Tomi Toukola

PHYSICAL EXERCISE AND SUDDEN CARDIAC DEATH

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Characteristics and risk factors

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Physical activity with regular physical exercise (PE) has long been advocated because it lowers morbidity and mortality. However, there have been concerns about a transiently increased risk of adverse cardiac events such as sudden cardiac death (SCD) during PE. Our aim was to identify risk factors related to SCD during PE and clarify the effect of PE on cardiovascular well-being in the general population.

In study I we found out that male gender as well as coronary artery disease (CAD), cardiac hypertrophy and myocardial scarring as autopsy-findings were clearly more common among exercise-related SCD. Typical northern activities in skiing and snow shoveling were among the three most common types of PE alongside cycling. In study II we analyzed the previously recorded electrocardiograms (ECG) of victims of SCD. Fragmented QRS complex (fQRS) in anterior leads was a common finding among subjects who died during exercise, especially among subjects with a prior diagnosis of CAD.

In study III, we collected retrospectively out-of-hospital sudden cardiac arrest (SCA) data in Northern Ostrobothnia between the years 2007 and 2012. The subjects who suffered SCA in relation to PE were younger and previously healthier, and they had more often a shockable rhythm as the initial rhythm. There was a markedly better prognosis for hospital discharge when SCA occurred during PE. In study IV, we noticed a decrease in cardiac mortality in subjects who were physically active or became active during follow-up in a population of 1,746 stable CAD patients. A similar effect could be seen affecting SCD mortality. No increase in cardiac mortality could be seen among those with the highest levels of habitual PE.

In conclusion, ischemic heart disease and male gender, especially when fQRS is present in anterior leads, are characteristics related to exercise-related SCD. On the other hand, when SCA takes place during PE, the prognosis is markedly better compared to SCA occurring at rest. An active lifestyle is also linked to decreased cardiac mortality.

Keywords: electrocardiography, leisure-time physical activity, physical exercise, resuscitation, sudden cardiac arrest, sudden cardiac death
Tiivistelmä

Säännöllinen aktiivinen elämäntapa on yhteydessä pienempiin fyysisten ja psykkisten sairauksien riskiin. Tutkimuksissa on kuitenkin havaittu raskaampiin liikuntaan liittyvä väliaikainen, mutta hieman sydänperäisen äkkikuoleman riski. Väitöskirjatutkimuksessa tutkitaan rasitukseen liittyvän sydänperäisen äkkikuoleman erityispiirteitä ja fyysisen aktiivisuuden merkitystä hyvinvoinnille.


Asiassanat: elektrokardiografia, elvytys, fyysinen rasitus, riskitekijät, sydän- ja verisuonitaudit, sydänperäinen äkkikuolema, sydänpysähys, vapaa-ajan liikunta
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Vaasa, April 2018

Tomi Toukola
### List of abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AED</td>
<td>Automated External Defibrillator</td>
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<tr>
<td>AMI</td>
<td>Acute Myocardial Infarction</td>
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<td>ARVC</td>
<td>Arrhythmogenic Right Ventricular Cardiomyopathy</td>
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<td>CAD</td>
<td>Coronary Artery Disease</td>
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<td>CPR</td>
<td>Cardiopulmonary Resuscitation</td>
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<td>CVD</td>
<td>Cardiovascular disease</td>
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<td>DCM</td>
<td>Dilated Cardiomyopathy</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>EMS</td>
<td>Emergency Medical System</td>
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<td>fQRS</td>
<td>Fragmented QRS Complex</td>
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<td>HCM</td>
<td>Hypertrophic Cardiomyopathy</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>LTPA</td>
<td>Leisure-Time Physical Activity</td>
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<tr>
<td>LVH</td>
<td>Left Ventricular Hypertrophy</td>
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<tr>
<td>MET</td>
<td>Metabolic Equivalent</td>
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<tr>
<td>PE</td>
<td>Physical Exercise</td>
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<tr>
<td>RBBB</td>
<td>Right Bundle Branch Block</td>
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<tr>
<td>SCA</td>
<td>Sudden Cardiac Arrest</td>
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<tr>
<td>SCD</td>
<td>Sudden Cardiac Death</td>
</tr>
<tr>
<td>TpTe</td>
<td>T-peak to T-end</td>
</tr>
<tr>
<td>VF</td>
<td>Ventricular Fibrillation</td>
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Original publications

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


* Equal contribution.
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1 Introduction

“Let exercise alternate with rest.” – Pythagoras

Good physical fitness through regular physical activity has been linked to better overall health for thousands of years. Regular physical exercise (PE) improves both the physical and mental aspects of our health. When the well-being of our heart is considered, regular physical training reduces cardiovascular risk factors, delays atherosclerosis and lowers both morbidity and mortality in cardiovascular disease (CVD). Information gathered during the past decades has created a well-established understanding of the relationship between an active physical lifestyle and reduced incidence of events of coronary artery disease (CAD). PE has also been shown to lower elevated blood pressure and improve glucose tolerance, insulin sensitivity, lipid profiles and weight control. PE is also advocated as an important factor in cardiac rehabilitation in subjects with diagnosed CAD.

By definition, sudden cardiac death (SCD) is natural unexpected death of cardiac origin. In witnessed cases, death occurs within a 1-hour time frame from the onset of symptoms. The subject might have a previously diagnosed heart disease, but the time and mechanism of the death is nonetheless unexpected. The annual incidence of SCD in Finland is estimated to be 0.1–0.2%, or 5,000–10,000 cases. SCD accounts for a significant proportion of years of potential life lost. Sudden cardiac arrest (SCA) is a potentially reversible medical emergency. This condition eventually leads to SCD if no actions are taken. National initiatives have been taken to improve the rates of bystander cardiopulmonary resuscitation (CPR) and the usage of automated external defibrillator (AED) by laypeople, but the overall survival rates remain low.

A structural cardiac abnormality can be found in up to 95% of cases of SCD. In nearly half of the cases, SCD is the first manifestation of the cardiac disease. CAD is the most common underlying heart disease and explains up to 70–80% of SCDs. Cardiomyopathies, such as hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC), are the second most important group of cardiac disease causing SCD. Aortic valve abnormality and inflammatory cardiac diseases are also possible autopsy findings in victims of SCD. Certain congenital heart diseases also increase the risk of SCD. In young subjects autopsy-negative findings are more common and in these cases an inherited arrhythmia syndrome can explain the
death. The cardiac abnormality acts as substrate for lethal ventricular arrhythmias when transient internal or external triggers are present.

PE, especially vigorous physical exertion, can act as a trigger for SCD in cases with an underlying cardiac abnormality. Strenuous exertion has been shown to transiently increase the risk of SCD and this risk is highest among habitually sedentary subjects. Approximately 5 to 10% of all SCD occurs during or shortly after exercise, and the idea of the paradox of exercise has been introduced. During the last decades, research has focused mainly on young athletes and sports-related SCD. SCD among young professional athletes is a devastating event and often raises broad public interest, but fortunately the overall incidence of SCD among young athletes is extremely low. In the general population the annual incidence of SCD during PE ranges from five to twenty cases per 100,000 person years. The challenge in preventing exercise-related SCD in the general population is the difficulty of identifying those at higher risk of adverse effects caused by PE. Findings that are more common among exercise-related deaths include male gender, CAD and age over 35 years.

The 12-lead electrocardiogram (ECG) is routinely taken in clinical medicine to detect cardiac electrical abnormalities, which could in turn reveal arrhythmia, myocardial infarction or inherited channelopathy. Several different ECG abnormalities are associated with an increased risk of SCD during follow-up in the general population, but all these separate findings have low predictive value by themselves, especially in previously healthy subjects.

While the amount of occupational physical activity is decreasing in Westernized countries, the importance of leisure-time physical activity (LTPA) is becoming more prominent. Large epidemiological studies have revealed a markedly better prognosis of subjects with higher levels of LTPA, although some studies have brought into attention the higher mortality rates among the most highly active subjects. It is, however, unclear how longitudinal changes in physical activity affect cardiovascular well-being in patients with diagnosed CAD.

The aim of this thesis is to elaborate the relationship of PE and cardiovascular events. These studies provide information on exercise-related sudden cardiac events with comprehensive autopsy data in the general population. The study on ECG abnormalities related to SCD during PE in the general population is the first of its kind.
2 Review of the literature

This review elaborates on SCD and the importance of PE. Special interest is given to the relationship between SCD and PE. This review also focuses on ECG abnormalities linked to SCD.

2.1 Sudden cardiac death

SCD is defined by the World Health Organization as a natural unexpected incident of cardiac origin. In witnessed cases, death occurs within a 1-hour time frame from the onset or rapid acceleration of symptoms. A 24-hour time frame after the subject has been seen alive in normal state of health has also been used as a definition of SCD. In large-scale autopsy studies, a 6-hour window after the onset of symptoms has been used to include lethal cardiac arrhythmia caused by an acute coronary event (A. J. Taylor et al., 2000). The mechanism behind SCD is often ventricular arrhythmia, which leads to collapse of the circulatory system (Huikuri, Castellanos, & Myerburg, 2001). SCA is used to describe cases who survived the unexpected cardiac arrest.

2.1.1 Epidemiology of sudden cardiac death

CVD, such as CAD and stroke, are still the leading causes of death globally. In the Western world the rate of cardiovascular mortality has decreased during the last decades in the working age population, defined as those under the age of 65 (Lozano et al., 2013). This is thought to be due to improvement in overall health parameters and advances in medical care. It is generally accepted that circa 50% of all deaths due to CAD are unexpected and sudden and thus categorized as SCD (Myerburg, 2001). A recent study conducted in the United States revealed that SCD accounted for 40 to 50% of years of potential life lost due to heart disease (Stecker et al., 2014).

The overall incidence of SCD varies substantially according to the definition of SCD and the extent of post-mortem investigations (Kong et al., 2011). In older populations, the incidence of SCD is substantially higher. In the United States, the estimates of the absolute number of SCD vary from 180,000 to 450,000 cases annually (Cobb, Fahrenbruch, Olsufka, & Copass, 2002; Zheng, Croft, Giles, & Mensah, 2001). A study published in 2014 introduced an extrapolated estimate of the incidence of SCD in the United States to be around 200,000 annually (Stecker
et al., 2014). The annual incidence is quite similar worldwide. In China, there were 42 SCDs per 100,000 person years (Hua et al., 2009). In the United States, it is estimated that 60 SCDs occur per 100,000 person years annually (Stecker et al., 2014). In Europe, the incidence rates are comparable (Byrne et al., 2008). In a recent Dutch study the age-specific incidence of SCD was 420 per 100,000 person years in an older study population and the age-specific incidence of SCD was decreasing (Niemeijer et al., 2015). No recent precise numbers of SCDs in Finland have been published. However, it is roughly estimated that around 5,000-10,000 SCDs take place in Finland annually, which comprises 10-20% of all deaths. The annual incidence of SCD is multiple times higher in high-risk subgroups compared to the general population, but most of the SCDs take place in populous low-risk subgroups (Myerburg, Mitrani, Interian, & Castellanos, 1998). We lack more sophisticated markers of risk of SCD in traditional low-risk populations.

2.1.2 Etiology and mechanisms of sudden cardiac death

It is widely accepted that ischemic heart disease is the underlying pathology in 70–80% of SCD cases in the general population (Junttila et al., 2016; Myerburg, 2001). On the other hand, 20–30% are due to non-ischemic cardiac abnormalities such as cardiomyopathies, primary arrhythmic syndromes and valvular heart disease. An autopsy is recommended by the European Society of Cardiology in victims of sudden death to ensure the diagnosis of the underlying cardiac abnormality (Priori et al., 2015). The updated guideline for post-mortem examinations in SCD cases was presented recently (Basso et al., 2017).

It is generally thought that the underlying cardiac condition leads to a potentially fatal arrhythmic event and eventually to SCD. These arrhythmias can be divided into tachyarrhythmic events, including ventricular fibrillation (VF) and ventricular tachycardia, and bradycardic events, including asystole and pulseless electrical activity (PEA). In older studies, VF was the most common arrhythmia preceding SCA, comprising up to 75% of the cases (Greene, 1990; Liberthson et al., 1974). It is thought that the fatal arrhythmia in myocardial ischemia primarily begins with ventricular tachycardia or VF, which over time ceases into PEA or asystole (de Luna, Coumel, & Leclercq, 1989; Wit & Janse, 1992). The prevalence of VF as the initial rhythm has been declining during the last decades and the portion of non-shockable rhythms (asystole or PEA) has increased (Cobb et al., 2002; Daya et al., 2015; Väyrynen, Boyd, Sorsa, Määttä, & Kuismia, 2011).
In a recent study conducted in Finland, a little over half of the cases of SCA had VF or ventricular tachycardia as the initial rhythm (Kauppila et al., 2018). In a Swedish study, the proportion of VF decreased to 32% and PEA increased to 26%, although the rates of bystander CPR increased and the time to rhythm monitoring shortened (Herlitz et al., 2000). VF is more often related to underlying CAD, and it is thought that the decreasing CAD-related mortality and the decreasing prevalence of VF go hand in hand (Cobb et al., 2002; Teodorescu et al., 2010). VF was also clearly a more common finding in ischemic SCA compared to non-ischemic cases (Kauppila et al., 2018).

Coronary atherosclerosis is a common phenomenon progressing with advancing age, and it is modified by environmental and genetic risk factors. Arterial atherosclerosis might eventually lead to symptomatic CVD, such as CAD and stroke. SCD is the first manifestation of CAD in around 15-20% of subjects (Hochman et al., 1997; Kannel, Cupples, & D'Agostino, 1987). It has been shown that the proportion of SCD due to ischemic origin is decreasing, and CAD accounts for around 70% of all SCDs (Junttila et al., 2016). Underlying CAD can cause fatal arrhythmias by several mechanisms. Acute myocardial infarction (AMI) causing acute ischemia can result in mechanical, metabolic and electrophysiological dysfunction. Spontaneous or iatrogenic reperfusion of the occluded vessel might also cause a substrate for arrhythmogenesis (Furukawa, Bassett, Furukawa, Kimura, & Myerburg, 1993). The heterogeneous electrical activation of the myocytes in and around the infarcted myocardium enables reentry of the impulse and thus arrhythmia (Carmeliet, 1999). Transient ischemia due to unstable plaque, dynamic coronary spasm or disparity between demand and supply of coronary circulation creates a substrate for arrhythmias and may also lead to SCD (Myerburg et al., 1992). In most cases of ischemic SCD, it was caused by stable plaque (>75% narrowing) (Kaikkonen, 2009). Plaque rupture was seen in less than 20% of the cases. Myocardial ischemia can also produce long-lasting risk of SCD by myocardial scarring and ischemic cardiomyopathy. In these cases, myocardial scarring acts as substrate to reentrant ventricular arrhythmias (de Bakker et al., 1988). On the other hand, myocardial scarring can originate from non-ischemic causes, too (Soejima et al., 2004).

