction delay (IVCD), fragmented QRS complexes (fQRS), and T wave inversions. The details of these measurements have been published elsewhere. (Aro et al. 2012, Aro et al. 2011a, Terho et al. 2014, Tikkanen et al. 2009).

4.3 Follow-up

The subjects were followed 35–41 years from the baseline examinations until the end of year 2007. Less than 2% of subjects were lost to follow-up mostly due to moving abroad, but the survival status could be determined for most of these subjects also. The follow-up time was defined as the number of days until the event of interest (hospitalization due to atrial fibrillation, coronary heart disease or congestive heart failure), death or end of the follow-up. Data of diagnoses of atrial fibrillation, coronary heart disease, congestive heart failure, and stroke were obtained from the Care Register for Health Care (HILMO) which registers nationwide data on all inpatient episodes in Finland, maintained by The National Institute for Health and Welfare. The mortality data were obtained from the Causes of Death Register provided by Statistics Finland. The validity of the diagnoses and
causes of deaths has proven to be good (Rapola et al. 1997, Sund 2012). Death of
cardiac causes was defined as International Classification of Diseases code of cause
of death representing code I20–I25 in the International Classification of Diseases
10. All deaths from cardiac causes were reviewed by two experienced cardiologists
using death certificates, hospital records and necropsy reports, if available, to
identify sudden deaths from arrhythmia based on the definitions presented in the
Cardiac Arrhythmia Pilot Study (Greene et al. 1989). Sudden deaths from
arrhythmia were defined as a spontaneous cessation of breathing and circulation
with loss of consciousness, either instantaneously or preceded by symptoms
attributable to myocardial ischemia or cardiac arrhythmia (e.g. syncope) in the
absence of heart failure. Deaths were also classified as sudden cardiac deaths if the
event was not witnessed, but no evidence of another cause was documented. In the
presence of severe congestive heart failure, deaths were not classified as arrhythmic
if death from heart failure was considered inevitable within four months before the
fatal episode. Of note, it is stationary in Finland to conduct an investigation to
determine the cause of death if death has been unexpected (Act of determining the
cause of Death, 459/73). During the follow-up, a necropsy was performed to
determine the cause of death in 30–40% of deaths in Finland, which is well above
the international average (Penttilä et al. 1999). Non-sudden cardiac death was
defined as a cardiac death which was not classified as SCD. In study IV, a non-fatal
cardiac event was defined as a hospitalization due to CHD or CHF.

4.4 Statistical methods

Continuous data are presented as means (standard deviation [SD], 95% confidence
interval [CI]) and categorical data as percentage (%) of subjects. Hazard ratios
(HRs) are presented as HR (95% CI). T test and ANOVA in case of multiple groups
were used to compare the means of continuous variables and Chi-square test was
used to assess the differences in the prevalence of categorical variables when the
study population was divided into groups according to attributes of interest. The
Cox proportional hazards model (Cox 1972) was the primary model used to
calculate the hazard ratios and their 95% CIs associated with variables of interest
for primary and secondary end-points in this study. In Study II, the Fine and Gray
competing risks model (Fine and Gray 1999) was used when hazard ratios for other
events than all-cause death were calculated to lessen the impact of a large number
of deaths during the follow-up. The covariates were chosen based on an established
evidence of an association with cardiovascular mortality. Age, systolic blood pressure, cholesterol, heart rate, PR interval, QRS axis, QRS duration, and QTc were used as continuous variables. Sex, baseline cardiac disease, use of cardiac medication, smoking, ECG signs of myocardial infarction, ECG signs of coronary artery disease, ECG LVH, inferolateral ER pattern, and T wave inversions were used as categorical variables. Body mass index was used as a continuous variable in studies I, II, and IV, and as a categorical variable in study III. For Study III, indicator variables were coded for ECGs containing major abnormalities or other abnormalities. Major abnormality was defined as the presence of at least one of the following abnormalities: Major Q waves (MC 1-1 or 1-2), Romhilt-Estes LVH score $\geq 5$, LBBB, IVCD, horizontal or downsloping ST-depressions $\geq 0.05$mV (MC 4-1 or 4-2), and $\geq 0.1$mV deep T wave inversions leads other than aVR, aVL, III, and V1 to V3. Other abnormality was defined as the presence of at least one of the following abnormalities: an inferior ER pattern with J point elevation $\geq 0.1$mV with horizontal or downsloping ST segment, QRS/T angle $\geq 100^\circ$, QTc $\geq 450$ms in males and $\geq 460$ms in females, and lateral fQRS pattern. The major abnormalities were chosen similarly as in a previous study by Auer et al. (2012) assessing the role of ECG abnormalities in CHD risk stratification of elderly subjects for uniformity. The other abnormalities were chosen based on previous evidence of an association with SCD or CHD mortality. Subjects having both major abnormalities and other abnormalities were coded as having major abnormalities. Integrated discrimination improvement, category-free net reclassification improvement and the change in C statistic were calculated to quantify the improvement of the risk prediction models associated with the addition of marker of interest (Uno et al. 2011, Uno et al. 2012). Subjects with missing data in the covariates used in the analyses of each original article were excluded. This results in slightly different numbers of participants between topics in the results section as slightly different sets of covariates were used in the Studies. Due to the lack of a standard cutoff point for abnormal 1-hour OGTT, a Receiver operating characteristics (ROC) analysis was carried out to find the optimal glucose concentration providing maximal sensitivity plus specificity in discriminating subjects whose cause of death was SCD from other subjects. All $p$ values presented are two-sided and 0.05 was used as the alpha level. The statistical analyses were performed with R version 3.1.2 (http://www.R-project.com packages cmprsk, survC1 and survIDINRI) and with the Statistical Package for Social Studies, version 22 (SPSS).
5 Results

5.1 QRS transition zone in the precordial leads of the ECG: occurrence site and prognostic significance

10,815 subject had QRS transition zone determinable in their ECGs. Among these subjects, QRS transition occurred very early (before lead V2) in 3.1%, early (before lead V3) in 26.4%, normally at V3 or before V4 in 57.2%. QRS transition was delayed (occurring at lead V4 or beyond) in 16.4% of subjects and a markedly delayed QRS transition (at lead V5 or V6) occurred in 1.3% of subjects. The characteristics of subjects according to QRS transition category are presented in Table 1. Subjects with early QRS transition were younger, leaner, less likely to smoke, and less likely to have a cardiac disease than the rest of the subjects. Delayed QRS transition became more common with advancing age and with increasing BMI. Hypertension and cardiac disease were more common among subjects with delayed QRS transition. The QRS axis of the subjects with delayed QRS transition also differed from subjects with normal QRS transition being generally more leftward.

Cox proportional hazards models were used to assess the prognostic significance of the site of QRS transition zone. When subjects with early QRS transition were compared with the rest of the population, a slightly improved overall survival was observed in an age- and sex-adjusted model, but the association diminished after further adjustments. The risk of hospitalization due to atrial fibrillation was lower in subjects with early QRS transition, even after multivariate adjustment (HR 0.85, 95% CI 0.76–0.95, p = 0.006). No significant differences were documented in coronary mortality, SCD occurrence, or hospitalizations due to CHD or CHF between subjects with early QRS transition and the rest of the cohort.

Subjects with delayed QRS transition zone were at increased risk of adverse events when compared with subjects in whom QRS transition occurred before lead V4. The numbers of adverse events and the HRs for these events associated with delayed QRS transition are presented in Table 2. An increased risk of all-cause death, coronary death, and SCD was documented in univariate models, the risk being even more pronounced in subjects with QRS transition occurring at V5 or later. Subjects with delayed QRS transition remained at increased risk for all-cause death even after multivariate adjustment. The risk of SCD was also increased in
subjects with delayed QRS transition despite adjustments for several important clinical and electrocardiographic confounders, but further adjustments for repolarization abnormalities attenuated this effect. However, subjects with markedly delayed QRS transition were at increased risk of SCD despite adjustments for all confounders. No marked increases in risks of hospitalizations due to CHD, atrial fibrillation, or CHF were observed. The exclusion of subjects with cardiovascular disease or subjects with QRS axis < -30° did not notably affect the results.
Table 1. Baseline characteristics of subjects according to QRS transition zone.