Different primary cardiomyopathies are divided into HCM, DCM, ARVC, restrictive cardiomyopathy and unclassified cardiomyopathy according to the morphofunctional phenotype by the European Society of Cardiology in 2007 (Elliott et al., 2007). These non-ischemic abnormalities account for around 15-20% of SCDs (Chugh et al., 2008; Junttila et al., 2016). In a large population of
autopsy-verified SCD, HCM, DCM and ARVC were uncommon findings among victims of non-ischemic SCD (Hookana et al., 2011). The most common causes of non-ischemic SCD were cardiomyopathy related to obesity and alcoholic cardiomyopathy.

There is most likely overlap between CAD and non-ischemic heart disease due to the often silent progression of atherosclerosis with advancing age. SCD has long been identified as a common cause of mortality in patients with HCM (Maron & Fananapazir, 1992; Maron et al., 2000). HCM is defined as left ventricular hypertrophy (LVH) without sufficient underlying hemodynamic abnormalities and is thought to have a prevalence of 1:500 in the general population (Maron et al., 1995). HCM is considered a familial cardiac disease with several possible genes responsible for the progression of the disease (Maron, Maron, & Semsarian, 2012). The initial rhythm causing SCD in HCM patients is often ventricular tachycardia or VF (Maron et al., 2007). Myocardial scarring and fibrosis are thought to cause intraventricular conduction disturbance and re-entry tachyarrhythmias (Saumarez et al., 1995). DCM is characterized by left ventricular enlargement and reduced left ventricular ejection fraction (Jefferies & Towbin, 2010). The majority of the cardiac mortality caused by DCM is due to end-stage heart failure and these deaths are not considered as SCD. However, implantable defibrillators reduce arrhythmic deaths in DCM patients, especially in subjects under the age of 70, highlighting also the importance of ventricular tachyarrhythmias as the mechanism of death (Kadish et al., 2004; Køber et al., 2016). ARVC is a hereditary disease causing loss of myocardium and replacement by fatty or fibrofatty tissue, most distinctively in the right ventricle (Basso et al., 1996). It is thought that the fibrofatty tissue alters intraventricular conduction, which enables re-entry tachyarrhythmias (Corrado, Link, & Calkins, 2017). Restrictive cardiomyopathy is a rare cardiac disease with restricted ventricular filling without significant ventricular wall hypertrophy and often initially preserved ejection fraction (Kushwaha, Fallon, & Fuster, 1997).

2.1.3 Primary arrhythmia syndromes

In around 5% of SCD victims, the heart is apparently normal in postmortem investigations (Chugh, Kelly, & Titus, 2000; Priori et al., 1992). The general view is that in these cases, SCD is caused by different primary arrhythmic syndromes. Long QT syndrome (LQTS) is one of the most important inherited contributors to lethal arrhythmia in the young. In Caucasians, the prevalence of LQTS has been
found to be around 1 per 2,500 (Schwartz et al., 2009). However, in Finland the prevalence of LQTS founder mutations has been documented to be as high as 1 per 250 to 1 per 500 (Marjamaa et al., 2009). Several genes have been found to be responsible for the prolongation of the QT interval, but most cases fall into three different genotypes: LQTS1, LQTS2 and LQTS3. QT interval prolongation is sometimes accompanied with T-wave alternans. Arrhythmic events, most notably torsades de pointes, are associated with LQTS. The most likely circumstance preceding arrhythmia varies between different genes; as opposed to LQTS2 and LQTS3, the majority of LQTS1 cases experience the cardiac event during exercise (Schwartz et al., 2001).

Catecholaminergic polymorphic ventricular tachycardia is a rare arrhythmogenic cardiac abnormality that manifests as bidirectional ventricular tachycardia or polymorphic ventricular premature beats or ventricular tachycardia during exercise or emotional stress leading to syncope or even sudden death (Leenhardt et al., 1995). There is no structural cardiac abnormality or changes in resting ECG. During exercise testing ventricular ectopic beats can be seen (Sumitomo et al., 2003). A rough estimate of the prevalence is 0.1 per 1,000 (Priori et al., 2014). Brugada syndrome is a fairly common cause of cardiac death in the young in Asian populations (Antzelevitch et al., 2005). Certain types of ST-segment elevation in right precordial leads are typical of Brugada syndrome (Priori et al., 2014). The clinical manifestations include chest discomfort, palpitations, syncope and SCD in patients with no structural heart disease. However, these events mostly occur at rest or while sleeping, and seldom during PE.

2.1.4 Characteristics of sudden cardiac death in the young

In the young, the incidence of SCD is low, but the number of years of potential life lost is relatively high. The term “young” often refers to subjects under the age of 35. An Australian study derived from autopsy registries regarding subjects between 5 and 35 years of age showed an incidence of 1.0 cases per 100,000 patient years (Puranik, Chow, Duflou, Kilborn, & McGuire, 2005). In the United Kingdom, the annual incidence of SCD among subjects between the ages 1 to 35 was 1.8 per 100,000 patient years (Papadakis et al., 2009). Although the incidence rates are low, the proportion of sudden deaths is relatively high among all deaths in the young (Winkel et al., 2010; Zheng et al., 2001). The incidence of SCA
among the young is highest in infants <1 year of age (Bardai et al., 2011). In competitive athletes the incidence numbers of SCD are low.

The underlying cardiac pathology of SCD varies considerably between different age groups. In populations under the age of 35, the proportion of sudden arrhythmic death with no structural cardiac abnormality is high. Doolan et al. stated that 31% of SCD cases were presumed to be due to primary arrhythmic syndromes (Doolan, Langlois, & Semsarian, 2004). In subjects between the ages 14 and 35 in Ireland, the proportion of autopsy-negative SCD cases was 26.7% (Margey et al., 2011). Similarly, in a recently published Swedish study, 31% of SCDs were considered to be caused by arrhythmic death syndrome (Wisten, Krantz, & Stattin, 2016). In Australia and New Zealand, up to 40% of SCDs were autopsy-negative (Bagnall et al., 2016). These findings highlight the importance of the different arrhythmogenic syndromes described previously. On the other hand, there are also studies presenting substantially lower numbers of autopsy-negative SCDs in the young. In the Veneto region, only 6% of SCD cases had a structurally normal heart after macroscopic evaluation and histological examination (Corrado, Basso, & Thiene, 2001). In northern Finland, the proportion of structurally normal heart in SCD victims <40 years was 3.8% (Hookana et al., 2011). CAD becomes more common with advancing age. CAD has been the most common cause of SCD in young subjects closer to the age of 35 (Arzamendi et al., 2011; Eckart et al., 2011).

In Italy, ARVC seems to be a common cardiac pathology causing SCD (Thiene, Nava, Corrado, Rossi, & Pennelli, 1988). In young athletes in the United Kingdom, ARVC was the second most common cause of SCD after idiopathic LVH (de Noronha et al., 2009). Among non-ischemic SCDs in northern Finland, idiopathic myocardial fibrosis was the most common etiology in subjects <40 years (Hookana et al., 2011). LVH and myocardial fibrosis were similarly common among young athletes with SCD in a recent study from the United Kingdom (Finocchiaro et al., 2016). HCM is also a common cardiac abnormality in the young, especially young athletes (Eckart et al., 2004; Maron, Doer, Haas, Tierney, & Mueller, 2009).

### 2.1.5 Prevention of sudden cardiac death

*Early recognition and treatment of patients with cardiac disease.* In the general population with mostly asymptomatic patients, it is important to detect subjects at high risk of occult cardiac disease and to limit exposure to risk factors, such as
smoking and sedentary lifestyle, and to treat modifiable risk factors, such as hypertension, diabetes and dyslipidemia, and to lower traditional risk factors for cardiac disease. Different risk scores for CAD have been presented; these calculations take into account factors such as age, gender, blood pressure, smoking, lipid profiles and family history (Peltonen et al., 2008; Wilson et al., 1998).

Screening the general population. ECG markers related to increased risk of SCD have been a topic of considerable interest in recent decades. These results are presented later in this review. In Japan, screening for prolonged QT-interval has been implemented in the entire population, but the effect of this screening program is difficult to assess (Yoshinaga et al., 2013). There is a consensus on preparticipation cardiovascular screening of young athletes, but whether routinely taken ECG is beneficial is under debate (Corrado et al., 2006; Harmon, Zigman, & Drezner, 2015; Maron, Friedman, & Caplan, 2015; Steinvil et al., 2011).

Pharmacotherapy for the prevention of SCD. The research in pharmacotherapy for the prevention SCD has mainly focused on lowering the ventricular arrhythmogenesis. Beta-blockers are considered somewhat safe and effective in reducing SCD. In patients with heart failure, beta-blockers lower the risk of SCD (Merit-HF Study Group, 1999). A meta-analysis published in 2013 presented a 31% reduction of SCD in heart failure patients treated with beta-blockers (Al-Gobari, El Khatib, Pillon, & Gueyffier, 2013). Kendall et al. showed the efficacy of beta-blockers in other cardiac disease, too (Kendall, Lynch, Hjalmarson, & Kjekshus, 1995). Amiodarone has been shown to reduce the risk of SCD, but not the overall mortality (Piccini, Berger, & O’Connor, 2009). However, considerable side effects have been linked to long-term amiodarone treatment, including pulmonary and thyroid toxicity, even with low daily doses (Harris et al., 1983; Vorperian, Havighurst, Miller, & January, 1997). Medications reducing the remodeling of the myocardium also decrease the rates of SCD, especially in patients with heart failure. These agents include drugs affecting the renin–angiotensin system (Domanski et al., 1999) and mineralocorticoid receptor antagonists (Bapoje et al., 2013). No significant difference has been noted between angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists (Pitt et al., 2000). A recently published study in heart failure patients without an implantable cardioverter defibrillator (ICD) showed a reduction of 44% in SCD from 1995 to 2014 (Shen et al., 2017). This finding emphasizes the role of modern pharmacotherapy in the prevention of SCD in heart failure patients.
Device therapy for the primary and secondary prevention of SCD. ICDs are set to detect and manage ventricular tachyarrhythmias by giving electric shocks or overdrive pacing. In secondary prevention ICDs are used in subjects who have previously been resuscitated from cardiac arrest or have suffered hemodynamically unstable ventricular tachyarrhythmia. These subjects benefit more from ICD therapy than from antiarrhythmic drugs (Connolly et al., 2000; Kuck, Cappato, Siebels, & Ruppel, 2000). In primary prevention, studies have shown the effectiveness of ICD therapy in patients at high risk of SCD both in ischemic and non-ischemic cardiomyopathy (Bardy et al., 2005; Goldenberg et al., 2010; Moss et al., 1996). A recent review article addressed the effect of ICD as primary prevention of SCD both in ischemic and non-ischemic heart disease and showed favorable outcomes (Kołodziejczak et al., 2017). Studies have also demonstrated the superiority of ICD therapy compared to antiarrhythmic drugs, often amiodarone (Bardy et al., 2005; Bokhari et al., 2004). Even though more sophisticated ICDs have been introduced, inappropriate shocks and post-operative complications are possible (Germano, Reynolds, Essebag, & Josephson, 2006). ICD shocks, appropriate or inappropriate, decrease the quality of life and can cause anxiety. The efficacy of primary prevention of SCD with ICD was originally shown in patients with a clearly lowered left ventricular ejection fraction (under 30 to 35%), but most subjects suffering from SCD have left ventricular ejection fraction of more than 35% (Wellens et al., 2014). In this population the predictability of SCD is low and thus the identification of high-risk subjects is critical in the future.

Resuscitation. The initial rhythm recorded in subjects with SCA is most commonly VF or asystole. The prevalence of VF as the initial rhythm has been declining during the last decades while the proportion of non-shockable rhythms (asystole or PEA) has increased (Cobb et al., 2002; Daya et al., 2015; Väyrynen et al., 2011). VF is most often the result of electrical disturbances caused by myocardial ischemia. Ventricular tachycardia is a less common finding as the initial rhythm. When potentially lethal arrhythmia occurs, it may still be a reversible situation, and sometimes it is possible to save the patient by prompt action. Therefore, time from circulatory collapse to initiation of effective resuscitation is the most important factor for SCA survival (Eisenberg, Bergner, & Hallstrom, 1979). CPR and time to defibrillation are important determinants when SCA occurs. In out-of-hospital SCAs, trained rescuers should start CPR with chest compressions followed by rescue breaths. Laypersons are encouraged to perform chest compression-only CPR if not previously trained in CPR with
ventilation (Kleinman et al., 2017). Studies have shown that compression-only CPR offers at least equal probability of survival compared to conventional CPR (Bobrow et al., 2010; Svensson et al., 2010). In Sweden, early CPR in out-of-hospital SCAs was associated with over 2-fold increase in the 30-day survival rate (Hasselqvist-Ax et al., 2015). A similar finding was presented in New York City, but only in cases with effective CPR (Gallagher, Lombardi, & Gennis, 1995). In the United States, the rate of bystander CPR has slowly been increasing, and in around 40% of cases bystander CPR is initiated (Adabag et al., 2017; P. S. Chan, McNally, Tang, Kellermann, & CARES Surveillance Group, 2014; Daya et al., 2015). A Finnish study showed a bystander CPR rate of 47% in Eastern Finland (Hiltunen et al., 2012). National initiatives have also been launched to disseminate automated defibrillators to public facilities, especially sports facilities. In SCA cases with a shockable rhythm (VF or VT) prompt defibrillation by an external defibrillator is the key initial treatment. Timely AED usage in public facilities is linked to better prognosis (Valenzuela et al., 2000). Actions have been taken to enlighten citizens to perform bystander CPR. These improvements have led to higher rates of bystander action and survival of out-of-hospital cardiac arrest (Hansen et al., 2015; Kitamura et al., 2010; Public Access Defibrillation Trial Investigators, 2004; Wissenberg et al., 2013). A recent Danish study showed a delightful increase in bystander CPR and also bystander defibrillation between the years 2001 and 2012 (Kragholm et al., 2017). In this Danish study, the rate of bystander CPR was as high as 80.6% and that of bystander defibrillation 16.8% at the end of the study period. Basic training of CPR in learning institutions increases the likelihood of CPR initiation (Wissenberg et al., 2013).

The survival rates after out-of-hospital SCA have remained low even though a slow improvement can be seen. In ten Northern American cities, the survival to hospital discharge increased to 10.4% among SCA cases during the study period between the years 2006 and 2010 (Daya et al., 2015). The improvement in this study was mostly due to increased survival among subjects with shockable initial rhythm. In Finland, the survival to hospital discharge after out-of-hospital SCA in urban areas has been around 13–14% (Kämäräinen, Virkkunen, Yli-Hankala, & Silfvast, 2007; Kuisma & Maatta, 1996). A more recent study in Eastern Finland showed a survival to hospital discharge of 19.9% (Hiltunen et al., 2012).
2.2 Physical activity and sudden cardiac death

Physical activity can be divided into sporting activity, LTPA and occupational physical activity. While the amount of occupational physical activity has been decreasing during the last few decades due to work becoming more stationary (Church et al., 2011), LTPA has become a more important part of our well-being in modern society (Macniven, Bauman, & Abouzeid, 2012). There is clear evidence of the beneficial effect of physical activity on both physical and mental health. While regular physical training offers broad beneficial effects, PE, especially vigorous exertion, transiently increases the risk of SCD.

2.2.1 Definition of physical activity

Physical activity is defined as any bodily movement that increases energy expenditure, which can be presented as kilocalories. LTPA takes place outside of work as opposed to occupational physical activity, which accounts for work-related physical chores (Bauman et al., 2012). In less developed countries, occupational physical activity comprises the most important form of physical activity (Macniven et al., 2012). LTPA can be further divided into transportation, recreational labor, exercise and sports. Exercise is defined as goal-directed regular training with a special aim of improving physical fitness and health. Sports activity includes competitiveness and often predefined rules. Transportation and recreational labor are performed for other objectives than physical fitness but can be equally demanding physically.

PE is divided into low-intensity, moderate-intensity and high-intensity activity according to the metabolic equivalent (MET) of the task. One MET is defined as the amount of oxygen consumed while sitting at rest and is equal to 3.5 mL O2/kg/min. Sedentary behavior is considered to be less than 1.6 METs. Physical activity ranging from 1.6 to 2.9 METs is considered low-intensity activity, 3.0–5.9 METs moderate-intensity, and at least 6.0 METs vigorous activity. Generally accepted estimates for MET values for different types of PE and labor have been presented (Ainsworth et al., 2011; Jette, Sidney, & Blümchen, 1990). However, the vigorousness of PE depends ultimately on individual characteristics, such as age and gender (Kenney, Wilmore, & Costill, 2015), and in unfit subjects even low-intensity activity can be demanding.
2.2.2 Measurement of physical activity

In research and interventions regarding physical activity, valid and accurate assessment of physical activity levels is a key element. The level of overall physical activity is measured to estimate health behavior on population level and its effect on morbidity and mortality. It can be acquired either by self-reporting measures, such as targeted questionnaires, or with mechanical and electronic devices as direct objective measurements. Daily physical activity tends to have high variability over time, which makes accurate assessment of average long-term physical activity level difficult. Therefore, the need for precise, low-cost and repeatable measurement of physical activity is obvious. On the other hand, the number of study subjects, the time frame of measurement and study funding also affect the selection of measurement. To include the most accurate assessment of habitual physical activity, questionnaires should take into account sports, physical activity at work, and recreational LTPA (Baecke, Burema, & Frijters, 1982).

Self-reporting measurement for physical activity is often suitable for population-wide studies because questionnaires and physical activity diaries are inexpensive, practical and subject-friendly. Numerous different questionnaires have been presented. The Saltin-Grimby physical activity level scale is a four-level questionnaire first published in 1968 (Saltin & Grimby, 1968). It has since been used with modifications in several studies, especially in the Nordic countries. The Saltin-Grimby scale has shown moderate concurrent validity when compared to accelerometer (Emaus et al., 2010) but a poor overall correlation with maximal oxygen uptake (Loe, Rognmo, Saltin, & Wisløff, 2013). Higher levels of LTPA measured with the Saltin-Grimby scale have been linked to more favorable cardiovascular risk profile (Aires, Selmer, & Thelle, 2003; Thune, Njølstad, Løchen, & Førde, 1998) and decreased cardiovascular mortality (Salonen, Puska, & Tuomilehto, 1982). Baecke’s questionnaire for habitual physical activity was presented in 1982 (Baecke et al., 1982). This questionnaire originally consisted of 22 questions regarding occupational, sporting and LTPA. Self-reporting questionnaires have been shown to separate physically active subjects from sedentary subjects (Wareham & Rennie, 1998). However, the large number of different types of physical activity also makes methodological comparisons difficult (van Poppel, Chinapaw, Mokkink, Van Mechelen, & Terwee, 2010). In a systematic review by Prince et al. there was no clear uniform bias of self-reporting measures compared to direct measurements (Prince, 2008).
The level of LTPA can also be measured directly with different mechanical and electronic monitors. The measurements can be made using motion sensors (such as accelerometers) and physiologic markers (such as cardiorespiratory fitness). Smartphone applications and other inexpensive devices have increased the availability of accelerometers and pedometers in recent years (Kwapisz, Weiss, & Moore, 2010). Accelerometers provide useful data and have been used in many recent epidemiological studies (Colley et al., 2011; Troiano et al., 2008). Accelerometer-measured physical activity is a useful tool in population-based studies and its relation to all-cause mortality has been shown (I. M. Lee et al., 2018). Pedometers are simpler motion sensors that count steps or distance. They are mainly used to assess the amount of walking. In a review article published in 2002, data produced by pedometers correlated strongly with data provided by accelerometers and directly observed activity (Tudor-Locke, Williams, Reis, & Pluto, 2002). Information from pedometers also correlates with fitness levels (Tudor-Locke, Williams, Reis, & Pluto, 2004). On the other hand, pedometers have been used successfully in increasing physical activity and improving health (Bravata et al., 2007; C. B. Chan, Ryan, & Tudor-Locke, 2004; Thomas & Williams, 2006), but conflicting results have also been presented (Moy et al., 2016; Newton, Wiltshire, & Elley, 2009). Heart rate monitoring is widely used in a variety of sports, also by laypersons. The assessment of physical activity by heart rate monitoring is based on the fact that any kind of movement increases heart rate, and this can be used to evaluate the time and intensity spent on training. Sympathetic activation caused by emotions, stimulants or medical conditions can similarly increase the heart rate. Therefore, heart rate monitoring is mostly used to assess time spent in moderate-to-vigorous intensity physical activity and energy expenditure.

### 2.2.3 Effect of physical activity on cardiovascular mortality

Occupational and LTPA is encouraged in all age groups by public health organizations, such as the World Health Organization and National Institute for Health and Welfare (Nelson et al., 2007; Pate et al., 1995; Sallis & Patrick, 1994). Modern guidelines recommend at least 30 minutes of moderate-intensity physical activity at least five days a week, or 20 minutes of vigorous activity three days a week, or different combinations of moderate and intense workout (Haskell et al., 2007). This guideline by the American College of Sports Medicine and American Heart Association presented in 2007 incorporated vigorous PE into the
recommendation. Higher levels of physical activity have been shown to reduce cardiovascular and all-cause mortality in a variety of populations. In older populations, results about an inverse association between physically active lifestyle and mortality are quite uniform (Bijnen et al., 1998; Holme & Anderssen, 2015; Kaplan, Seeman, Cohen, Knudsen, & Guralnik, 1987; Wannamethee, Shaper, & Walker, 1998). These findings were confirmed in a recent meta-analysis in adults over the age of 60 (Hupin et al., 2015). In the general population, a similar finding of reduced cardiovascular mortality has been noted (Hu et al., 2005; D. Lee et al., 2014; Leon, Connett, Jacobs, & Rauramaa, 1987).

In a Finnish prospective twin cohort study, it was shown that higher levels of LTPA were associated with reduced overall mortality later in life (Kujala, Kaprio, Sarna, & Koskenvuo, 1998). In epidemiological studies, a regular active lifestyle has been shown to reduce the risk of events of CVD in primary (Berlin & Colditz, 1990; Haheim, Holme, Hjermann, & Leren, 1993; Lindenstrom, Boysen, & Nyboe, 1993; Sesso, Paffenbarger, & Lee, 2000; Smith, Greenland, & Grundy, 2000) and secondary prevention (Martin et al., 2012; Witt et al., 2004). In supervised programs, high-intensity exercise is effective and relatively safe in patients with CAD (Ø Rognmo, Hetland, Helgerud, Hoff, & Slørdahl, 2004; O. Rognmo et al., 2012). The European Society of Cardiology recommends at least 30 minutes of moderate intensity PE five times a week to patients after AMI (Graham et al., 2007). Physical activity alongside dietary changes prevents and treats metabolic diseases such as obesity and type 2 diabetes (Ball, Owen, Salmon, Bauman, & Gore, 2001; Helmrich, Ragland, Leung, & Paffenbarger Jr, 1991). Sufficient levels of physical activity in patients with diabetes mellitus also lower cardiovascular mortality (Hu et al., 2005; Tanasescu, Leitzmann, Rimm, & Hu, 2003). There is also evidence of a beneficial effect between LTPA and later dementia and Alzheimer’s disease (Rovio, 2005). Physical activity has also been shown to reduce depressive symptoms (Camacho, 1991).

Even though physical activity has clear beneficial effects on cardiovascular health, some studies have in recent years introduced a J-shaped association between LTPA and cardiovascular mortality. In practice, this means that the most sedentary subjects possess the highest risk for cardiovascular events, but also the most highly active population have higher cardiovascular mortality compared to moderately active subjects. In a German study, those performing strenuous PE daily seemed to have higher cardiovascular and all-cause mortality compared to subjects exercising 2 to 6 times a week (Mons, Hahmann, & Brenner, 2014). A similar finding was presented in a Danish population, where strenuous joggers...
were more likely to suffer cardiovascular death during follow-up than light and moderate joggers (Schnohr, O’Keefe, Marott, Lange, & Jensen, 2015). However, in the same Danish study population, long-term high intensity cycling was related to better prognosis compared to light to moderate intensity cycling (Schnohr, Marott, Jensen, & Jensen, 2012). There are studies that have not identified increased risk of regular vigorous physical activity on cardiovascular mortality (Arem et al., 2015; Gebel et al., 2015). However, different definitions and measurements of physical activity hinder the comparability of these studies.

### 2.2.4 Sudden cardiac death in relation to physical activity

SCD is defined as exercise-related when the fatal event takes place during PE or within a 1-hour time frame after exertion. It is believed that only vigorous PE has the potential to trigger SCD. Exercise-related SCD requires a cardiac substrate, and physical activity acts as one of the triggers. Other contributing factors are often present. Exercise-related SCD accounts for a minority of SCD cases. The proportion of exercise-related SCD ranges from 5 to 17% (Libarthson et al., 1974; Torell et al., 2017; H. Wang et al., 2013). In young athletes, as many as 90% of SCDs might take place in relation to exercise (Maron et al., 1996). The exact incidence numbers are difficult to acquire due to the small number of cases in the general population. Male gender is significantly overrepresented among cases of exercise-related SCD.

In subjects under the age of 35, the incidence of exercise-related SCD per person year is significantly lower compared to elderly populations. However, the proportion of exercise-related SCD can be as high as 90% of all SCD when only athletes are considered. Autopsy-based data among military recruits showed that 47% of SCDs occurred during exertion in subjects under the age of 35 (Eckart et al., 2011). In Denmark, the incidence rate of sports-related SCD was 3.76 cases per 100,000 person years overall in the age group of 12 to 35 years and only 1.21 cases per 100,000 person years among competitive athletes (Holst et al., 2010). The incidence rates, however, vary greatly due to methodological reasons. In young basketball players the overall rate of SCD was found to be approximately 1:43,000 student-athletes per year (Harmon, Asif, Klossner, & Drezner, 2011).

African-American athletes are overrepresented among exercise-related SCD in the young (Harmon, Drezner, Wilson, & Sharma, 2014). Especially HCM seems to be a more common diagnosis at autopsy among black athletes (Maron et al., 2009). In Canada, the incidence of SCA during competitive sports in persons 12
to 45 years of age was as low as 0.76 cases per 100,000 athlete years, and almost half of the athletes survived the event (Landry et al., 2017).

It is thought that SCD usually requires a structurally abnormal heart when PE acts as a trigger. Among young adults under 40 years of age, HCM, coronary artery abnormalities, ARVC, premature CAD, myocarditis and other hereditary or congenital cardiovascular substrates are the most common cardiovascular abnormalities behind exercise-related SCD. In a 25-year review of autopsy-findings in SCD among young US military recruits, coronary artery pathology was the leading cause (61%), and anomalous coronary artery was the most common finding in this disease entity (Eckart et al., 2004). A notably high share of myocarditis was noted in this study, with a share of 20% at autopsy. In an older study, severe coronary atherosclerosis was found in 26% and HCM in 24% of sports-related SCD, and HCM was clearly more common among exercise-related deaths (Burke, Farb, Virmani, Goodin, & Smialek, 1991). In Italy, ARVC was found to be the most common autopsy finding among young athletes suffering exercise-related SCD, especially prior to the launch of preparticipation screening (Corrado et al., 2006). Eckart et al. did not find any statistically significant differences in underlying cardiac pathology between exertional and nonexertional SCDs (Eckart et al., 2011).

In older subjects, CAD, either diagnosed or occult, is the leading cause of exercise-related SCD. A study by Marijon et al. 2011 showed that 86% of sports-related SCD had CAD as the primary autopsy finding (Marijon et al., 2011). CAD as an autopsy finding accounted for 51% of all etiologies among a Spanish population suffering SCD during recreational sports (Suárez-Mier, Aguilera, Mosquera, & Sánchez-de-León, 2013). A recent Chinese study of sports-related SCD in the general population among subjects over the age of 35 had CAD as the most common autopsy finding (64%) (Wu et al., 2017). Studies have shown that CAD is also the leading pathology among subjects who die during running (Thompson, Funk, Carleton, & Sturmer, 1982; Waller & Roberts, 1980). The etiology of exercise-related SCD varies considerably depending on the age distribution and geography of the study in question. All in all, it can be concluded that the older the study population, the more common CAD is at autopsy.