<table>
<thead>
<tr>
<th>QRS transition zone</th>
<th>Early (&lt; V3, n = 2861)</th>
<th>Normal (V3, n = 6184)</th>
<th>Delayed (V4, n = 1624)</th>
<th>Very delayed (V5/6, n = 146)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (%)</td>
<td>52.1</td>
<td>51.8</td>
<td>54.6</td>
<td>49.3</td>
<td>0.196</td>
</tr>
<tr>
<td>Age (years)</td>
<td>43.6 (8.5, 43.3–43.9)</td>
<td>43.7 (8.4, 43.5–43.9)</td>
<td>45.4 (8.4, 45.0–45.8)</td>
<td>48.5 (8.1, 47.1–49.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.6 (3.6, 25.5–25.8)</td>
<td>25.7 (3.7, 25.6–25.8)</td>
<td>27.0 (4.4, 26.8–27.2)</td>
<td>29.0 (5.3, 28.1–29.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>136.3 (20.1, 135.6–137)</td>
<td>138.1 (21, 137.6–138.7)</td>
<td>142.3 (23.7, 141.2–143.5)</td>
<td>147.8 (28.3, 143.2–152.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>81.2 (11.8, 80.8–81.7)</td>
<td>81.8 (12.1, 81.5–82.1)</td>
<td>85.1 (13.7, 84.5–85.8)</td>
<td>88.8 (16.6, 86.1–91.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>6.5 (1.3, 6.5–6.6)</td>
<td>6.5 (1.3, 6.5–6.5)</td>
<td>6.5 (1.3, 6.4–6.6)</td>
<td>6.7 (1.4, 6.4–6.9)</td>
<td>0.547</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>32.6</td>
<td>34.5</td>
<td>35.0</td>
<td>29.5</td>
<td>0.166</td>
</tr>
<tr>
<td>Cardiac disease (%)</td>
<td>6.7</td>
<td>7.7</td>
<td>11.1</td>
<td>19.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Chronotropic medication (%)</td>
<td>3.2</td>
<td>3.8</td>
<td>7.4</td>
<td>10.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>75.7 (15.5, 75.2–76.3)</td>
<td>75.4 (15.0, 75.1–75.8)</td>
<td>75.5 (15.9, 74.8–76.3)</td>
<td>81.1 (18.7, 78.1–84.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>85 (11, 84–85)</td>
<td>85 (11, 85–85)</td>
<td>86 (11, 85–86)</td>
<td>87 (11, 85–89)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>QRS axis (°)</td>
<td>37.3 (27.4, 36.3–38.3)</td>
<td>39.3 (30.9, 38.5–40.1)</td>
<td>32 (40.3, 30–33.9)</td>
<td>11.1 (55.7, 1.9–20.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>408 (27, 407–408)</td>
<td>408 (27, 407–409)</td>
<td>409 (28, 408–411)</td>
<td>416 (31, 411–411)</td>
<td>0.001</td>
</tr>
<tr>
<td>QRS-T angle (°)</td>
<td>24.2 (21.8, 23.4–25)</td>
<td>28.3 (23.6, 27.7–28.9)</td>
<td>36 (29.5, 34.5–37.4)</td>
<td>51.9 (38.8, 45.4–58.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ECG LVH (Romhilt-Estes ≥ 5, %)</td>
<td>6.2</td>
<td>6.3</td>
<td>8.8</td>
<td>11.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ECG LVH (Sokolow-Lyon ≥ 3.5mV, %)</td>
<td>35.3</td>
<td>33.2</td>
<td>19.9</td>
<td>11.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Inferior or lateral ER ≥ 0.1mV (%)</td>
<td>6.5</td>
<td>5.6</td>
<td>5.2</td>
<td>5.6</td>
<td>0.259</td>
</tr>
<tr>
<td>T-wave inversions (%)</td>
<td>1.1</td>
<td>1.0</td>
<td>1.9</td>
<td>1.4</td>
<td>0.032</td>
</tr>
</tbody>
</table>
### 5.2 Prevalence and prognostic implications of abnormal P terminal force

PTF $0.04-0.049$ mm·s was present in 512 subjects (4.8%), PTF $0.05-0.059$ mm·s was present in 158 subjects (1.5%), and PTF $\geq 0.06$ mm·s was present in 126 subjects (1.2%). No marked PTF was observed in ECGs of 9,851 subjects and they formed the reference group. Subjects with abnormal PTF were older, more hypertensive, more obese, and other electrocardiographic abnormalities and cardiac disease were more prevalent among them. The complete characteristics of subject with different degrees of PTF are shown in Table 3.

During the follow-up 5,989 subjects died. The mortality was lowest in subjects without marked PTF (55.0%) and got higher with increasing PTF being 66.4% in subjects with PTF $0.04-0.049$ mm·s, 76.6% in subjects with PTF $0.05-0.059$, and 93.4% in subjects with PTF $\geq 0.06$ mm·s.

In survival models, PTF $\geq 0.06$ mm·s was associated with an increased risk of death and atrial fibrillation after multivariate adjustment. Univariately, PTF $\geq 0.04$ mm·s was associated with an increased risk of death, cardiac death, and congestive heart failure, and PTF $\geq 0.06$ mm·s predicted also atrial fibrillation in addition to the aforementioned end-points. The results of these models and covariates used are presented in Table 4. In similar models in which subjects with cardiac disease in baseline and subjects with signs of myocardial infarction or CHD in their ECGs were excluded, PTF $\geq 0.06$ mm·s was still associated with all-cause mortality and atrial fibrillation after multivariate adjustments. In these models, the HR for death was 1.44 (95% CI 1.11–1.88, $p = 0.006$) and HR for atrial fibrillation was 2.38 (95% CI 1.54–3.68, $p < 0.001$). PTF was a relatively common finding also in subjects without a pre-existing cardiac disease or ECG signs of CHD as the prevalence of PTF $\geq 0.04$ mm·s was 4.4% and the prevalence of PTF $\geq 0.06$ mm·s was 0.8%.

The ability of PTF to improve discrimination of subjects in the multivariate models was assessed by calculating integrated discrimination indices, but no statistically significant improvements were detected.
**Table 2. The results of Cox proportional hazards models about the risk of death among subjects with delayed QRS transition zone.**

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<table>
<thead>
<tr>
<th>QRS transition zone</th>
<th>Transition ≤ V3 (n = 9045)</th>
<th>Transition ≥ V4 (n = 1770)</th>
<th>Transition ≥ V5 (n = 146)</th>
<th>p value ≤ V3 vs ≥ V4</th>
<th>p value ≤ V3 vs ≥ V5</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality, no. of deaths</td>
<td>4946</td>
<td>1154</td>
<td>109</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted HR (95% CI)</td>
<td>1</td>
<td>1.38 (1.29–1.47)</td>
<td>1.92 (1.59–2.32)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age and sex-adjusted HR (95% CI)</td>
<td>1</td>
<td>1.18 (1.10–1.26)</td>
<td>1.44 (1.19–1.75)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Multivariate adjusted HR, Model A (95% CI)¹</td>
<td>1</td>
<td>1.15 (1.07–1.22)</td>
<td>1.30 (1.07–1.58)</td>
<td>&lt; 0.001</td>
<td>0.010</td>
</tr>
<tr>
<td>Multivariate adjusted HR, Model B (95% CI)²</td>
<td>1</td>
<td>1.13 (1.05–1.21)</td>
<td>1.27 (1.04–1.56)</td>
<td>0.001</td>
<td>0.020</td>
</tr>
<tr>
<td>Coronary mortality, no. of deaths</td>
<td>1571</td>
<td>382</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted HR (95% CI)</td>
<td>1</td>
<td>1.42 (1.27–1.59)</td>
<td>2.01 (1.45–2.79)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age and sex-adjusted HR (95% CI)</td>
<td>1</td>
<td>1.21 (1.08–1.36)</td>
<td>1.56 (1.13–2.17)</td>
<td>0.001</td>
<td>0.008</td>
</tr>
<tr>
<td>Multivariate adjusted HR, Model A (95% CI)¹</td>
<td>1</td>
<td>1.12 (1.00–1.26)</td>
<td>1.32 (0.94–1.85)</td>
<td>0.050</td>
<td>0.11</td>
</tr>
<tr>
<td>Multivariate adjusted HR, Model B (95% CI)²</td>
<td>1</td>
<td>1.08 (0.96–1.21)</td>
<td>1.18 (0.84–1.68)</td>
<td>0.23</td>
<td>0.34</td>
</tr>
<tr>
<td>Sudden cardiac death, no. of deaths</td>
<td>631</td>
<td>160</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted HR (95% CI)</td>
<td>1</td>
<td>1.46 (1.23–1.74)</td>
<td>2.49 (1.58–3.94)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age and sex-adjusted HR (95% CI)</td>
<td>1</td>
<td>1.28 (1.08–1.53)</td>
<td>2.11 (1.34–3.33)</td>
<td>0.005</td>
<td>0.001</td>
</tr>
<tr>
<td>Multivariate adjusted HR, Model A (95% CI)¹</td>
<td>1</td>
<td>1.23 (1.03–1.47)</td>
<td>1.89 (1.18–3.03)</td>
<td>0.029</td>
<td>0.008</td>
</tr>
<tr>
<td>Multivariate adjusted HR, Model B (95% CI)²</td>
<td>1</td>
<td>1.15 (0.96–1.38)</td>
<td>1.64 (1.00–2.69)</td>
<td>0.14</td>
<td>0.048</td>
</tr>
</tbody>
</table>