There is considerable variation in the types of exertion related to SCD. In the French general population, 65% of SCDs were related to cycling, jogging or football (Marijon et al., 2011). In Germany, football, running and tennis were the most common sports disciplines when SCD was sports-related (Bohm, Scharhag, & Meyer, 2016). On the other hand, in Southern China SCD was most likely to
occur during heavy physical labor, with a share of over 50% of all exercise-related SCD cases (Wu et al., 2017). Cold weather independently increases the risk of SCD through sympathetic activation, increased oxygen demand and prothrombotic effects (Hintsala et al., 2013; Keatinge et al., 1984; Manou-Stathopoulou et al., 2015). PE in cold weather might further enhance these physiological changes (Juneau, Johnstone, Dempsey, & Waters, 1989). Snow shoveling, for example, is considered a high-risk activity by the American Heart Association (Thompson et al., 2007).

2.2.5 Mechanism of exercise-related sudden cardiac death

Exercise-related SCD requires a cardiac abnormality as a substrate for fatal arrhythmia, and vigorous PE acts as a transient factor that triggers the event. In previously asymptomatic CAD patients, disruption of a vulnerable plaque causing acute coronary occlusion has been shown to be a common pathological finding at autopsy when SCD is exercise-related (Burke et al., 1999). This study also showed that exercise-related deaths were more likely linked to rupture in the midcap of a thin fibrous cap. Plaque disruptions include plaque rupture, erosion and infrequently calcified nodule with coronary artery occlusion (Virmani, Kolodgie, Burke, Farb, & Schwartz, 2000). It is thought that acute increase in heart rate and blood pressure caused by exertion leads to arterial wall stress and therefore triggers plaque rupture or erosion (Black, Gensini, & Black, 1975). Especially in sedentary subjects, transiently increased coagulation activity due to acute exercise might alter the progress of coronary occlusion (Green, Seroppian, & Handin, 1980; Kestin et al., 1993). Myocardial scarring due to previous myocardial infarction or other cardiac abnormalities acts as a substrate for exercise-induced scar-related re-entry ventricular arrhythmia.

The substrate for lethal ventricular arrhythmia is often AMI or infarct scar, but also stable CAD can cause SCD. Rapid increase of heart rate and systolic blood pressure also increase the oxygen demand of the myocardium. When a hemodynamically significant coronary artery atheroma is present, the increased demand caused by vigorous exercise can lead to demand ischemia and lethal arrhythmia. In a study on SCA among long-distance runners, there were no cases with plaque rupture or fresh thrombus, and the cause of death was defined as demand-ischemia due to severe CAD (Kim et al., 2012). Electrolyte abnormalities caused by prolonged excessive exertion might also provide a mechanism for SCD during heavy exercise, and the majority of cardiovascular events occur during the
last quartile of marathon running (Redelmeier & Greenland, 2007). Exercise can also induce coronary artery flexing or spasm in atherosclerotic arteries (Gordon et al., 1989). The mechanism for immediate post-exercise SCD is thought to result from reduced coronary perfusion. Sudden cessation of exercise and muscle activation reduces venous return, leading to lower cardiac output and blood pressure. All these different mechanisms result in depolarization and repolarization alterations or conduction abnormalities, leading to ventricular ectopic activation and possible lethal arrhythmias.

2.2.6 Prevention of exercise-related sudden cardiac death

The transient risk of vigorous exercise is highest among the least fit population (Albert et al., 2000; Siscovick, Weiss, Fletcher, & Lasky, 1984). It is shown that the risk of SCD during exercise is lower among those who engage in regular physical activity. In the general population, the benefits of regular PE exceed the risks and it should therefore be encouraged. Patients with symptomatic CAD benefit from PE (O. Rognmo et al., 2012; R. S. Taylor et al., 2004), even though a transient risk of SCD is present in relation to exercise. However, a subgroup of young athletes with occult or diagnosed cardiac abnormality, such as HCM or ARVC, might possess a risk of adverse effects greater than the benefits of competitive sports. Neither the European Society of Cardiology nor the American Heart Association recommend competitive or high-intensity sports for subjects with ARVC or HCM (Maron et al., 2004; Pelliccia et al., 2006). Also subjects with LQTS-related symptoms or LQTS manifestation on ECG were disqualified from competitive sports in guidelines (Pelliccia et al., 2005; Zipes et al., 2005). However, data published in recent years have shown a low rate of adverse cardiac events in these subjects and self-disqualification is recommended (Johnson & Ackerman, 2013). In adult population, preparticipation exercise testing is recommended by both the American College of Sports Medicine and the American Heart Association only for patients at high risk of exercise-related acute cardiovascular events during unaccustomed vigorous exercise (American College of Sports Medicine, 2013; Thompson et al., 2007). Preparticipation screening of young athletes is widely recommended but the routine usage of a 12-lead standard ECG is more controversial. The European Society of Cardiology recommends the inclusion of ECG in preparticipation screening of young athletes (Mont et al., 2016), whereas the American Heart Association does not recommend such a protocol (Maron et al., 2015). Most of the exercise-related SCDs occur in
recreational sports and LTPA in non-athletes, but screening of this population has not been shown to be effective. Even in athletes a clear majority of exercise-related SCDs take place during LTPA (Landry et al., 2017).

2.2.7 Epidemiology of sudden cardiac arrest in relation to exercise

In recent years, a few studies have been published regarding sports-related out-of-hospital SCA. In the Netherlands, the overall incidence of exercise-related SCA was 2.1 per 100,000 person years in the general population (Berdowski et al., 2013). In subjects under the age of 35, the incidence of exercise-related cardiac arrest was found to be 0.3 per 100,000 person years. A clear male dominance was seen among the exercise-group, with a share of 93%. Exercise-related cases occurred more often in public locations, they had more often a shockable rhythm as the initial rhythm recorded by emergency medical system (EMS), and the rate of bystander CPR and AED usage was higher. Overall, the prognosis of exercise-related SCA was markedly better compared to non-exercise related SCA (46% vs. 16%). In a middle-aged US-based population studied by Marijon et al. the incidence of sports-related SCA was 2.17 per 100,000 person years (Marijon et al., 2015). The results were fairly similar in comparison to the study by Berdowski et al. However, the rate of bystander CPR was lower and AED usage by laypersons was sparse in the North American study population. Survival to hospital discharge was also clearly lower, with a survival rate of 23% among sports-related SCA. Marijon et al. did, however, only include subjects 35 to 65 years of age. In the London area, the incidence of exercise-related SCA was found to be somewhat lower, with an overall incidence of 0.6 per 100,000 person years in the general population (Edwards & Fothergill, 2015). All the studies described above on exercise-related SCA only included sporting activity and excluded heavy labor. In line with this, the proportion of exercise-related SCA was 7.5% of all SCAs and the rate of bystander CPR as high as 65% in a Swedish study (Torell et al., 2017)).

2.3 Electrocardiographic abnormalities related to sudden cardiac death

The electrical activity of the heart was presented for the first time in the 19th century. In 1901 Willem Einthoven, a Dutch physiologist and medical doctor, introduced the string galvanometer, whereby the human ECG could be recorded (Fisch, 2000). The standard 12-lead ECG has since then spread into widespread
usage in clinical practice. During the last decades, there has been research around ECG that has focused on ECG abnormalities as risk factors for SCD. Several ECG patterns have been associated with increased cardiac mortality either with or without previous diagnosis of cardiac disease. However, the prognostic value of an individual ECG abnormality is low, especially in the general population. Very little is known about ECG abnormalities predisposing to exercise-related SCD.

2.3.1 Heart rate

Resting heart rate is a simple, easily obtainable marker normally presented as beats per minute. Resting heart rate and heart rate variability are closely related to autonomic tone and therefore SCD susceptibility (Schwartz, La Rovere, & Vanoli, 1992). Higher resting heart rate is associated with an increased risk of SCD (Jouven et al., 2005; Shaper, Wannamethee, Macfarlane, & Walker, 1993). A similar finding was made in the Oregon Sudden Unexpected Death Study independently of left ventricular systolic dysfunction and arrhythmic drugs (Teodorescu et al., 2013). The smaller the difference between maximum heart rate and resting heart, the higher the risk of SCD (Jouven et al., 2005). In a Norwegian cohort study, subjects with an increase in heart rate during follow-up had higher cardiac and all-cause mortality (Nauman, Janszky, Vatten, & Wisløff, 2011). The increase in all-cause mortality shows the influence of several other non-cardiac factors on resting heart rate. Heart rate variability represents the normal variation between heartbeats and this marker is measured over a certain time period (Malik, 1996). Low heart rate variability has long been associated with excessive risk of SCD in the general population (Algra, Tijssen, Roelandt, Pool, & Lubsen, 1993; Mäkikallio et al., 2001). This finding has also been verified in patients with heart failure (La Rovere et al., 2003).

2.3.2 Depolarization abnormalities

Abnormalities of the myocardium might lead to conduction delay in the affected myocardium. It was Boineau and Cox in 1973 who first showed altered synchronization of the electrical activity due to acute ischemia in canine hearts (Boineau & Cox, 1973). Conduction alteration during ventricular depolarization can, in turn, cause different types of notching in the QRS complex without a typical bundle-branch block. The ECG criteria for fragmented QRS complex (fQRS) include different RSR’ patterns with QRS duration less than 120ms in at
least two contiguous leads in a single coronary artery region. Das et al. introduced the widely used definition of fQRS as an additional R wave or notching of the S or R wave, or the presence of at least two R waves in two contiguous leads (Das, Khan, Jacob, Kumar, & Mahenthiran, 2006). The definition of fQRS has, however, been questioned (Haukilahti, Eranti, Kenttä, & Huikuri, 2016; Maheshwari et al., 2013). It is suggested that more attention should be given to the actual morphology of the fQRS.

**Fig. 1. Different fQRS morphologies including various RSR' patterns according to Das et al. (2009). ECG samples were collected from the Finnish Health 2000 Study.**

It is thought that fQRS represents heterogeneous activation of the myocardium due to prior infarction (Gardner, Ursell, Fenoglio, & Wit, 1985; Varriale & Chryssos, 1992). Q waves have become less common with better and more rapid treatment of AMI, and Das et al. showed a notably higher sensitivity of fQRS in detecting myocardial scar compared to Q waves (Das et al., 2006), although contradictory results have been presented (D. D. Wang, Buerkel, Corbett, & Gurm, 2010). ECG leads in which fQRS appears seem to correlate well with the anatomical location of the myocardial abnormality (Das & Zipes, 2009; Mahenthiran, Khan, Sawada, & Das, 2007). The significance of fQRS alongside a widened QRS complex (> 120ms) has also been studied (Das et al., 2008).
Mahenthiran et al. showed that fQRS complexes were related to more excessive myocardial abnormalities in myocardial perfusion imaging (Mahenthiran et al., 2007). fQRS is not specific to CAD-related scarring, and other myocardial abnormalities causing fibrosis and inflammation have also been linked to a higher prevalence of fQRS (Basaran et al., 2011; Homsi, Alsayed, Safadi, Mahenthiran, & Das, 2009).

The prognostic significance of fQRS in cardiovascular mortality has been studied avidly in recent years. Among patients with CAD, fQRS has been shown to increase the risk of cardiac events, arrhythmia and mortality (Das et al., 2007; Das et al., 2010). Patients with resolved Q waves and constant fQRS after AMI had over 2-fold risk of new cardiac events compared to patients with resolved Q waves but without fQRS (Pietrasik, Goldenberg, Zdzienicka, Moss, & Zareba, 2007). In patients with prior AMI, a high number of leads (≥3 leads) affected by fQRS was also a significant predictive factor for cardiovascular death independent of the affected leads (Torigoe et al., 2012). In the general population, the prevalence of fQRS was found to be 19.7% and inferior leads were the most common localization (Terho et al., 2014). Among subjects with a previous diagnosis of CVD in the general population, fQRS in lateral leads (I, aVL, and V4 - V6) increased the risk of cardiac mortality and sudden arrhythmic death (Terho et al., 2014). In patients with ischemic cardiomyopathy, fQRS, especially when identified in inferior leads, predicted SCD in MADIT II (Brenyo et al., 2012). Increased risk of SCD has also been noted among patients with HCM and fQRS in the anterior territory (Debonnaire et al., 2015). Conduction delay in Brugada patients, presented as fQRS, is a marker for high risk of VF (Morita et al., 2008). When all knowledge about fQRS is taken into account, it can be concluded that fQRS represents a marker of more severe underlying cardiac disease and a higher mortality of both overall cardiac mortality and SCD. No studies have been conducted describing the correlation between fQRS and exercise-related SCD.

The electrical activity that paces the contraction of the myocardium comes through the atroventricular node to ventricles. The His-Purkinje conduction system transmits impulses to both ventricles and enables a simultaneous contraction of the myocardium. The QRS complex describes the rapid depolarization of the right and left ventricle. QRS duration is calculated from the beginning of the earliest to the end of the last QRS waveform in all leads. The method of measurement, age and gender have an effect on QRS duration. Prolongation of the QRS complex is due to intraventricular conduction delay caused by myocardial abnormalities such as ventricular hypertrophy, fibrosis,
acute ischemia or infiltrative lesions, or abnormality in the His-Purkinje conduction system itself. Functional changes can also be seen in QRS duration depending on heart rate. QRS prolongation can be caused by complete or incomplete left or right bundle branch block (LBBB or RBBB), nonspecific conduction delay, or pre-excitation due to an accessory conduction pathway.

Prolongation of the QRS complex has been linked to an increased risk of SCD in patients with stable CAD (Teodorescu et al., 2011). It has also been shown that intraventricular conduction delay with or without a specific bundle branch block increases the risk of SCD in the general population (Aro et al., 2011b; Kurl, Makikallio, Rautaharju, Kiviniemi, & Laukkanen, 2012). In a study by Kurl et al. in males, each 10 ms prolongation of the QRS duration increased the risk of SCD by 27%, and subjects with QRS duration over 110 ms had a 2.5-fold risk of SCD compared to subjects in the lowest QRS duration quintile (Kurl et al., 2012). The study by Aro et al. included almost 11,000 subjects, both male and female, in the general population; QRS duration of more than 110 ms without specific bundle branch block and pre-excitation was considered intraventricular conduction delay, and subjects with this finding had a 2.53-fold risk of cardiac death during follow-up (Aro et al., 2011b). In a Swedish study, LBBB in the general population was associated with an increased risk of cardiac mortality and especially sudden death over 28 years of follow-up (Eriksson, Wilhelmsen, & Rosengren, 2005). In older populations, also RBBB has been linked to an excessive cardiovascular mortality rate (Badheka et al., 2013; Bussink et al., 2012), but differing results have also been presented (Aro et al., 2011b; Rotman & Triebwasser, 1975).

LVH can be assessed from a 12-lead standard ECG. Sokolow-Lyon is the most commonly used method of assessment of LVH; this measurement takes into account S wave in lead V1 and R wave in lead V5 or V6 (Sokolow & Lyon, 1949). LVH on ECG by Sokolow-Lyon criteria is a marker of worse cardiovascular outcome and higher incidence of SCD (Kannel, Gordon, & Offutt, 1969; Kannel, Doyle, McNamara, Quickenton, & Gordon, 1975; Sullivan, Vander Zwaag, El-Zeky, Ramanathan, & Mirvis, 1993). Other ECG methods for LVH measurement include Cornell voltage criteria and the Romhilt-Estes point score system. Regression of ECG changes in LVH during antihypertensive medication reduces the risk of SCD (Wachtell et al., 2007). LVH calculated with the Romhilt-Estes point score is also predictive of SCA (Darouian et al., 2017).
Fig. 2. Different depolarization abnormalities. Example A shows LVH. The Sokolow-Lyon index is 41 mm. In example B, QRS duration is slightly prolonged (around 115 ms).

2.3.3 Repolarization abnormalities

Elevation of the J point from baseline on standard ECG is considered early repolarization (Klatsky, Oehm, Cooper, Udaltsova, & Armstrong, 2003) and the prevalence varies from 1 to 13% (Klatsky et al., 2003; Rollin et al., 2012; Tikkanen et al., 2009). The exact mechanism of the J wave has not been established, and some studies have classified the J wave as a late depolarization abnormality (Hoogendijk, Potse, & Coronel, 2013). A recent consensus statement presented the following definition of early repolarization pattern: 1) notching or slurring on the downslope of the R wave, 2) J point elevation of at least 0.1 mV in two contiguous ECG leads, and 3) QRS duration less than 120 ms (Macfarlane et al., 2015). Automated detection of early repolarization has been developed (Kenttä et al., 2015). For decades, early repolarization was seen as a somewhat benign formation, but findings during the last decade have linked early
repolarization to SCD and VF in the general population (Haïssaguerre et al., 2008; Rosso et al., 2008; Tikkanen et al., 2009). A recent meta-analysis also showed a markedly increased risk of SCD in subjects with structural heart disease and early repolarization pattern (Cheng et al., 2017). Early repolarization is associated with arrhythmic events but not with non-arrhythmic events (Junttila et al., 2014). This finding emphasizes the role of early repolarization as a factor enabling ventricular tachyarrhythmias. However, only certain types of early repolarization are seen as malignant. Elevated J point accompanied with a horizontal or descending ST segment is associated with SCD (Rosso et al., 2012), but subjects with inferolateral early repolarization and a rapidly ascending ST segment do not have an increased risk of tachyarrhythmic events (Tikkanen et al., 2011). Brugada syndrome also presents J point and ST segment elevation, but only in the right precordial leads. (Antzelevitch et al., 2005).

The time from the beginning of the QRS complex to the end of the T wave comprises the QT interval, and represents the time it takes for the ventricles to depolarize and repolarize. QT interval is measured in milliseconds. As the QT interval is significantly affected by the heart rate, QT interval is usually corrected with Bazett’s formula (corrected QT interval = QT / √RR). However, a scientific statement by Rautaharju et al. recommends the use of linear regression functions in QT interval corrections (Rautaharju, Surawicz, & Gettes, 2009). The Bazett formula tends to overreact to QT prolonging drugs (Vandenberk et al., 2016). The QT interval is shown to be on average somewhat longer in females and therefore different upper limits for normal QT interval have been established for males and females. In men, a corrected QT interval over 450 ms is considered prolonged whereas in women, the limit is 460 ms (Rautaharju et al., 2009). The cutoff for short corrected QT interval is 390 ms in both genders (Rautaharju et al., 2009). When the interest is specifically on ventricular repolarization JT interval might be the appropriate measurement (Zhou, Wong, Rautaharju, Karnik, & Calhoun, 1992). This excludes the effect of variation in QRS duration. In subjects with wide QRS complex, JT interval predicts CHD events (Crow, Hannan, & Folsom, 2003).

Prolongation of the QT interval is often caused by QT-prolonging medication (Roden, 2004). A congenital genetic background is less common and LQTS is described earlier. In some cases, QT-prolonging medications provoke QT prolongation in subjects with genetic vulnerability. Torsades de pointes is a typical lethal manifestation of prolonged QT interval which might eventually lead to SCD. In the general population, prolonged corrected QT interval has been
linked to an increased risk of cardiovascular and arrhythmic mortality (Elming et al., 1998; Schouten et al., 1991). In a Dutch study population of 6,134 elderly subjects representing the general population, an abnormally prolonged corrected QT interval (>470 ms in women and >450 ms in men) was linked to a 2.5-fold increase in risk of SCD compared to those with normal QT interval (Straus et al., 2006). The same study showed that in subjects between the ages 55 and 68, the risk of SCD was 8.0-fold among those with abnormal QT interval prolongation. A case-control study setting with CAD patients showed a 5-fold probability of idiopathic abnormal QT prolongation in SCD cases (Chugh et al., 2009).

T wave alternans describes the repeating variation in T wave morphology between back-to-back heartbeats and is associated with heterogeneity of ventricular repolarization (Verrier et al., 2011). T wave alternans is linked to vulnerability to ventricular arrhythmogenesis. A large meta-analysis showed good negative predictive value for arrhythmic events of microvolt T wave alternans in different cardiac diseases compared to subjects without this finding (Gehi, Stein, Metz, & Gomes, 2005). However, significant variation between study populations was noted. Ventricular hypertrophy or ischemia might lead to T wave inversions in various ECG leads. Negative T wave is normally seen in aVR lead and is often seen as normal variation also in leads III and aVL. In young people, T-inversions in right precordial leads (V1-V3) are common (Rautaharju et al., 2009). Even though right precordial T wave inversions can be seen in different cardiac abnormalities, such as right ventricular strain, no adverse outcome was seen in middle-aged subjects during decades of follow-up (Aro et al., 2012). However, T wave inversions in other than right precordial leads were associated with cardiac mortality and SCD (Aro et al., 2012). A similar finding was noted regarding isolated T wave inversion (Laukkanen et al., 2014). The difference between the direction of depolarization and repolarization can also be calculated. This marker, also known as the QRS-T angle, includes both depolarization and repolarization of the ventricles. A widened spatial QRS-T (>100°) angle reflecting either depolarization or repolarization abnormalities is associated with an increased risk of cardiac death and SCD in the general population (Kardys et al., 2003; Yamazaki, Froelicher, Myers, Chun, & Wang, 2005). A frontal QRS-T angle that is more easily available in a standard 12-lead ECG has also been linked to SCD (Aro et al., 2011a).

T-peak to T-end (TpTe) interval is another repolarization marker and is measured from the peak of the T wave to the end of the T wave. The TpTe interval represents the vulnerable period to arrhythmogenesis during
repolarization (Gupta et al., 2008). TpTe interval prolongation is therefore thought to express an extended risk of ventricular tachyarrhythmia due to increased transmural dispersion of repolarization or global dispersion of repolarization (Antzelevitch et al., 1999; Kors, van Eck, Henk J Ritsema, & van Herpen, 2008). There is no clear cut-off value for prolonged TpTe interval, but a meta-analysis on TpTe interval showed a mean cut-off value of 103 ms for TpTe prolongation (Tse et al., 2017). In the general population, TpTe interval was significantly longer in SCD cases compared to controls with significant CAD in a case-control study setting (Panikkath et al., 2011). However, a Finnish follow-up study did not find an association between TpTe interval and risk of SCD in the general population (Porthan et al., 2013).

Fig. 3. Different repolarization abnormalities. Example A demonstrates variation in T wave morphology seen in T wave inversions (arrows). The measurement of QT interval and TpTe interval is shown in example B. In example C early repolarization is seen in leads II and III (arrows).
3 Purpose of the study

The aim of this thesis was to provide information about the relation between PE and cardiac events, especially SCD, and to assess the characteristics of victims and the risk factors associated with exercise-related SCD in the general population. The current serial study also wanted to find out what kind of effect LTPA has on cardiac death and SCD among patients with diagnosed CAD.

The specific aims of the study were:

1. to provide information on the risk factors, characteristics and autopsy findings of subjects who suffer exercise-related SCD in the general population. (I)
2. to identify abnormalities in the 12-lead resting ECG in the general population preceding SCD during exercise. (II)
3. to compare the differences in patient characteristics, initial rhythm, resuscitation and survival rates between sudden SCA related to PE and SCA at rest. (III)
4. to study the effect of LTPA and its changes on cardiovascular mortality in patients with stable diagnosed CAD. (IV)
4 Materials and Methods

4.1 Study populations

4.1.1 FinGesture (Study I-III)

The Finnish study of Genotype and Phenotype Characteristics of Sudden Cardiac Death (FinGesture) is an observational retrospective study including a consecutive series of autopsy-verified out-of-hospital victims of SCD in a specific geographical area in northern Ostrobothnia in northern Finland. All cases with a non-cardiac cause of death were included in the study population. This study population includes SCDs in our study area since 1998. In Finland, a medicolegal autopsy is mandatory according to Finnish law (Act on the Inquest into the Cause of Death, 459/1973, 7th paragraph) when death is sudden and unexpected, the subject has not been treated by a physician during the last illness, and death is not due to a known disease. Therefore, the FinGesture study population includes virtually all unexpected sudden deaths of cardiac origin, which essentially reduces possible selection bias. Although the overall autopsy rates are declining, the rates of medico-legal autopsy have increased to around 20 to 25% of all deaths in Finland (Lahti, Sarna, & Penttilä, 1998) and the diagnostics skills of forensic pathologists are thus of high quality. Pre-defined autopsy-criteria for the diagnosis of underlying heart disease have previously been presented in detail regarding the FinGesture study (Hookana et al., 2011). The information about the circumstances at the time of death, prior medical history, and prior medication were acquired from death certificates, medical records, police office reports and questionnaires to relatives. In the FinGesture study, SCD was defined to take place within a 6-hour time frame after the onset of symptoms or 24 hours after the subject was last seen in a normal state of health. This time frame has been used in a previous autopsy-based study population (A. J. Taylor et al., 2000) and includes lethal arrhythmias taking place a few hours after the onset of symptoms in acute coronary syndromes.

In the first original publication (Study I) we included 2,674 consecutive SCD victims from the FinGesture study between the years 1998 and 2007. Death certificates, police reports and relatives of victims provided the information about physical activity at the time of death. In studies I, II and III, physical activity was divided into two separate groups: PE and rest. We only included witnessed cases
in all substudies. We defined exercise as moderate-to-high intensity physical activity and excluded activities that were considered as low-intensity. We used the estimates of Jette et al. (Jette et al., 1990) when we assessed the METs of different physical activities. We only included activities that reached at least four METs. Death was considered exercise-related when it took place during or within a 1-hour time frame after physical activity. Different types of PE included a range of activities from heavy occupational and recreational labor to varying sporting activities. By definition, death took place at rest when the subject was sleeping, lying down or sitting. Low-intensity activity and cases with insufficient information about the circumstances at the time of death were excluded from the analysis. Therefore 1,204 subjects fulfilled the criteria of either PE or rest and were eventually included in this substudy; out of these, 328 died in relation to PE.

Subject selection in study I is illustrated in Figure 4.

In the second original article (Study II) we used the FinGesture study population between the years 1998 and 2012, and acquired the previously recorded ECG from the Oulu University Hospital archives. ECGs were taken incidentally prior to the SCD for various reasons such as palpitations, chest pain and dyspnea. Almost half of the ECGs (48%) were taken as preoperative evaluation before a surgical intervention. The time between ECG recording and SCD varied, but was less than 5 years in the majority of cases. A total of 648 cases with a previously recorded ECG could be identified in the FinGesture study, and 276 deaths were either exercise-related (n=40) or occurred at rest (n=236). All acquired ECGs were assessed independently by two researchers and we used pre-defined criteria for different ECG abnormalities. We also used a control population representing the middle-aged general population in the analysis. The control population was acquired from the Social Insurance Institution’s Coronary Heart Disease Study and included 10,904 subjects. This study population was originally gathered between 1966 and 1972. Several traditional risk factors for CAD were gathered alongside a resting ECG at baseline (Reunanen et al., 1983).
Autopsy-verified SCD; between the years 1998 and 2007

\[ n = 2,674 \]

Excluded:
- Unwitnessed cases
- Insufficient information about physical activity
- Low-intensity activity

\[ n = 1,204 \]

Exercise-related SCD
\[ n = 328 \]

SCD at rest
\[ n = 876 \]

During exercise
\[ n = 286 \]

Post-exercise
\[ n = 42 \]

Fig. 4. Study groups in study I.
4.1.2 EMS study population (Study III)

The study population derived retrospectively from the EMS data from the Oulu University Hospital area (population: 409,938 inhabitants) between 2007 and 2012 consisted originally of 659 out-of-hospital SCA victims with a documented initial rhythm, and where emergency physician was consulted or went to the scene. Cardiac arrests due to trauma, intoxication or acts of violence were excluded. In subjects who died, a comprehensive medico-legal autopsy was conducted and only cases with a cardiac cause were included in the study. Coronary angiography, echocardiography and other appropriate clinical examinations were used to reveal the possible underlying cardiac cause in patients who survived to hospital admission, and cases with a non-cardiac cause were further excluded. In the Oulu University Hospital district, the Utstein recommendation for uniform documentation of cardiac arrest is used by EMS, and our data includes information about the initial rhythm monitored by the first-response unit, time delay from collapse to EMS arrival, possible bystander CPR and AED usage, and description of circumstances surrounding SCA. Utstein templates are recommended for uniform recording of resuscitation information within hospitals and EMS (Jacobs et al., 2004). Information about prior medications and diagnosed cardiac disease was acquired from electronic medical records from Oulu University Hospital when the subject survived until hospital admission. In cases with a medicolegal autopsy, information about prior medications and medical history was available from the FinGesture study data.