¹ Adjusted for age, gender, BMI, systolic blood pressure, electrocardiographic LVH, baseline cardiovascular disease, QRS duration, QRS axis, and heart rate².
² Adjusted for age, gender, BMI, systolic blood pressure, electrocardiographic LVH, baseline cardiovascular disease, QRS duration, QRS axis, heart rate, QTc, inferior or lateral early repolarization, T-wave inversions, and QRS-T angle.
Table 3. Baseline characteristics of subjects with different degrees of PTF. Modified from Eranti et al. 2014 with permission from publisher. Copyright © Wolters Kluwer Health.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PTF normal (n = 9851)</th>
<th>PTF 0.04–0.049mm·s (n = 512)</th>
<th>PTF 0.05–0.059mm·s (n = 158)</th>
<th>PTF ≥ 0.06mm·s (n = 126)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (%)</td>
<td>53.5</td>
<td>43.2</td>
<td>39.9</td>
<td>51.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>(8.4, 43.5–43.8)</td>
<td>(8.2, 46.7–48.1)</td>
<td>(7.9, 48.3–50.8)</td>
<td>(8.1, 47.8–50.7)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8</td>
<td>27.3</td>
<td>27.2</td>
<td>27.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>(3.8, 25.7–25.9)</td>
<td>(4.6, 26.9–27.7)</td>
<td>(4.0, 26.6–27.9)</td>
<td>(4.1, 26.9–28.3)</td>
<td></td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>34.6</td>
<td>29.7</td>
<td>24.1</td>
<td>31.7</td>
<td>0.005</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>6.49</td>
<td>6.54</td>
<td>6.54</td>
<td>6.73</td>
<td>0.222</td>
</tr>
<tr>
<td></td>
<td>(1.32, 6.47–6.52)</td>
<td>(1.28, 6.43–6.65)</td>
<td>(1.33, 6.33–6.75)</td>
<td>(1.64, 6.44–7.01)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>137.3</td>
<td>149.3</td>
<td>158.8</td>
<td>152.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>(20.6, 136.9–137.7)</td>
<td>(25.8, 147.0–151.5)</td>
<td>(29.8, 154.1–163.5)</td>
<td>(26.9, 148.1–157.5)</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>81.7</td>
<td>88.2</td>
<td>89.9</td>
<td>88.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>(12.1, 81.5–81.9)</td>
<td>(13.7, 87.0–89.3)</td>
<td>(15.8, 87.4–92.4)</td>
<td>(14.7, 86.3–91.5)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease (%)</td>
<td>7.5</td>
<td>11.1</td>
<td>14.6</td>
<td>29.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cardiac medication (%)</td>
<td>3.6</td>
<td>9.2</td>
<td>15.8</td>
<td>15.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ECG LVH (Sokolow-Lyon ≥ 3.5mV, %)</td>
<td>31.1</td>
<td>35.0</td>
<td>39.9</td>
<td>46.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>74.9</td>
<td>82.8</td>
<td>85.5</td>
<td>81.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>(14.9, 74.6–75.2)</td>
<td>(17.2, 81.3–84.3)</td>
<td>(18.0, 82.7–88.3)</td>
<td>(15.8, 79.0–84.5)</td>
<td></td>
</tr>
<tr>
<td>PR interval (ms)</td>
<td>156.2</td>
<td>159.6</td>
<td>164.1</td>
<td>166.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>(22.1, 155.8–156.7)</td>
<td>(21.5, 157.7–161.5)</td>
<td>(21.6, 160.7–167.4)</td>
<td>(28.3, 161.2–171.2)</td>
<td></td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>84.8</td>
<td>85.5</td>
<td>85.4</td>
<td>87.6</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>(10.9, 84.6–85.0)</td>
<td>(9.9, 84.6–86.4)</td>
<td>(11.6, 83.6–87.3)</td>
<td>(14.0, 85.2–90.1)</td>
<td></td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>407.2</td>
<td>418.2</td>
<td>422.6</td>
<td>419.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>(27.3, 406.7–407.7)</td>
<td>(26.9, 415.9–420.6)</td>
<td>(31.5, 417.7–427.6)</td>
<td>(29.4, 413.8–424.2)</td>
<td></td>
</tr>
<tr>
<td>Characteristic</td>
<td>PTF normal (n = 9851)</td>
<td>PTF 0.04–0.049mm·s (n = 512)</td>
<td>PTF 0.05–0.059mm·s (n = 158)</td>
<td>PTF ≥ 0.06mm·s (n = 126)</td>
<td>p</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>-----------------------</td>
<td>-------------------------------</td>
<td>-----------------------------</td>
<td>---------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>ECG signs of myocardial infarction (%)</td>
<td>0.5</td>
<td>2.1</td>
<td>0.6</td>
<td>7.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ECG signs of coronary artery disease (%)</td>
<td>8.7</td>
<td>14.5</td>
<td>21.5</td>
<td>23.0</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Table 4. HRs for adverse events in subjects with different degrees of PTF compared to normal subjects. Modified from Eranti et al. 2014 with permission from publisher. Copyright © Wolters Kluwer Health.

<table>
<thead>
<tr>
<th>Group</th>
<th>PTF normal (n = 9851)</th>
<th>PTF 0.04–0.049mm·s (n = 512)</th>
<th>p</th>
<th>PTF 0.05–0.059mm·s (n = 158)</th>
<th>p</th>
<th>PTF ≥ 0.06mm·s (n = 126)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-Cause Mortality</strong></td>
<td>5415</td>
<td>340</td>
<td></td>
<td>121</td>
<td></td>
<td>113</td>
<td></td>
</tr>
<tr>
<td>Unadjusted HR (95% CI)</td>
<td>1</td>
<td>1.39 (1.25–1.55)</td>
<td>&lt; 0.001</td>
<td>1.79 (1.50–2.15)</td>
<td>&lt; 0.001</td>
<td>2.00 (2.41–3.50)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Multivariate-adjusted^2 HR (95% CI)</td>
<td>1</td>
<td>1.00 (0.90–1.12)</td>
<td>0.962</td>
<td>1.00 (0.83–1.20)</td>
<td>0.987</td>
<td>1.76 (1.45–2.12)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Cardiac Mortality</strong></td>
<td>1719</td>
<td>119</td>
<td></td>
<td>48</td>
<td></td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Unadjusted HR (95% CI)</td>
<td>1</td>
<td>1.39 (1.15–1.67)</td>
<td>&lt; 0.001</td>
<td>1.91 (1.43–2.56)</td>
<td>&lt; 0.001</td>
<td>1.88 (1.36–2.60)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Multivariate-adjusted^2 HR (95% CI)</td>
<td>1</td>
<td>1.02 (0.83–1.25)</td>
<td>0.85</td>
<td>1.28 (0.94–1.74)</td>
<td>0.12</td>
<td>1.01 (0.71–1.44)</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>Atrial Fibrillation</strong></td>
<td>1458</td>
<td>83</td>
<td></td>
<td>28</td>
<td></td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Unadjusted HR (95% CI)</td>
<td>1</td>
<td>1.11 (0.89–1.39)</td>
<td>0.35</td>
<td>1.23 (0.84–1.80)</td>
<td>0.29</td>
<td>2.29 (1.63–3.23)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Multivariate-adjusted^2 HR (95% CI)</td>
<td>1</td>
<td>0.96 (0.76–1.20)</td>
<td>0.69</td>
<td>1.02 (0.69–1.50)</td>
<td>0.92</td>
<td>1.91 (1.34–2.73)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Congestive Heart Failure</strong></td>
<td>1499</td>
<td>114</td>
<td></td>
<td>33</td>
<td></td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Unadjusted HR (95% CI)</td>
<td>1</td>
<td>1.55 (1.28–1.88)</td>
<td>&lt; 0.001</td>
<td>1.43 (1.01–2.04)</td>
<td>0.045</td>
<td>2.49 (1.78–3.48)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Multivariate-adjusted^2 HR (95% CI)</td>
<td>1</td>
<td>1.06 (0.87–1.31)</td>
<td>0.56</td>
<td>0.85 (0.59–1.22)</td>
<td>0.39</td>
<td>1.38 (0.95–2.00)</td>
<td>0.087</td>
</tr>
</tbody>
</table>

^1 The Cox Proportional Hazards model was used to compute HRs for deaths and the Fine and Gray competing risks model was used for other end-points.