In our substudy (Study III) about the relation between physical activity and SCA we only included witnessed cases with up to 15 minutes between collapse and EMS arrival. After this exclusion we were left with 237 cases. We used the same pre-defined criteria for PE and rest as in study I. Physical activity was considered as PE when the activity level reached at least 4 METs while rest was defined as sitting, sleeping or lying down at the time of death. PE comprised both the activity itself and a 1-hour time frame after exercise. Subject selection is presented in Figure 5.
4.1.3 ARTEMIS (Study IV)

The ARTEMIS (Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection) study population was derived from stable CAD patients in the Oulu University Hospital district. A total of 1,946 subjects were collected from a consecutive series of patients who had undergone coronary angiography 3–6 months earlier and were diagnosed with CAD. Baseline examinations included blood pressure measurement, 12-lead resting ECG, echocardiography, 24h Holter monitoring, exercise stress test, comprehensive health questionnaires, and urine samples alongside fasting venous blood samples. Left ventricular mass and left
ventricular ejection fraction were measured with the biplane Simpson’s method. LTPA at the baseline and after 2 years of follow-up was measured by a questionnaire modified from the Saltin-Grimby physical activity level scale (Saltin & Grimby, 1968). In this substudy we excluded the subjects without information about the LTPA at the 2-year time point. According to the level of habitual physical activity, subjects were divided into four groups: no LTPA, irregular LTPA, moderate-intensity LTPA 2-3 times weekly, and moderate-to-high intensity LTPA at least 4 times weekly. Similarly, when we analyzed the effect of changes in LTPA during the initial follow-up on cardiovascular mortality we created four groups: 1) Active-Active group (at least irregular LTPA at both time points), 2) Inactive-Active (No LTPA at the baseline changed to at least irregular LTPA at the follow-up time point), 3) Active-Inactive (LTPA previously at least irregular regressed to no LTPA at 2 years), and 4) Inactive-Inactive (No LTPA at both time points). The follow-up period consisted of the initial two-year time frame after which measurements and questionnaires were repeated, and the subsequent follow-up time. Our primary endpoint in study IV was cardiac death. Secondary composite endpoint was SCD including resuscitation from SCA. The follow-up information about a possible cardiac death was gathered from several data sources: national death registries (Statistics Finland, Helsinki, Finland), from patients or relatives by inquiry, and from electronic medical records.

Patients with an acute coronary syndrome less than 3 months before enrollment were excluded. Other exclusion criteria included age under 18 years or over 85 years, end-stage renal disease, severe heart failure with NYHA class IV, implanted cardioverter defibrillator, and pre-diabetic state of hyperglycemia. Patients with less than one year of life expectancy and those who were mentally or physically unfit to participate were also excluded. The ARTEMIS study followed the Declaration of Helsinki, and the Regional Ethics Committee of the Northern Ostrobothnia Hospital District approved the study protocol.

4.2 Electrocardiographic measurement

All ECGs both in the control population and in subjects acquired from the FinGesture study population were taken as standard 12-lead recording at rest in a supine position with a paper speed of 50 mm/s and calibration of 1mV/10 mm. ECGs from the FinGesture study subjects were assessed independently by two researchers. In the control population, ECGs were first analyzed at the baseline by nine specialists. At that point the presence of bundle branch block and LVH by
Sokolow-Lyon criteria were evaluated. In addition, QT interval corrected with heart rate according to Bazett’s formula was also measured. The ECGs from the control population were later reevaluated by a varying number of researchers for several different ECG variables.

fQRS was defined as different RSR' patterns including at least one additional R wave or notched S or R wave and different combinations of these findings (Figure 1). These abnormalities in the QRS morphology needed to be in at least two consecutive leads within the same anatomical territory. ECG leads were categorized as lateral (I, aVL, V4-V6), anterior (V1-V3) and inferior (II, III, aVF). The aVR lead was excluded from the analysis. Pathologic Q waves in leads V2 or V3 were defined as a Q wave wider than 20ms or if QS complex was present. In other leads Q waves wider than 30 ms and deeper than 0.1 mV or QS complex were considered pathologic.

4.3 Statistical analysis

All continuous variables were tested for Gaussian distribution by skewness test. Normally distributed data (|skewness| < 1) are presented as mean (standard deviation). If variables with skewed distribution were encountered, we used median (1st–3rd quartile) values. With dichotomous variables, the results are presented as percentage (%) of the group population. Chi-square (χ²) analyses were used for dichotomous data and two-tailed t-test for continuous data to detect statistically significant differences between the study groups. Variables that were available for more than two groups were tested for a possible significant main effect between groups. In variables with a significant main effect between groups, pairwise comparisons by χ² were made. All statistical analyses were performed with SPSS (SPSS, Inc., Chicago, IL) versions 21 or 23, and a p-value <0.05 was considered statistically significant.

In study I we had two study groups (PE group and rest group) and the prevalence of different patient and autopsy characteristics was presented as the absolute number of cases and percentages. Comparisons between the two study groups were made with either two-tailed t-test or χ² test. Odds ratios (OR) for exercise-related SCD and their 95% confidence intervals (CI) were calculated with univariate logistic regression analysis. Similar statistical analyses were used in study III that also included two study groups. However, multivariate regression analysis was used to acquire multivariate OR for survival to hospital discharge. We included PE, age, gender, bystander CPR, prior cardiac disease and initial
rhythm recorded in the multivariate analysis. In study II, ORS were calculated first by binary logistic regression. The analysis was thereafter continued with multivariate regression, and fQRS in anterior leads, pathologic Q wave in anterior leads and prior diagnosed CAD were included. We also performed multivariate regression that included all measured ECG variables. Study IV included several study groups. In this data set, a chi-square adjusted for multiple comparisons was made for dichotomous variables. Continuous variables were analyzed by either one-way ANOVA or Kruskal-Wallis followed by appropriate post hoc analyses depending on whether the variable was normally distributed or skewed. Hazard ratios (HR) and their 95% confidence intervals are presented as HR (95% CI). Univariate and multivariate Cox regression was performed to detect the predictive value of different LTPA variables. Age, sex, baseline BMI, prior AMI, type 2 diabetes, left ventricular ejection fraction (as continuous variable), Canadian Cardiovascular Society grading for angina pectoris, cardiovascular event during the initial 2-year follow-up, smoking status at 2 years and alcohol consumption at 2 years were included in the adjustment. Survival curves for different groups of LTPA development were created simply with Kaplan-Meier analysis.
5 Results

5.1 Characteristics of exercise-related victims of sudden cardiac death (Study I)

Our study population consisted of 328 victims of exercise-related SCD (PE group) and 876 cases of SCD that occurred at rest (rest-group). The number of SCDs taking place within the predefined 1-hour time frame after exercise was 42, which was only 13% (42/328) of all exercise-related SCDs. Only five exercise-related cases (5/328, 1.5%) occurred with subjects under the age of 40. Prior cardiovascular diagnosis (including CAD, hypertension, AMI, dyslipidemia) and prior diagnosed AMI were less common findings among those dying immediately after exercise compared to those dying during the actual exercise phase (27% vs. 45%, \(p=0.019\), and 0% vs. 14%, \(p=0.007\), respectively). No other differences were statistically significant.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>SCD at PE</th>
<th>SCD at Rest</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (years)</td>
<td>62.0 (10.6)</td>
<td>63.1 (12.2)</td>
<td>0.14</td>
</tr>
<tr>
<td>Body mass index (kg/m2)</td>
<td>27.4 (4.7)</td>
<td>27.2 (6.6)</td>
<td>0.64</td>
</tr>
<tr>
<td>Male gender</td>
<td>309/328 (94%)</td>
<td>678/876 (77%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior cardiac disease</td>
<td>134/316 (42%)</td>
<td>350/842 (42%)</td>
<td>0.797</td>
</tr>
<tr>
<td>Prior diagnosed AMI</td>
<td>37/297 (12.5%)</td>
<td>71/811 (8.8%)</td>
<td>0.066</td>
</tr>
<tr>
<td>Prior diagnosed CAD</td>
<td>72/298 (24%)</td>
<td>150/796 (19%)</td>
<td>0.052</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>33/290 (11%)</td>
<td>76/799 (9.5%)</td>
<td>0.364</td>
</tr>
<tr>
<td>Hypertension</td>
<td>86/287 (31%)</td>
<td>309/796 (39%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>40/297 (13%)</td>
<td>160/816 (20%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>44/290 (15%)</td>
<td>67/806 (8.3%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>16/290 (5.5%)</td>
<td>89/805 (11%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

The values are mean (SD) or number of patients (percentage). AMI = acute myocardial infarction, CAD = coronary artery disease, PE = physical exercise, SCD = sudden cardiac death.

Victims of exercise-related SCD were more often men and had more often dyslipidemia than those dying at rest. Hypertension, diabetes mellitus and congestive heart failure were significantly more common in the rest group. No statistically significant difference could be detected in mean age, body mass index, overall occurrence of prior cardiac disease, prior diagnosed AMI or CAD (Table 2).
Table 2. Autopsy Findings of SCD Victims

<table>
<thead>
<tr>
<th>Autopsy findings</th>
<th>SCD at PE</th>
<th>SCD at Rest</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease (CAD)</td>
<td>299/328 (91%)</td>
<td>657/876 (75%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonischemic CMP</td>
<td>18/328 (5.5%)</td>
<td>159/876 (18%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HCM</td>
<td>3/328 (0.91%)</td>
<td>6/876 (0.68%)</td>
<td>0.680</td>
</tr>
<tr>
<td>Unspecific myocardial fibrosis</td>
<td>0/328 (0%)</td>
<td>34/876 (3.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dilated CMP</td>
<td>0/328 (0%)</td>
<td>11/876 (1.3%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Alcoholic CMP</td>
<td>2/328 (0.61%)</td>
<td>33/876 (3.7%)</td>
<td>0.004</td>
</tr>
<tr>
<td>CMP related to obesity</td>
<td>11/327 (3.3%)</td>
<td>59/875 (6.7%)</td>
<td>0.026</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>3/328 (0.9%)</td>
<td>8/876 (0.9%)</td>
<td>0.998</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>8/328 (2.4%)</td>
<td>11/876 (1.3%)</td>
<td>0.142</td>
</tr>
<tr>
<td>Myocardial scarring</td>
<td>194/328 (59%)</td>
<td>370/876 (42%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertrophied heart</td>
<td>243/327 (74%)</td>
<td>585/876 (67%)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

The values are number of patients (percentage). Abbreviations: CAD = coronary artery disease, CMP = cardiomyopathy, PE = physical exercise, SCD = sudden cardiac death.

The prevalence of different autopsy findings in the PE group and rest group is presented in Table 3. Exercise-related SCDs were more commonly of ischemic origin. Myocardial scarring and hypertrophy were also related to SCD at PE. Nonischemic cardiomyopathy, apart from HCM, was more often the underlying cardiac abnormality among the rest group compared to exercise-related SCDs. Myocarditis was a rare finding in both groups. There were only three autopsy-negative cases: one in the exercise group and two in the rest group. The only exercise-related autopsy-negative SCD carried LQT mutation KCNQ1-FIN (G589D). In subjects under the age of 40, HCM was significantly more common among exercise-related deaths (2/5, 40% vs. 1/27, 3.7%, p=0.011).

The information about medications of SCD victims is presented in Table 4. Beta-blockers, digoxin, acetylsalicylic acid and nitroglycerin were all used slightly more often in the rest group, although statistical significance was not reached. Diuretics were clearly more common in the rest group, and a similar finding was observed in antipsychotics usage.
Table 3. Medications of victims of SCD.

<table>
<thead>
<tr>
<th>Medication</th>
<th>SCD at PE</th>
<th>SCD at Rest</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blocker</td>
<td>54/239 (23%)</td>
<td>189/679 (28%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Digoxin</td>
<td>12/239 (5.0%)</td>
<td>53/678 (7.1%)</td>
<td>0.148</td>
</tr>
<tr>
<td>Warfarin</td>
<td>21/241 (8.7%)</td>
<td>51/683 (7.5%)</td>
<td>0.535</td>
</tr>
<tr>
<td>Diuretics</td>
<td>29/240 (12%)</td>
<td>128/679 (19%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>39/239 (16%)</td>
<td>136/679 (20%)</td>
<td>0.209</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>46/242 (19%)</td>
<td>151/686 (22%)</td>
<td>0.329</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>12/239 (5.0%)</td>
<td>94/682 (14%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The values are number of patients (percentage in parenthesis). PE = physical exercise, SCD = sudden cardiac death.

The northern geographical location can be seen in the most common types of exertion that triggered SCD. Skiing was the most common and snow shoveling the third most common type of exertion among our study population, while cycling was the second most common. Other common types of physical activity were jogging, logging, hunting and yard work (Table 5). Intercourse was the type of exertion in only 0.9% of exercise-related SCDs.

Table 4. Type of Exertion Related to SCD.

<table>
<thead>
<tr>
<th>Type of Exertion</th>
<th>Number of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skiing</td>
<td>38</td>
<td>12%</td>
</tr>
<tr>
<td>Cycling</td>
<td>36</td>
<td>11%</td>
</tr>
<tr>
<td>Snow shoveling</td>
<td>30</td>
<td>9.1%</td>
</tr>
<tr>
<td>Jogging</td>
<td>28</td>
<td>8.5%</td>
</tr>
<tr>
<td>Logging</td>
<td>25</td>
<td>7.6%</td>
</tr>
<tr>
<td>Hunting</td>
<td>20</td>
<td>6.1%</td>
</tr>
<tr>
<td>Yard work</td>
<td>18</td>
<td>5.5%</td>
</tr>
<tr>
<td>Berry picking</td>
<td>11</td>
<td>3.3%</td>
</tr>
<tr>
<td>Fishing</td>
<td>7</td>
<td>2.1%</td>
</tr>
<tr>
<td>Dancing</td>
<td>7</td>
<td>2.1%</td>
</tr>
<tr>
<td>Ball games</td>
<td>7</td>
<td>2.1%</td>
</tr>
<tr>
<td>Running</td>
<td>6</td>
<td>1.8%</td>
</tr>
<tr>
<td>Farming</td>
<td>6</td>
<td>1.8%</td>
</tr>
<tr>
<td>Swimming</td>
<td>4</td>
<td>1.2%</td>
</tr>
<tr>
<td>Intercourse</td>
<td>3</td>
<td>0.9%</td>
</tr>
<tr>
<td>Other</td>
<td>83</td>
<td>25%</td>
</tr>
</tbody>
</table>
5.2 Electrocardiographic abnormalities as predictors of exercise-related sudden cardiac death (Study II)

There were a total of 648 cases in the FinGesture study population between the years 1998 and 2012 with a previously recorded ECG. The exercise group consisted of 40 subjects, 35 of whom died during exercise while 5 deaths occurred immediately after exercise. In 236 cases SCD took place at rest. Other cases did not fulfill the criteria of either rest or PE, or lacked information about physical activity at the time of death. Those with exercise-related SCD had more often fQRS in anterior leads (V1-V3) compared to the rest group. A pathologic Q wave in anterior leads was similarly more common in the exercise group (9/40, 23% vs. 26/236, 11%, p=0.044). QRS duration was on average somewhat wider in the PE group than in the rest group. T wave inversion in anterior leads seemed to be less common in the PE group (Table 6). Otherwise, no differences in the distribution of ECG variables could be detected between the PE group and rest group. The information about different ECG abnormalities in the PE group and the rest group is provided in Table 6. We also performed multivariate regression analysis that included all ECG variables presented in Table 6. Only fQRS in anterior leads reached statistical significance with an odds ratio of 2.9 [1.3-6.8] for exercise-related SCD.
Table 5. The prevalence of ECG abnormalities in PE group vs. rest group.

<table>
<thead>
<tr>
<th>ECG abnormality</th>
<th>PE group (n=40)</th>
<th>Rest group (n=236)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>fQRS, anterior leads</td>
<td>17/40 (43%)</td>
<td>51/236 (22%)</td>
<td>0.005</td>
</tr>
<tr>
<td>fQRS, inferior leads</td>
<td>20/40 (50%)</td>
<td>109/236 (46%)</td>
<td>0.56</td>
</tr>
<tr>
<td>fQRS, lateral leads</td>
<td>12/40 (30%)</td>
<td>66/236 (28%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Q wave, anterior leads</td>
<td>9/40 (23%)</td>
<td>26/236 (11%)</td>
<td>0.044</td>
</tr>
<tr>
<td>QTc time, median</td>
<td>459 (439-490)</td>
<td>474 (443-510)</td>
<td>0.11</td>
</tr>
<tr>
<td>QRS duration, median</td>
<td>100 (89-116)</td>
<td>94 (86-108)</td>
<td>0.047</td>
</tr>
<tr>
<td>LBBB</td>
<td>2/40 (5.0%)</td>
<td>18/236 (7.6%)</td>
<td>0.55</td>
</tr>
<tr>
<td>RBBB</td>
<td>3/40 (7.5%)</td>
<td>10/236 (4.2%)</td>
<td>0.37</td>
</tr>
<tr>
<td>LVH</td>
<td>4/40 (10%)</td>
<td>17/236 (7.2%)</td>
<td>0.50</td>
</tr>
<tr>
<td>TpTe interval</td>
<td>113±22</td>
<td>119±24</td>
<td>0.46</td>
</tr>
<tr>
<td>Inverted T-wave, anterior leads</td>
<td>0/40 (0%)</td>
<td>22/236 (9.3%)</td>
<td>0.044</td>
</tr>
<tr>
<td>Inverted T-wave, lateral leads</td>
<td>10/40 (25%)</td>
<td>60/236 (25%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Inverted T-wave, inferior leads</td>
<td>10/40 (25%)</td>
<td>48/236 (20%)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Comparisons were made between PE and rest group. ECG = Electrocardiogram, fQRS = fragmented QRS complex, LBBB = left bundle branch block, LVH = Left ventricular hypertrophy, PE = Physical exercise, RBBB = right bundle branch block, TpTe = T-peak to T-end.

We also compared different ECG variables between the PE group and the control population that represented the general population. All previously presented ECG variables were not available in the control population data. The results are presented in Table 7.
Table 6. The distribution of ECG abnormalities in PE group vs. control population.

<table>
<thead>
<tr>
<th>ECG abnormality</th>
<th>PE group (n=40)</th>
<th>Control population (n=10,904)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>fQRS, anterior leads</td>
<td>17/40 (43%)</td>
<td>1714/10471 (16%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>fQRS, inferior leads</td>
<td>20/40 (50%)</td>
<td>1714/10471 (16%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>fQRS, lateral leads</td>
<td>12/40 (30%)</td>
<td>848841 (1.0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>QTc time, median</td>
<td>459 (439-490) ms</td>
<td>407±27 ms</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>QRS duration, median</td>
<td>100 (89-116) ms</td>
<td>87±8.6 ms</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LBBB</td>
<td>2/40 (5.0%)</td>
<td>35/10864 (0.3%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RBBB</td>
<td>3/40 (7.5%)</td>
<td>78/10864 (0.7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVH</td>
<td>4/40 (10%)</td>
<td>3410/10904 (31%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Inverted T-wave, anterior leads</td>
<td>0/40 (0%)</td>
<td>56/10808 (0.5%)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Comparisons were made between PE and control population. ECG = Electrocardiogram, fQRS = fragmented QRS complex, LBBB = left bundle branch block, LVH = Left ventricular hypertrophy, PE = Physical exercise, RBBB = right bundle branch block.

5.3 Sudden cardiac arrest in relation to physical exercise (Study III)

There were a total of 64 exercise-related SCAs during our study period. The incidence of exercise-related SCA was therefore 2.6 cases per 100,000 person years. After the exclusion of cases with EMS arrival time >15 minutes, a total of 36 cases (36/237, 15%) took place during the actual physical activity and 11 cases (11/237, 4.6%) immediately after PE. Therefore, the group of exercise-related SCA included 47 cases. The number of cases occurring at rest was 43 (43/237, 18%). Other cases were excluded because the level of physical activity at the time of death was unknown or did not meet the pre-defined criteria of either PE or rest. We compared the characteristics of exercise-related SCA to those occurring at rest. Table 8 describes the differences between the two study groups. The PE group was on average somewhat younger. Male gender was more common although this finding did not reach statistical significance. The time between emergency call and EMS arrival was quite similar between the groups. The prevalence of previously diagnosed CVD did differ significantly between the two groups; especially congestive heart failure was more frequently previously diagnosed among subjects suffering SCA at rest. The underlying cause of SCA was somewhat more often due to ischemic reason in the exercise-group but this finding did not reach statistical significance.
Table 7. Characteristics of subjects with SCA in the exercise group and rest group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exercise-related SCA (n=47)</th>
<th>SCA at rest (n=43)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>60 (14)</td>
<td>67 (14)</td>
<td>0.016</td>
</tr>
<tr>
<td>Male gender</td>
<td>92%</td>
<td>79%</td>
<td>0.094</td>
</tr>
<tr>
<td>Time to EMS arrival, min (SD)</td>
<td>7.1 (5.0)</td>
<td>9.0 (4.3)</td>
<td>0.065</td>
</tr>
<tr>
<td>Prior diagnosed CAD</td>
<td>17%</td>
<td>30%</td>
<td>0.14</td>
</tr>
<tr>
<td>Prior congestive heart failure</td>
<td>2.1%</td>
<td>24%</td>
<td>0.002</td>
</tr>
<tr>
<td>Prior cardiac disease</td>
<td>40%</td>
<td>63%</td>
<td>0.034</td>
</tr>
<tr>
<td>SCA due to CAD</td>
<td>89%</td>
<td>81%</td>
<td>0.28</td>
</tr>
</tbody>
</table>

CAD = Coronary Artery Disease, EMS = Emergency Medical Service, SCA = Sudden Cardiac Arrest, SD = Standard Deviation

VF was the most common initial rhythm in both the exercise group and the rest group. The initial rhythm was more often shockable (VF or ventricular tachycardia) in the exercise group. Bystander CPR was less likely initiated if the SCA took place at rest. Survival to hospital discharge was substantially higher among exercise-related SCAs. This finding was evident and similar both in subjects under and over the age of 65 years (Table 9). Even subjects over the age of 65 had a fairly good likelihood of hospital discharge in exercise-related cases, although we did not have information about the neurologic condition that followed.

Table 8. Resuscitation and survival information among the two study groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exercise-related SCA (n=47)</th>
<th>SCA at rest (n=43)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial rhythm recorded</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VF</td>
<td>77%</td>
<td>50%</td>
<td>0.016</td>
</tr>
<tr>
<td>Asystole</td>
<td>21%</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>PEA</td>
<td>2.1%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td><strong>Initial rhythm recorded</strong></td>
<td></td>
<td></td>
<td>0.009</td>
</tr>
<tr>
<td>Shockable</td>
<td>77%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Non-shockable</td>
<td>23%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td><strong>Bystander CPR</strong></td>
<td></td>
<td></td>
<td>0.020</td>
</tr>
<tr>
<td>Survival to hospital discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 65 years</td>
<td>50%</td>
<td>13%</td>
<td>0.005</td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>47%</td>
<td>5.3%</td>
<td>0.003</td>
</tr>
</tbody>
</table>

CPR = Cardiopulmonary Resuscitation, PEA = Pulseless Electrical Activity, SCA = Sudden Cardiac Arrest, VF = Ventricular Fibrillation.

The unadjusted OR for death before hospital discharge was 9.3-fold (2.9–30, p=0.00020) when SCA occurred at rest compared to exercise-related SCA.
Thereafter, we included PE, age, gender, bystander CPR, prior cardiac disease and initial rhythm recorded in a multivariate regression analysis. PE remained statistically significant in this analysis with an OR of 7.0 (1.4–35, p=0.019).

5.4 Longitudinal changes in leisure-time physical activity and cardiac mortality in stable coronary artery disease patients (Study IV)

A total of 68 (3.9%) cases of cardiac death and 29 (1.7%) SCDs occurred during the main follow-up period. Age (HR = 1.10 (1.05-1.14) p<0.001), type 2 diabetes mellitus (HR = 2.13 (1.24-3.66), p=0.006), left ventricular ejection fraction (HR = 0.95 (0.93-0.97), p<0.001) and Canadian Cardiovascular Society grading for angina pectoris class at least 2 (HR = 2.62 (1.47-4.67), p=0.001) were all related to an increased adjusted risk of overall cardiac death without LTPA variables. When only SCD cases were considered, left ventricular ejection fraction (HR = 0.95 (0.92-0.98), p=0.001), Canadian Cardiovascular Society grading for angina pectoris class at least 2 (HR = 3.84 (1.54-9.59), p=0.004) and any non-fatal cardiovascular event during the initial 2-year follow-up (HR = 0.22 (0.05-0.93), p=0.039) were statistically significant variables in multivariate analysis during follow-up before the inclusion of LTPA variables.

The study population (n=1,746) was divided into four groups of patients according to changes in LTPA. The Active-Active group included subjects who were at least irregularly active at both study points and comprised 1,351 subjects. Inactive subjects who became active during the initial follow-up formed the Inactive-Active group of 53 subjects. Subjects in the Active-Inactive group in turn became inactive, and there were a total of 228 of them. The Inactive-Inactive group included 114 subjects.

Table 10 shows the univariate predictive value of LTPA for overall cardiac death. Inactive lifestyle both at baseline and at 2 years was associated with a significantly increased unadjusted risk of cardiac death. There was no difference between the Highly Active group and Active group either at baseline or at 2 years. Subjects who became active during the initial follow-up had a similar risk of cardiac death compared to those who remained active. However, those who remained inactive or became inactive had a clearly higher risk of cardiac death. The unadjusted survival curves for changes in LTPA during the initial follow-up are shown in Figure 6.
Table 9. Unadjusted hazard ratios (95% CI) for different LTPA variables.

<table>
<thead>
<tr>
<th>LTPA variables at Baseline</th>
<th>All-cause mortality (n=147)</th>
<th>Cardiac death (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly active</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Active</td>
<td>1.1 (0.6-1.8)</td>
<td>1.0 (0.4-2.3)</td>
</tr>
<tr>
<td>Irregularly active</td>
<td>1.2 (0.7-2.0)</td>
<td>1.4 (0.6-3.2)</td>
</tr>
<tr>
<td>Inactive</td>
<td>3.7 (2.1-6.4)**</td>
<td>4.7 (2.1-10.6)**</td>
</tr>
</tbody>
</table>

LTPA after the 2-year follow-up

| Highly active             | Reference                   | Reference           |
| Active                    | 2.0 (0.9-4.3)               | 1.9 (0.6-5.7)       |
| Irregularly active        | 2.8 (1.3-5.9)**             | 1.7 (0.6-5.3)       |
| Inactive                  | 7.1 (3.4-14.7)*             | 8.0 (2.8-22.4)**    |

LTPA Baseline – 2-year follow-up

| Active – Active           | Reference                   | Reference           |
| Inactive – Active         | 2.2 (1.0-4.8)*              | 1.6 (0.4-6.7)       |
| Active – Inactive         | 2.7 (1.8-4.0)**             | 3.7 (2.1-6.7)**     |
| Inactive - Inactive       | 5.2 (3.4-7.8)**             | 7.6 (4.2-13.6)**    |

*p<0.05, ** p<0.01 and *** p<0.001 vs. reference. CI = confidence interval, LTPA = leisure time physical activity SCD = sudden cardiac death.

In multivariate analysis, inactive habitual level of LTPA both at baseline and after the initial 2-year follow-up was related to an increased risk of cardiac death. Subjects who became inactive or remained inactive during the initial follow-up had higher cardiac mortality compared to those who remained active. Those who became at least irregularly active did not have an excessive risk of cardiac death. The hazard ratios for all-cause and cardiac mortality are presented in Table 11.
Table 10. Adjusted hazard ratios (95% CI) for different LTPA variables.

<table>
<thead>
<tr>
<th>LTPA variables</th>
<th>All-cause mortality (n=143)</th>
<th>Cardiac death (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LTPA at Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highly active</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Active</td>
<td>1.2 (0.7-2.1)</td>
<td>0.9 (0.4-2.2)</td>
</tr>
<tr>
<td>Irregularly active</td>
<td>1.2 (0.7-2.2)</td>
<td>1.1 (0.5-2.6)</td>
</tr>
<tr>
<td>Inactive</td>
<td>2.9 (1.5-5.4)**</td>
<td>2.6 (1.0-6.4)*</td>
</tr>
<tr>
<td><strong>LTPA after the 2-year follow-up</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highly active</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Active</td>
<td>2.0 (0.9-4.3)</td>
<td>1.7 (0.6-5.2)</td>
</tr>
<tr>
<td>Irregularly active</td>
<td>2.4 (1.1-5.3)*</td>
<td>1.3 (0.4-4.0)</td>
</tr>
<tr>
<td>Inactive</td>
<td>4.6 (2.1-10.0)**</td>
<td>4.2 (1.4-12.6)*</td>
</tr>
<tr>
<td><strong>LTPA Baseline – 2-year follow-up</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active – Active</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Inactive – Active</td>
<td>2.1 (0.9-4.6)</td>
<td>1.1 (0.3-4.8)</td>
</tr>
<tr>
<td>Active – Inactive</td>
<td>1.9 (1.2-3.0)**</td>
<td>2.4 (1.3-4.5)**</td>
</tr>
<tr>
<td>Inactive - Inactive</td>
<td>3.6 (2.2-6.2)**</td>
<td>4.9 (2.4-9.8)**</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01 and ***p<0.001 vs. reference. CI = confidence interval, SCD = sudden cardiac death.