^2 Adjusted for age, sex, BMI, baseline cardiovascular disease, use of cardiac medication, systolic blood pressure, smoking, cholesterol, heart rate, electrocardiographic LVH, electrocardiographic signs of myocardial infarction and electrocardiographic signs of coronary artery disease.
5.3  **Body mass index as a predictor of SCD risk and value of ECG in risk stratification in subjects with different relative weights**

There were 374 lean (BMI < 20 kg/m²), 4,334 normal weight (BMI 20–24.9 kg/m²), 4,390 overweight (BMI 25–29.9 kg/m²), and 1,445 obese (BMI ≥ 30 kg/m²) subjects in the population. Age, blood pressure, and the prevalence of cardiovascular disease were higher with increasing BMI. The characteristics of subjects according to BMI group are presented in Table 5.

During the follow-up, 56.2% of subjects died, the mortality and cardiac mortality being higher with increasing BMI. No marked differences were observed in the proportion of cardiac deaths being sudden in the BMI groups. The detailed mortality numbers in the BMI groups are specified in Table 6.

The role of BMI as a risk factor of SCD was assessed in Cox proportional hazards models. The results of these models are presented in Table 7. In the whole population, overweight and obese subjects were at increased risk for SCD. No marked between-sex differences were observed when the analyses were conducted separately for males and females. The results remained largely alike also when subjects with cardiac disease in the baseline and subjects presenting with electrocardiographic abnormalities were excluded from the whole population. Similar Cox proportional hazards models were conducted also with non-sudden cardiac death as the end-point in the whole population. In these models, the multivariate adjusted HRs were 1.17 (95% CI 1.02–1.33, p = 0.024) and 1.62 (95% CI 1.37–1.92, p < 0.001) among the overweight and obese, respectively.
Table 5. Characteristics of subjects according to BMI group. Modified from Eranti et al. 2016a with permission from publisher. Copyright © Elsevier.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>&lt; 20 (n = 374)</th>
<th>20.0–24.9 (n = 4334)</th>
<th>25.0–29.9 (n = 4390)</th>
<th>≥ 30 (n = 1445)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (%)</td>
<td>39.8</td>
<td>55.1</td>
<td>56.6</td>
<td>36.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>41.5 (8.9, 40.6–42.4)</td>
<td>42.5 (8.4, 42.2–42.7)</td>
<td>44.5 (8.2, 44.3–44.7)</td>
<td>47.4 (8.0, 47.0–47.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19.1 (0.8, 19.0–19.2)</td>
<td>23.0 (1.3, 22.9–23.0)</td>
<td>27.1 (1.4, 27.1–27.2)</td>
<td>32.7 (2.7, 32.6–32.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>132.1 (18.9, 130.1–134.0)</td>
<td>135.1 (20.1, 134.5–135.7)</td>
<td>139.3 (21.0, 138.7–139.9)</td>
<td>147.3 (24.5, 146.1–148.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>75.3 (11.2, 74.1–76.4)</td>
<td>78.3 (1.6, 78.0–78.7)</td>
<td>84.0 (11.5, 83.7–84.4)</td>
<td>90.2 (12.6, 89.5–90.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total cholesterol (mmol/liter)</td>
<td>6.3 (1.3, 6.2–6.4)</td>
<td>6.4 (1.3, 6.4–6.5)</td>
<td>6.6 (1.3, 6.5–6.6)</td>
<td>6.5 (1.3, 6.5–6.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>44.1</td>
<td>41.6</td>
<td>31.2</td>
<td>18.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>0.3</td>
<td>0.6</td>
<td>0.6</td>
<td>1.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cardiovascular disease (%)</td>
<td>7.2</td>
<td>6.9</td>
<td>7.9</td>
<td>12.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cardiac medication (%)</td>
<td>1.1</td>
<td>2.0</td>
<td>4.2</td>
<td>11.9</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Table 6. Numbers of deaths in the BMI groups. Modified from Eranti et al. 2016a with permission from publisher. Copyright © Elsevier.

<table>
<thead>
<tr>
<th>BMI group</th>
<th>&lt; 20 (n = 374)</th>
<th>20.0–24.9 (n = 4334)</th>
<th>25.0–29.9 (n = 4390)</th>
<th>≥ 30 (n = 1445)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>179 (47.9%)</td>
<td>2154 (49.7%)</td>
<td>2546 (58.0%)</td>
<td>1044 (72.2%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cardiac deaths</td>
<td>43 (24.0%)</td>
<td>647 (30.0%)</td>
<td>882 (34.6%)</td>
<td>387 (37.1%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Non–sudden cardiac deaths (% of cardiac deaths)</td>
<td>24 (55.8%)</td>
<td>392 (60.6%)</td>
<td>525 (59.5%)</td>
<td>249 (64.3%)</td>
<td>0.377</td>
</tr>
<tr>
<td>Sudden cardiac deaths (% of cardiac deaths)</td>
<td>19 (44.2%)</td>
<td>255 (39.4%)</td>
<td>357 (40.5%)</td>
<td>138 (35.7%)</td>
<td>0.377</td>
</tr>
</tbody>
</table>

The p value is for a single Chi-Square test conducted to assess whether the frequencies of non-sudden and sudden cardiac deaths are independent of the BMI group.

Cox proportional hazards models were also used to examine the risk of SCD associated with major, other, and any ECG abnormalities in the BMI groups. The prevalence of these abnormalities and HRs for SCD associated with these abnormalities in the BMI groups are presented in Table 8. In univariate models, the presence of these abnormalities predicted SCD largely similarly in the BMI groups. However, in multivariate models, the HRs for SCD associated with ECG abnormalities were lower among the obese and no statistical significance was reached among the obese in multivariate models. The models were conducted also separately for males and females, but no significant differences in HRs associated with the presence of ECG abnormalities in the BMI groups between genders were found within limits of 95% CIs.

The ability of ECG abnormalities to improve the multivariate models used was assessed by calculating the change in C statistics, continuous net reclassification improvement and integrated discrimination improvement. No statistically significant improvements in C statistics were documented for any of the ECG abnormality variables in any of the BMI groups. Significant improvements in integrated discrimination improvement were seen in the normal weight group when the other ECG abnormalities variable (0.015, 95% CI 0.004–0.035, p = 0.013) and any abnormalities variable (0.017, 95% CI 0.005–0.037, p = 0.007) were added to the model. Also continuous net reclassification improvement was positive in the normal weight group when other abnormalities variable was added to the model (0.229, 95% CI 0.135–0.405, p = 0.013) and when the any abnormalities variable was added to the model (0.262, 95% CI 0.168–0.360, p = 0.007). No statistically significant improvements in continuous net reclassification improvement or
integrated discrimination improvement were seen with addition of any of the ECG variables in groups of lean, overweight, or obese subjects.

Table 7. The HRs for SCD associated with BMI group. Modified from Eranti et al. 2016a with permission from publisher. Copyright © Elsevier.

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>No. of SCD</th>
<th>Unadjusted HR (95% CI)</th>
<th>p value</th>
<th>Multivariate–adjusted¹ HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20 (n = 374)</td>
<td>19</td>
<td>0.87 (0.54–1.38)</td>
<td>0.546</td>
<td>1.11 (0.70–1.77)</td>
<td>0.660</td>
</tr>
<tr>
<td>20.0–24.9 (n = 4334)</td>
<td>255</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25.0–29.9 (n = 4390)</td>
<td>357</td>
<td>1.43 (1.22–1.68)</td>
<td>&lt; 0.001</td>
<td>1.33 (1.13–1.56)</td>
<td>0.001</td>
</tr>
<tr>
<td>≥ 30 (n = 1445)</td>
<td>138</td>
<td>1.89 (1.53–2.32)</td>
<td>&lt; 0.001</td>
<td>1.79 (1.44–2.23)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

¹Adjusted for age, sex, smoking status, systolic blood pressure, diabetes, cholesterol, baseline cardiac disease, and the any ECG abnormality variable.

5.4 Diabetes, glucose tolerance, and the risk of SCD

Diabetes was present in 82 (0.8%) of the study participants. The ROC analysis yielded maximal sensitivity plus specificity in discriminating subjects whose cause of death was SCD from other subjects based on blood glucose concentration in the 1-hour OGTT at 9.58mmol/l. The use of this cut off to diagnose IGT yielded 3,806 subjects with IGT (35.9%) and left 6706 subjects with normal glucose tolerance. The treatments used for diabetes were insulin (n = 24), biguanides (n = 8), sulphonylureas (n = 23), or both (n = 9), and diet (n = 18). The baseline characteristics of subjects with diabetes, IGT, and normal glucose tolerance are shown in Table 9. Subjects with diabetes and IGT were older, had higher blood pressures and blood cholesterol levels, and cardiac disease was more prevalent among them than in subjects with normal glucose tolerance.

During the follow-up, 5,946 subjects died. Mortality was higher among men and among subjects with IGT or diabetes. The proportions of deaths being cardiac and SCD in groups of subjects with normal glucose tolerance, IGT, and diabetes are shown in Table 10 and Table 11. A greater proportion of deaths was cardiac among subjects with IGT and especially among diabetes patients. However, the proportion of SCD of all cardiac deaths did not differ between the groups.

Cox proportional hazards models were used to assess the roles of IGT and diabetes as risk factors for SCD, non-sudden cardiac deaths, and non-fatal cardiac events (hospitalization due to CHD or CHF). The results of these models are shown in Table 12. IGT predicted adverse events in univariate models, but adjustment for confounders attenuated this effect. Diabetes predicted adverse events strongly, also
after multivariate adjustment. A subgroup analysis was conducted after exclusion of subjects who had cardiac disease in the baseline or who were hospitalized due to CHD or CHF during the follow-up. In this model with covariates as in model 1 in Table 12, diabetes predicted SCD significantly (HR 4.21, 95% CI 1.55–11.40, p = 0.005). A similar model with non-sudden cardiac death as the end-point presented a virtually similar HR. A separate analysis was conducted after exclusion of diabetes patients who were using insulin. In these analyses, diabetes patients with tablet medication or diet treatment were similarly at high risk for adverse events.

Finally, a general linear model was conducted to compare age- and sex-adjusted mean heart rates and QTc intervals between diabetes patients who had died of SCD, who had died of non-sudden cardiac death, and other diabetes patients. No statistically significant differences were observed in these models.
Table 8. The prevalence of electrocardiographic abnormalities and hazard ratios examining the risk of sudden cardiac deaths related to these abnormalities in the body mass index groups. Modified from Eranti et al. 2016a with permission from publisher. Copyright © Elsevier.

<table>
<thead>
<tr>
<th>BMI group</th>
<th>&lt; 20 (n = 374)</th>
<th>20.0–24.9 (n = 4334)</th>
<th>25.0–29.9 (n = 4390)</th>
<th>≥ 30 (n = 1445)</th>
<th>25.0–29.9 and ≥ 30 combined (n = 619)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major ECG abnormalities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects with ECG–abnormality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>29 (7.8%)</td>
<td>427 (9.9%)</td>
<td>439 (10.0%)</td>
<td>180 (12.5%)</td>
<td>619 (10.6%)</td>
</tr>
<tr>
<td>SCDs among subjects with ECG–abnormality</td>
<td>3 (10.3%)</td>
<td>38 (8.9%)</td>
<td>64 (14.6%)</td>
<td>23 (12.8%)</td>
<td>87 (14.1%)</td>
</tr>
<tr>
<td>Unadjusted HR</td>
<td>2.78 (0.81–9.54), p = 0.105</td>
<td>2.01 (1.43–2.84), p &lt; 0.001</td>
<td>2.58 (1.96–3.39), p &lt; 0.001</td>
<td>1.89 (1.20–2.97), p = 0.006</td>
<td>2.38 (1.88–3.01), p &lt; 0.001</td>
</tr>
<tr>
<td>Multivariate–adjusted HR²</td>
<td>2.90 (0.78–10.83), p = 0.113</td>
<td>1.38 (0.97–1.98), p &lt; 0.001</td>
<td>2.03 (1.53–2.70), p &lt; 0.001</td>
<td>1.27 (0.79–2.05), p = 0.317</td>
<td>1.78 (1.39–2.27), p &lt; 0.001</td>
</tr>
<tr>
<td>Other ECG abnormalities³</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects with ECG–abnormality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 (8.0%)</td>
<td>312 (7.2%)</td>
<td>267 (6.1%)</td>
<td>91 (6.3%)</td>
<td>358 (6.1%)</td>
</tr>
<tr>
<td>SCDs among subjects with ECG–abnormality</td>
<td>3 (10.0%)</td>
<td>36 (11.5%)</td>
<td>29 (10.9%)</td>
<td>13 (14.3%)</td>
<td>42 (11.7%)</td>
</tr>
<tr>
<td>Unadjusted HR</td>
<td>2.67 (0.76–9.37), p = 0.126</td>
<td>2.57 (1.80–3.68), p &lt; 0.001</td>
<td>1.65 (1.13–2.43), p = 0.010</td>
<td>1.86 (1.05–3.32), p = 0.035</td>
<td>1.71 (1.25–2.36), p = 0.001</td>
</tr>
<tr>
<td>Multivariate–adjusted HR³</td>
<td>2.79 (0.75–10.35), p = 0.124</td>
<td>2.03 (1.41–2.91), p &lt; 0.001</td>
<td>1.34 (0.91–1.96), p = 0.141</td>
<td>1.46 (0.81–2.64), p = 0.210</td>
<td>1.36 (0.99–1.88), p = 0.061</td>
</tr>
<tr>
<td>BMI group</td>
<td>&lt; 20</td>
<td>20.0–24.9</td>
<td>25.0–29.9</td>
<td>≥ 30</td>
<td>25.0–29.9 and ≥ 30 combined</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------</td>
<td>-----------</td>
<td>-----------</td>
<td>-------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>(n = 374)</td>
<td>(n = 4334)</td>
<td>(n = 4390)</td>
<td>(n = 1445)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Any ECG abnormalities**

| No. of subjects with ECG–abnormality | 59 (15.8%) | 739 (17.1%) | 706 (16.1%) | 271 (18.8%) | 977 (16.7%) |
| SCDs among subjects with ECG–abnormality | 6 (10.2%) | 74 (10.0%) | 93 (13.2%) | 36 (13.3%) | 129 (13.2%) |

**Unadjusted HR**

- 2.89 (1.10–7.61), p = 0.032
- 2.39 (1.83–3.14), p < 0.001
- 2.19 (1.73–2.78), p < 0.001
- 1.88 (1.28–2.75), 2.11 (1.73–2.58), p = 0.001

**Multivariate–adjusted HR**

- 3.03 (1.09–8.40), p = 0.032
- 1.75 (1.32–2.31), p < 0.001
- 1.74 (1.37–2.22), p < 0.001
- 1.34 (0.90–1.99), 1.61 (1.31–1.98), p = 0.155

1Q-waves, LBBB, Romhilt–Estes LVH score ≥ 5, IVCD, ST–segment depressions, and T–wave inversions.

2Adjusted for age, sex, smoking status, systolic blood pressure, diabetes, cholesterol, and baseline cardiac disease.

3Inferior ER pattern with horizontal/downsloping ST-segment, abnormal QTc, abnormal QRS/T angle, and lateral fQRS.

4Also major ECG abnormalities were added as a covariate.
Table 9. Baseline characteristics of subjects according to the presence of diabetes or IGT. Modified from Eranti et al. 2016b.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal (n = 6706)</th>
<th>IGT (n = 3806)</th>
<th>Diabetes (n = 82)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>53.3</td>
<td>51.4</td>
<td>57.3</td>
<td>0.142</td>
</tr>
<tr>
<td>Age (years)</td>
<td>42.9 (8.2, 42.7–43.1)</td>
<td>45.7 (8.5, 45.4–45.9)</td>
<td>50.1 (7.6, 48.5–51.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.6 (3.6, 25.5–25.7)</td>
<td>26.3 (4.1, 26.2–26.5)</td>
<td>28.5 (5.3, 27.3–29.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>134.8 (19.8, 134.3–135.2)</td>
<td>144.6 (22.7, 143.6–145.3)</td>
<td>148.4 (25.6, 142.8–154.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80.6 (11.8, 80.4–80.9)</td>
<td>84.7 (13.0, 84.3–85.2)</td>
<td>87.9 (13.3, 84.9–90.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>6.4 (1.3, 6.4–6.5)</td>
<td>6.6 (1.4, 6.5–6.6)</td>
<td>6.9 (1.5, 6.6–7.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>36.0</td>
<td>30.6</td>
<td>30.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cardiak disease (%)</td>
<td>6.9</td>
<td>9.6</td>
<td>23.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>73.6 (14.1, 73.2–73.9)</td>
<td>78.8 (16.5, 78.3–79.3)</td>
<td>79.3 (15.8, 75.8–82.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>86.9 (84.8, 86.7–87.1)</td>
<td>87.1 (86.8, 86.8–87.3)</td>
<td>88.5 (11.9, 85.9–91.1)</td>
<td>0.163</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>404.6 (269.9, 403.9–405.2)</td>
<td>414.6 (275.4, 413.7–415.4)</td>
<td>415.4 (312.1, 408.5–422.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ECG LVH (Sokolow-Lyon ≥ 3.5mV, %)</td>
<td>30.5</td>
<td>33.2</td>
<td>25.6</td>
<td>0.008</td>
</tr>
<tr>
<td>ECG signs of myocardial infarction (%)</td>
<td>0.4</td>
<td>0.7</td>
<td>4.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ECG signs of coronary artery disease (%)</td>
<td>8.5</td>
<td>11.9</td>
<td>23.2</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Table 10. Proportions of cardiac and non-cardiac deaths according to diabetes status. Modified from Eranti et al. 2016b.

<table>
<thead>
<tr>
<th>Group</th>
<th>Normal (n = 3504)</th>
<th>IGT (n = 2364)</th>
<th>Diabetes (n = 80)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cardiac</td>
<td>2370 (67.6%)</td>
<td>1558 (65.9%)</td>
<td>45 (56.3%)</td>
<td>0.050</td>
</tr>
<tr>
<td>Cardiac</td>
<td>1134 (32.4%)</td>
<td>806 (34.1%)</td>
<td>35 (43.8%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 11. Proportions of SCD and non-sudden cardiac deaths according to diabetes status. Modified from Eranti et al. 2016b.

<table>
<thead>
<tr>
<th>Group</th>
<th>Normal (n = 1134)</th>
<th>IGT (n = 806)</th>
<th>Diabetes (n = 35)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suddenness of cardiac death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-sudden</td>
<td>697 (61.5%)</td>
<td>470 (58.3%)</td>
<td>23 (65.7%)</td>
<td>0.302</td>
</tr>
<tr>
<td>Sudden</td>
<td>437 (38.5%)</td>
<td>336 (41.7%)</td>
<td>12 (34.3%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 12. The results of Cox proportional hazards models assessing the risk of SCD, non-sudden cardiac death, and non-fatal cardiac events in subjects with IGT or diabetes. Modified from Eranti et al. 2016b.

<table>
<thead>
<tr>
<th>Group</th>
<th>Normal (n = 6706)</th>
<th>IGT (n = 3806)</th>
<th>Diabetes (n = 82)</th>
<th>p</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCD, no. of events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted HR</td>
<td>1 (reference)</td>
<td>1.51 (1.31–1.74)</td>
<td>&lt; 0.001</td>
<td>5.52 (3.10–9.82)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Model 1 ^1</td>
<td>1 (reference)</td>
<td>1.16 (1.00–1.35)</td>
<td>0.045</td>
<td>2.62 (1.46–4.70)</td>
<td>0.001</td>
</tr>
<tr>
<td>Model 2 ^2</td>
<td>1 (reference)</td>
<td>1.14 (0.98–1.32)</td>
<td>0.088</td>
<td>2.40 (1.34–4.33)</td>
<td>0.003</td>
</tr>
<tr>
<td>Non-sudden cardiac death, no. of events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted HR</td>
<td>1 (reference)</td>
<td>1.36 (1.21–1.53)</td>
<td>&lt; 0.001</td>
<td>8.43 (5.50–12.81)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Model 1 ^1</td>
<td>1 (reference)</td>
<td>0.94 (0.83–1.06)</td>
<td>0.321</td>
<td>3.05 (1.99–4.67)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Model 2 ^2</td>
<td>1 (reference)</td>
<td>0.92 (0.82–1.04)</td>
<td>0.194</td>
<td>2.90 (1.89–4.46)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Non-fatal cardiac events, no. of events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted HR</td>
<td>1 (reference)</td>
<td>1.27 (1.19–1.35)</td>
<td>&lt; 0.001</td>
<td>6.47 (4.95–8.44)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Model 1 ^1</td>
<td>1 (reference)</td>
<td>0.99 (0.92–1.05)</td>
<td>0.693</td>
<td>3.63 (2.77–4.75)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Model 2 ^2</td>
<td>1 (reference)</td>
<td>0.99 (0.92–1.05)</td>
<td>0.680</td>
<td>3.50 (2.67–4.59)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

^1Model 1: Adjusted for age, sex, BMI, systolic blood pressure, cholesterol, smoking, and baseline cardiac disease.

^2Model 2: Adjusted for age, sex, BMI, systolic blood pressure, cholesterol, smoking, baseline cardiac disease, heart rate, QTc, electrocardiographic signs of myocardial infarction, and electrocardiographic signs of coronary artery disease.
6 Discussion

6.1 QRS transition zone in the precordial leads of the ECG: occurrence site and prognostic significance

The results of this study indicate that delayed QRS transition is associated with adverse prognosis. In addition, a markedly delayed QRS transition seemed a novel risk factor of SCD.

The prevalence and prognostic significance of delayed QRS transition had previously been assessed in a big study based on Japanese population (Nakamura et al. 2012). In that study, the prevalence of delayed QRS transition was 8%, which is significantly lower than in the present study. However, it is likely that the differences in demographics of the populations, including the differences in genetic background affecting body composition as well as the prevalence of hypertension, explain this. In that study, a 15% increase in all-cause mortality was observed in subjects with delayed QRS transition. Early QRS transition was associated with a lower risk of cardiovascular disease death in a multivariate model (HR 0.81, 95% CI 0.70–0.94, p = 0.006), but no significant association with the risk of all-cause death observed. Thus, our findings of the prognostic significance of QRS transition seem largely similar as in the aforementioned study. A more posterior direction of the horizontal QRS axis which is closely related to QRS transition zone has also been shown to be a marker of adverse prognosis in a small study of elderly CHF patients (Xiao et al. 2005).

Also the prevalence and prognostic significance of a related electrocardiographic parameter, poor R wave progression, has been recently assessed in a Finnish general population cohort. Defined as R wave amplitude in lead V3 ≤ 0.3mV and ≥ R wave amplitude in lead V2, poor R wave progression was present in 2.7% of males and 7.0% of females. Poor R wave progression became more common with advancing age and was more prevalent in subjects with cardiac disease and was associated with all-cause and cardiac mortality. (Anttila et al. 2010). Because of the definition, most of the subjects with poor R wave progression are likely also have delayed QRS transition.

The pathophysiological basis of the relationship of delayed QRS transition and adverse prognosis has not been completely established. In a study using computed tomography to assess cardiac posture in the thorax, anatomic rotation of the heart explained early or delayed QRS transition only in two thirds of subjects (Tahara et al. 2010).
Poor R wave progression may be a normal variant or caused by anterior myocardial infarction, LVH, or right ventricular hypertrophy (Zema and Kligfield 1982). Clockwise rotation of the heart in the horizontal plane in vectorcardiogram, representing the same phenomenon as delayed QRS transition, has been documented in severe aortic insufficiency with left ventricular dilatation (Sobrino et al. 1975). Delayed QRS transition is also a frequent finding in acute massive pulmonary embolism (Yoshinaga et al. 2003). However, the aforementioned severe cardiac diseases (excluding LVH) are not likely to explain the presence of delayed QRS transition in subjects drawn from the general population. Recently, it was shown in an SCD case-control population that delayed QRS transition zone was associated with LVH in addition to previous myocardial infarction and reduced LVEF (Aro et al. 2016). Thus, it is reasonable to assume that most of the presumably healthy cases presenting with delayed QRS transition zone are explained by changes of the electrical function of the heart related to those seen in LVH. This hypothesis is supported by the fact that generally electrocardiographic LVH criteria have low sensitivities and the sensitivity of purely voltage-based LVH criteria is even worse among the obese and obesity was relatively common among subjects with delayed QRS transition (Fraley et al. 2005, Hancock et al. 2009).

In the present study, numerous important cardiovascular risk factors such as hypertension and obesity were more prevalent among subjects with delayed QRS transition. Thus, one might argue that the association of delayed QRS transition and adverse prognosis is mediated by these risk factors despite efforts to control their effects with adjustments in the models. However, the recent results regarding the cardiac pathology such as LVH and previous myocardial infarction seen in subjects with delayed QRS transition zone suggest that delayed QRS transition zone is related to cardiac structural abnormalities (Aro et al. 2016). It is unlikely that aforementioned severe cardiac conditions (pulmonary embolism, anterior myocardial infarction, or severe aortic insufficiency) would explain the increased risk of adverse events given the prevalence of delayed QRS transition and the observation that excluding subjects with cardiac disease did not markedly alter the results.

6.2 Prognostic implications of abnormal PTF

In this study, it was documented that an abnormal PTF is a relatively common finding in ECGs of middle-aged subjects and also among those with no pre-existing
cardiac disease. It was also shown that it is associated with mortality and the risk of atrial fibrillation, even after a thorough multivariate adjustment.

Current evidence suggests that PTF may develop with multiple mechanisms. Degeneration of interatrial conduction routes may lead to left atrial activation through the superiorly located Bachmann’s bundle. This results in left atrial depolarization vector propagating away from the lead V1 resulting in negative terminal portion of P wave in this lead. (Platonov 2012). Increased left atrial pressure has been shown to correlate with PTF, both in acute settings and chronic cardiac conditions and in acute settings PTF diminishes as left atrial pressure normalizes (Heikkilä et al. 1973, Kasser and Kennedy 1969, Kölbl et al. 1977). PTF has also been shown to correlate with echocardiographically assessed left atrial size (Hazen et al. 1991, Miller et al. 1983). It has also been documented that lung disease causing emphysema leads to diaphragmatic flattening and downward rotation of the right atrium, which may lead to a predominantly negative P wave in lead V1 (Chhabra et al. 2013).

The prevalence of abnormal PTF in presumably healthy middle-aged subjects in previous reports have been of similar magnitude as in our study (Forfang and Erikssen 1978, Soliman et al. 2013). Despite PTF $\geq 0.04$ mm·s being associated with atrial pathology it is also a relatively common finding in among junior elite athletes and healthy military recruits with prevalence 14% and 3.2% in these populations, respectively (Lynch 1983, Sharma et al. 1999). The prognostic significance of abnormal PTF in middle-aged subjects has received only little attention previously. Recent reports have identified it as a marker of worse prognosis with respect to mortality, SCD, atrial fibrillation, congestive heart failure, CHD hospitalizations, and stroke (Magnani et al. 2014, Tereshchenko et al. 2014). Among myocardial infarction patients, the presence of abnormal PTF is a marker of adverse prognosis even after adjustment for left ventricular ejection fraction (Liu et al. 2012). In the present study, no associations were found between PTF and the risk of SCD, stroke, and CHD hospitalizations. This may be due to the younger population and thus a greater proportion of subjects having abnormal PTF due to anatomical factors in the absence of cardiac pathology in our study. In addition, in the study that linked PTF with an increased risk of SCD, only PTFs that were $\geq 0.1$mV deep were considered abnormal (Tereshchenko et al. 2014). Also the follow-up time in our study was longer and thus more subjects who experienced adverse events may have developed PTF only during the follow-up.

The exact pathophysiologic mechanism which links abnormal PTF to adverse prognosis has been under debate. PTF may serve as a marker of left atrial
enlargement which is one indicator of pathologic remodelling in the heart as a response to hypertension, heart failure, or elevated left atrial pressure. Left atrial enlargement has been linked to an increased risk of AF, stroke, CHF, and death (Abhayaratna et al. 2006). Recent studies also suggest that PTF is a risk marker of atrial fibrillation which is a condition carrying a 2-fold risk of death (Benjamin et al. 1998). Also multiple pathologic cardiac conditions such as diastolic left ventricular dysfunction and LVH increase the risk of atrial fibrillation, but are asymptomatic in their early phases. Thus, PTF may also be a marker of these subclinical cardiac conditions. Anyhow, a distinctly abnormal PTF ($\geq 0.06$ mm·s) should be considered a marker of adverse prognosis and a sign of subclinical cardiac disease, also in the middle-aged general population. Also milder degrees of PTF warrant a close clinical evaluation of the patient.

6.3 Body mass index as a predictor of SCD risk and value of ECG in risk stratification in subjects with different relative weights

It was documented in this study that overweight and obese subjects are at increased risk of SCD, but the proportion of SCD of cardiac deaths was not pronounced in these groups. ECG risk markers of SCD were associated similarly with SCD risk in subjects with different BMIs in univariate models. However, in multivariate models, no statistical significance was reached among the obese and greatest improvements in models after the addition of ECG abnormality variables were measured in the normal weight group.

Obesity is an established risk factor of CHD and often presents with multiple other important CHD risk factors related to the metabolic syndrome. Obesity is also an established risk factor of CHF. (Bastien et al. 2014). These associations at least partly explain the increased risk of SCD and non-sudden cardiac death documented in the present study. However, also eccentric left ventricular hypertrophy, fat infiltration in the heart, fibrosis, QTc interval prolongation, increased ventricular ectopy, and decreases in heart rate variability have been documented among the obese which may further explain the SCD risk in the obese. (Plourde et al. 2014).

Despite the aforementioned associations, evidence of the relationship of BMI and SCD risk has been conflicting. High BMI has been shown to be a risk factor of SCD in both males and females in some studies (Albert et al. 2003, Jouven et al. 1999). However, in some other studies, this relationship has not appeared (Cupples et al. 1992, Thorgeirsson et al. 2005, Wannamethee et al. 1995). This may be due to the well-known limitations of BMI in reflecting body composition as both
increases in fat mass and lean mass increase BMI. This is supported by recent studies in which measures of abdominal obesity have been strong predictors of SCD (Adabag et al. 2014, Bertoia et al. 2012, Empana et al. 2004). Our results indicate that BMI may be used as a measure of obesity in estimating one’s risk of SCD, at least if measures of abdominal obesity are unavailable.

Whether the proportion of cardiac deaths being sudden increases in obese subjects has yielded conflicting results as well. In male populations, increases in the proportion of SCDs among the obese have been documented in early studies, and in one study, the incidence of SCD increased more than the incidence on non-fatal myocardial infarction (Doyle et al. 1976, Empana et al. 2004, Rabkin et al. 1977). In one study, no difference in BMI was observed when SCD and non-sudden cardiac death victims were compared (Escobedo and Zack 1996). We did not detect an increase in the proportion of cardiac deaths being sudden with increasing BMI. However, the most dramatic changes caused by obesity in heart have been documented in morbidly obese subjects (Wong and Marwick 2007). Our results can not be applied to morbidly obese subjects as only 222 subjects in our study had BMI > 35 kg/m².

In our study, no increases SCD risk were documented among the lean. An obesity paradox, in which subjects with BMI in the high-normal or overweight range have got better prognosis than lean subjects, has been observed in multiple epidemiologic studies. However, it has been proposed that this may be caused by the confounding effect of higher prevalence of smoking and pre-existing illness as the cause of low weight, among other potential confounders. (Lavie et al. 2014).

It is well known that body composition affects the ECG and also the changes in cardiac structure associated with obesity may reflect to the ECG (Fraley et al. 2005). However, the value of electrocardiographic SCD risk markers had not been compared between subjects with different relative weights before. We documented largely similar HRs for SCD associated with the ECG abnormalities in univariate models. However, ECG abnormalities provided most value in risk stratification among normal weight subjects. We believe that this is because in the normal weight group the prevalence of traditional cardiovascular risk factors was lowest. Among the overweight and obese, a higher prevalence of hypertension and hypercholesterolemia, as well as higher prevalence of cardiac disease may have explained the SCDs.
6.4 Diabetes, glucose tolerance, and the risk of SCD

In this study, the role of diabetes and IGT as risk factors of adverse cardiac events was assessed. Particular attention was paid to whether the risk of SCD would increase among diabetes patients over the risk of non-sudden cardiac death and also to the timing of the risk. In this study, diabetes was expectedly associated with an increased risk of SCD and similarly with the risk of non-sudden cardiac death. Also a high risk of hospitalizations due to CHD or CHF was observed among diabetes patients. Diabetes was associated with a remarkably elevated risk of SCD already before the development of overt heart disease. This detail has received only little attention before. In most prospective population based studies, diabetes has been a similar predictor of both SCD and non-sudden cardiac death (Kucharska-Newton et al. 2009, Siscovick et al. 2010). The hazard ratios for SCD associated with diabetes have been largely similar in previous studies regardless of inclusion or exclusion of subjects with pre-existing cardiac disease (Bertoia et al. 2012, Zaccardi et al. 2014). However, in the Paris Prospective Study, diabetes was associated with an increased risk of SCD, but the risk of non-fatal myocardial infarction was not increased among diabetes patients (Balkau et al. 1999). Also in two studies that followed CHD patients after myocardial infarction a greater proportion of deaths was sudden among diabetes patients compared to myocardial infarction patients without diabetes (Junttila et al. 2010, Yeung et al. 2012).

In type 2 diabetes, coronary atherosclerosis begins and proceeds already in the prediabetic dysglycemic state. Cardiac autonomic neuropathy, heart failure, and cardiac fibrosis which have been linked strongly to arrhythmogenesis develop late in the course of diabetes. (Rydén et al. 2013). Thus, it seems reasonable that the early and rapid development of CHD explains the high risk of SCD in diabetes patients already before the development of overt heart disease as SCD may be the first manifestation of heart disease. Based on previous findings in post myocardial infarction patients in whom the duration of diabetes is probably longer than among participants of prospective population based studies, the risk of SCD in diabetes patients might pronounce over the risk of non-sudden cardiac death late in the course of diabetes (Junttila et al. 2010, Yeung et al. 2012). Thus, in future studies, this issue should be addressed stratified for the duration of diabetes. Discriminating subjects at high risk for specifically SCD from subjects who are generally at high risk of death would be beneficial in targeting the preventive ICD therapy. However, diabetes seems to lack the specificity like numerous other risk markers. (Wellens et al. 2014).
In this study, IGT predicted SCD in a univariate model but adjustment for confounders attenuated this effect. IGT is an important risk factor of diabetes and often presents with other important risk factors of CHD as a part of the metabolic syndrome. Thus, it is difficult to separate the individual contributions of these risk factors. (Grundy 2012). Our results are generally in line with previous studies. In a meta-analysis, IGT was associated with a 1.2-fold risk of a combined end-point of fatal and non-fatal cardiac events, but the authors stated that the degree of adjustment was limited in many of the included studies (Ford et al. 2010). In one study, males with IGT were at increased risk of SCD based on a survival curve analysis (Balkau et al. 1999). In another study, males of Japanese ancestry living in Hawaii with IGT were at increased risk for SCD. The multivariate-adjusted HR for SCD was 1.59 in subjects with plasma glucose concentration 8.39–12.44 mmol/l in 1-hour OGTT and the HR increased to 2.22 in subjects with OGTT result ≥ 12.55 mmol/l. (Curb et al. 1995). Recently, also impaired fasting plasma glucose was shown to be associated with an increased risk of SCD in a Finnish male population (Laukkanen et al. 2012).

No significant differences were found in heart rates or QTc intervals between diabetes patients grouped according to their causes of death. Elevated heart rate and QTc lengthening are characteristic in CAN (Bergner and Goldberger 2010, Vinik et al. 2013). In one case-control study following diabetes patients without cardiac disease, subjects in the longest QT interval quintile were at 3-fold risk of SCD when compared with the shortest QT quintile (Whitsel et al. 2005). However, the negative result in our study may be due to the small number of diabetes patients in our study leading to insufficient statistical power to detect differences in variables with large between-subject variance. Also the age of the subjects in the aforementioned study was markedly older (mean 65 years) and the follow-up-time to SCD was shorter (mean 5.1 years), whereas it was 12.8 years in our study. Thus, in our study, diabetes patients about to die of SCD may have developed CAN leading to QTc lengthening and acceleration of heart rate during the follow-up.

6.5 Strengths and limitations

The strengths of this study include the long and comprehensive follow-up with only a small fraction of subjects lost to follow-up. Also the generalizability of the results due to the large population which represented the Finnish middle-aged population well is a strength. The large population size and long follow-up yielded a sufficient number of events for meaningful statistical analysis. The thoroughly and precisely
conducted baseline examinations allowed for the adjustment for multiple important confounders. Thus, the study design was statistically strong enough to show associations between ECG abnormalities, cardiovascular risk factors, and SCD. However, due to the length of the follow-up, the associations found in this study should be studied in the future also regarding their ability to predict the risk in a shorter and clinically more relevant time window. The main weakness in this study is the lack of echocardiographic data which led to the inability to take into account the left ventricular ejection fraction among other important parameters. Also the lack of waist circumference measurements and the inability to diagnose IGT according to the present-day standards somewhat limit the utility of the results. Finally, no bystander reports were available for the classification of cardiac deaths to sudden or non-sudden as the classification was performed after the follow-up.

6.6 Future directions

Overall, methods for the screening of subjects at high risk for SCD from the general population accurate enough to guide the selection of subjects to specific antiarrhythmic therapies are still lacking. Efforts to reduce the overall cardiovascular risk factor burden, both at population level and at individual level reduce cardiac events and thus also SCDs. These efforts include interventions to reduce smoking, promote healthy living habits, and to correct elevated blood pressure and atherogenic dyslipidemia. In the clinical practice, left ventricular ejection fraction remains the cornerstone guiding the selection of patients with ischemic or non-ischemic dilated cardiomyopathy to ICD therapy. (Priori et al. 2015). There is also room for improvement in this approach as a large part of ICD patients never receive appropriate therapies and device-related complications are common (Van der Heijden et al. 2015).

The current consensus is that it seems unlikely that a single risk marker would be accurate enough to be applicable for population-level screening of subjects at high risk of SCD. Thus, it has been suggested that in the future, the assessment of SCD risk might be stepwise. This assessment would first utilize family history and traditional cardiovascular risk factors and electrocardiographic risk markers. After the initial screening, the subjects at highest risk would be tested further using genetic testing, cardiac imaging, and autonomous nervous system testing. (Deyell et al. 2015, Wellens et al. 2014). Due to the recent advances in digital ECG signal processing, automated screening of subjects at risk from hospital ECG archives might be possible (Kenttä et al. 2015, Waks et al. 2016). Small devices that record
ECG to mobile devices have become available and high risk patients might be able to screen their ECG daily for arising abnormalities indicating susceptibility to arrhythmias in the future. Also efforts to increase public awareness of the need to urgently alert medical emergency services if symptoms related to coronary event present are of importance as it has been shown that 51% of SCD subjects experience warning symptoms before the event (Marijon et al. 2016).
7 Conclusions

In the present study, delayed QRS transition zone was identified as a novel ECG risk marker of SCD. It was also documented that a markedly abnormal PTF is a marker of adverse prognosis in the middle-aged general population. The finding that PTF $\geq 0.06$ mm·s was associated with an increased risk for AF was interesting, as identifying subjects with subclinical paroxysmal AF, especially among stroke patients, is of great interest given the improvement in prognosis associated with anticoagulation therapy. The presence of a markedly delayed QRS transition and a deep and broad PTF may be used as markers of cardiac pathology in the clinical setting and their presence warrants a close evaluation of the patient. We also showed that subjects with higher BMIs are at increased risk of both SCD and non-sudden cardiac death, but the proportion of SCD of cardiac deaths is not pronounced. This contributed to the unraveling of the conflicting results in existing literature. It was also documented that ECG risk markers of SCD provide most value in risk stratification among normal weight subjects presenting with less traditional cardiovascular risk factors. Thus, the conversant clinician should be alert if a lean subject with a low burden of cardiovascular risk factors presents with abnormal ECG. In the analyses of this study, we replicated the previous association of diabetes and a 2–3-fold SCD risk. Of importance, it was observed that diabetes patients are at high risk for SCD already before the development of overt heart disease. Also IGT was shown to be an indicator of SCD risk, but its independent contribution warrants further research as the effect was attenuated by adjustments for potential confounders. The results of the present thesis contribute to the growing understanding of the role of electrocardiographic abnormalities and traditional cardiovascular risk factors as markers of SCD risk.
References


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THE ROLE OF ELECTROCARDIOGRAPHIC ABNORMALITIES, OBESITY, AND DIABETES IN RISK STRATIFICATION FOR SUDDEN CARDIAC DEATH IN THE GENERAL POPULATION