We also had the information about a possible SCD during the main follow-up and included this information in the analyses. Table 12 presents both the unadjusted and adjusted hazards ratios of SCD for different LTPA variables. Those who were physically active at baseline had a lower risk of SCD compared to highly active subjects. Otherwise, the hazard ratios of SCD for different levels of LTPA at baseline did not differ statistically significantly. Inactivity after the initial 2-year follow-up meant a higher unadjusted risk of SCD, but this finding did not remain statistically significant after adjustments. When analyzing the longitudinal changes in LTPA levels, subjects who remained at least irregularly active or became at least irregularly active during the initial follow-up had a similar risk of SCD. However, subjects who became inactive had a 2.8-fold risk of SCD even after adjustments for potential confounders. Study subjects who were inactive both at baseline and at 2 years had a significantly higher risk of SCD. After adjustments, HR of SCD was 5.8-fold in the Inactive-Inactive group. The unadjusted survival curves for different groups of longitudinal LTPA changes are presented in Figure 3.
Table 11. Hazards ratios of SCD for different LTPA variables.

<table>
<thead>
<tr>
<th>SCD (n=29)</th>
<th>Unadjusted HR (95%CI)</th>
<th>Adjusted HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LTPA at Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highly active</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Active</td>
<td>0.3 (0.1-1.1)</td>
<td>0.2 (0.1-0.8)*</td>
</tr>
<tr>
<td>Irregularly active</td>
<td>0.6 (0.2-1.6)</td>
<td>0.4 (0.1-1.1)</td>
</tr>
<tr>
<td>Inactive</td>
<td>2.1 (0.8-5.9)</td>
<td>1.0 (0.3-3.5)</td>
</tr>
<tr>
<td><strong>LTPA after the 2-year follow-up</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highly active</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Active</td>
<td>1.9 (0.4-8.9)</td>
<td>1.7 (0.4-8.5)</td>
</tr>
<tr>
<td>Irregularly active</td>
<td>1.5 (0.3-7.4)</td>
<td>1.0 (0.2-5.4)</td>
</tr>
<tr>
<td>Inactive</td>
<td>6.2 (1.4-27.4)*</td>
<td>4.3 (0.9-21.6)</td>
</tr>
<tr>
<td><strong>LTPA Baseline – 2-year follow-up</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active – Active</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Inactive – Active</td>
<td>1.7 (0.2-12.9)</td>
<td>1.2 (0.1-9.7)</td>
</tr>
<tr>
<td>Active – Inactive</td>
<td>3.1 (1.3-7.7)*</td>
<td>2.8 (1.0-7.4)*</td>
</tr>
<tr>
<td>Inactive - Inactive</td>
<td>6.3 (2.6-15.7)**</td>
<td>5.8 (1.9-17.9)**</td>
</tr>
</tbody>
</table>

*p<0.05, ** p<0.01 and *** p<0.001 vs. reference. CI = confidence interval, LTPA = Leisure-time physical activity, SCD = sudden cardiac death. # Adjusted for age, sex, baseline body mass index, type 2 diabetes, history of myocardial infarction, left ventricular ejection fraction, Canadian Cardiovascular Society grading for angina pectoris, cardiovascular event during initial 2-year follow-up, smoking status at 2 years and alcohol consumption at 2 years.
Fig. 6. Unadjusted survival curves according to changes in LTPA
6 Discussion

The main findings in Study I and Study II were the clear male dominance and CAD, myocardial scarring and cardiac hypertrophy at autopsy, and fQRS in anterior leads in exercise-related SCD. In Study III we showed a markedly better prognosis of exercise-related SCA, probably due to younger victims, higher rate of bystander CPR and shockable rhythm, and healthier subjects. Finally, in Study IV, the main finding was that LTPA and its changes are independent predictors of cardiac death as well as SCD in patients with stable CAD. In this section these findings are discussed in more detail, and the current results are linked to previously gathered information.

6.1 Subject characteristics and electrocardiographic abnormalities in victims of exercise-related sudden cardiac death in the general population

6.1.1 Characteristics and autopsy findings of exercise-related sudden cardiac death

The number of exercise-related SCD was quite high in our series. Almost one third of witnessed SCDs (328/1,204, 27%) took place during or immediately after PE. We also excluded all unwitnessed cases and activity that could not be considered to be either PE or rest. A clear majority of exercise-related deaths occurred during exercise, and only 42/328 (13%) during the 1-hour time frame after exercise. Only five exercise-related SCDs (5/328, 1.5%) occurred in study subjects under the age of 40. This finding emphasizes the importance of PE as a trigger of SCD in the older population.

The overall proportion of exercise-related SCD is somewhat higher than in previous studies. In an old study by Libethson, 17% of out-of-hospital VF occurred during moderate or vigorous physical stress (Libethson et al., 1974). In the Oregon Sudden Unexpected Death Study, the findings by Reddy showed that vigorous or moderate PE preceded 18% of all cases of SCA (Reddy et al., 2009). Even smaller proportions of exercise-related SCAs have been published (Berdowski et al., 2013; Torell et al., 2017). This could be due to different definitions of PE. We included various kinds of physically demanding chores, not only sports or activities performed for physical fitness. We also excluded all
unwitnessed cases and light activity. We revealed a significant male dominance among those whose death was exercise-related, with only 6% of exercise-related SCDs occurring in women. In a French population, 95% of sports-related SCD occurred in men (Marijon et al., 2011). In the Netherlands, 93% of exercise-related cases of SCA were men (Berdowski et al., 2013). The differences between sexes can be explained by the higher rate of PE participation and higher exercise intensities among males. CAD is fairly uncommon in young and middle-aged women compared to men, which might reduce the absolute risk of exercise-related SCD among women. A study by Whang et al. presented a very low risk (1 per 36 million hours of risk) of SCD during PE in women (Whang et al., 2006).

A clear majority (91%) of victims of exercise-related SCD had CAD at medicolegal autopsy. The information from large-scale autopsy series about the underlying cardiac abnormality causing exercise-related SCD is limited. In a small Chinese study, 93% of exertion-related cases of SCD had CAD as the primary autopsy finding (Wu et al., 2017). The exact mechanism of SCD can not be confirmed by postmortem investigations and it is possible that in some cases CAD did not cause the death, thus overestimating the proportion of moderate coronary atherosclerosis. In our study, more than half of those dying due to CAD did not have a prior diagnosis or symptoms of CAD, and the SCD during exercise was their first heart disease event. CAD was clearly less common among victims under the age of 40, and the extremely low number of exercise-related SCD in this age group could partly be explained by this finding, but the significance of this result is limited due to the very small sample size. Our present results also show that PE in subjects with non-ischemic cardiomyopathy is not likely to significantly increase the risk of SCD, but the effect of PE on different subgroups needs to be evaluated in the future. Certain subgroups might benefit from PE without an increase in exercise-related SCD. Hypertrophic cardiomyopathy was a common underlying substrate of exercise-related SCD among younger victims (<40 years of age), a finding that was also noted in previous studies (Burke et al., 1991; Maron et al., 1996).

The occurrence of myocardial scarring at autopsy was high among our study population (47%) even though only 10% of our SCD victims had been diagnosed with prior AMI according to medical records. Myocardial scarring or ischemic tissue can act as substrate for reentrant ventricular arrhythmias if triggering factors are present. Myocardial scarring can also occur in association with certain nonischemic cardiomyopathies. However, the difference between the prevalence of myocardial scarring at autopsy and prior diagnosed AMI also highlights the
importance of “silent” myocardial infarctions. Studies have shown that a notable number of myocardial infarctions go undiagnosed (Arenja et al., 2013; Kannel & Abbott, 1984). A study by Van der Ende showed recently a high prevalence of electrocardiographic signs (in this case Q waves) of unrecognized myocardial infarction in the general population, and unrecognized MI was also related to increased mortality (van der Ende, M Yldau et al., 2017). In our study, we noticed a higher incidence of myocardial scarring as an autopsy finding among exercise-related SCDs, but prior diagnosed AMI in patient history did not predict a significant difference between the exercise group and rest group (Table 3). This finding emphasizes the important role of screening for “silent” myocardial infarctions in subjects with traditional cardiovascular risk factors, especially before engaging in heavy exercise programs.

Cardiac hypertrophy can be associated with several cardiac diseases, and in our study up to 69% of SCD victims had a hypertrophied heart defined as increased total heart weight at autopsy. A hypertrophied heart and ischemic heart disease together with myocardial scarring probably comprise a specific high-risk substrate for exercise-triggered SCD. On the other hand, exercise itself can result in a hypertrophied heart, which could partly explain the presence of hypertrophy among those who died during exercise.

Obesity-related cardiomyopathy and alcoholic cardiomyopathy were somewhat more common autopsy findings in the rest group. Especially cardiomyopathy related to obesity was relatively common in both study groups. Obesity is already a major global problem and severe obesity is thought to eventually cause cardiomyopathy and congestive heart failure (Alpert, 2001). However, contrasting opinions of the link between obesity and cardiomyopathy has also been presented (Owan & Litwin, 2007). More research is needed in the future to enable more precise identification of this cardiomyopathy of obesity. Currently, cardiomyopathy of obesity is mainly a postmortem diagnosis.

Beta-blocker usage lowers mortality in patients after myocardial infarction (Dargie, 2001; Gottlieb, McCarter, & Vogel, 1998). A meta-analysis by Al-Gobari et al. concluded a clear reduction in SCD mortality also in heart failure patients with beta-blocker usage (Al-Gobari et al., 2013). Beta-blockers lower the heart rate during physical exertion, which could beneficially prevent SCD during exercise by lowering wall stress and therefore reducing exercise-induced ischemia and plaque rupture. We did not find any statistically significant differences in beta-blocker usage between our two study groups. Diuretics were used more frequently in the rest group, which is probably due to the higher incidence of prior
diagnosis of congestive heart failure in this group. Psychotropic medications seemed to be more common in the rest group. Especially antipsychotics have previously been linked to an increased risk of SCD (Honkola et al., 2012; Ray, Chung, Murray, Hall, & Stein, 2009). Antipsychotics tend to prolong the QTc interval, most notably during low heart rate at rest. This could explain part of the rest-related deaths. However, those suffering from psychosis and other psychiatric disease do little exercise, which could explain a big part of this difference.

Skiing (12%) and cycling (11%) were found to be the most common types of exertion behind exercise-related SCD. Cycling has been the most important trigger of exercise-related SCDS in some studies (Berdowski et al., 2013; Suárez-Mier & Aguilera, 2002). Sexual intercourse was found to be an uncommon trigger of SCD. Skiing and snow shoveling are, however, typical types of vigorous physical activity during wintertime in our study area in northern Finland. Cross-country skiing has been linked to SCD in Finland (Vuori, Mäkäräinen, & Jääskeläinen, 1978). Snow shoveling has previously been linked to an excessive risk of SCD and other acute coronary syndromes (Chowdhury et al., 2003; Nichols et al., 2012) and it is regarded as high-risk physical activity by the American Heart Association (Thompson et al., 2007). Already by themselves, cold weather and cold spells cause an increase in SCD rates (Gerber, Jacobsen, Killian, Weston, & Roger, 2006; Ryti et al., 2017), and exertion in cold weather might create an especially significant trigger effect for SCD.

6.1.2 Electrocardiographic abnormalities in victims of exercise-related sudden cardiac death

There is very little information available on ECG abnormalities preceding exercise-related SCD. fQRS in at least two consecutive anterior leads was associated more commonly with exercise-related SCD in comparison to the rest group and the control population that represented the general population. Heterogeneous activation of the myocardium due to myocardial scarring, fibrosis or inflammation leads to conduction disturbances, which might appear as fQRS (Das et al., 2006; Konno et al., 2015; Schuller et al., 2011). In the general population, fQRS did not increase cardiovascular mortality in previously healthy subjects, but in subjects with previous cardiac disease fQRS in lateral leads was linked to a threefold risk of arrhythmic death (Terho et al., 2014). Previous studies have also shown that fQRS among patients with CAD regardless of the affected anatomical area is an independent risk factor for cardiac events and mortality.
Das et al., 2007; Das et al., 2010). A similar finding of worse cardiac outcome has been noted in HCM and DCM (Kang et al., 2014; Sha et al., 2011). CAD patients with fQRS in at least three leads regardless of the affected leads possessed a worse cardiac prognosis (Torigoe et al., 2012). In study II, the prevalence of fQRS in anterior leads was accentuated among those with a prior diagnosis of CAD and exercise-related SCD. On the other hand, subjects with manifest CAD but without fQRS were not overrepresented among exercise-related SCDs. Vigorous PE is considered a trigger of ventricular arrhythmias only when a substrate is present. fQRS in anterior leads might reveal an underlying cardiac abnormality, such as scarring or fibrosis, affecting the septal and/or anterior myocardium. These abnormalities in the myocardium in turn reflect an increased risk of ventricular arrhythmias and in our current sample, an increased risk of exercise-related SCD. In study I we already showed a higher prevalence of CAD, myocardial scarring and hypertrophy at autopsy in exercise-related SCDs, and these underlying cardiac abnormalities might cause fQRS. Pathologic Q waves in anterior leads were also more commonly present in the exercise group. There is most likely overlap between pathologic Q waves and fQRS because both might reflect similar abnormality in the myocardium. When adjusted in a multivariate regression analysis, the effect of fQRS in anterior leads remained significant as opposed to Q waves. This finding about the relation between exercise-related SCD and fQRS or pathologic Q waves could not be expanded to leads in other anatomical areas.

The median QRS duration was somewhat wider among exercise-related SCDs compared to the rest group; a similar finding has not been previously published. In the general population, prolonged QRS duration due to nonspecific conduction delay is associated with an excessive rate of arrhythmic death (Aro et al., 2011b). Another Finnish study presented a similar finding in men (Kurl et al., 2012). A prolonged QRS duration could be a marker of fibrosis, left ventricular dysfunction or other depolarization abnormalities, which may lead to ventricular arrhythmias in the presence of a trigger, such as PE. In our study, the wider QRS complex might manifest a more severe underlying cardiac disease.

Higher prevalence of other ECG variables, such as presence of T wave inversions, mean corrected QT interval (Bazett’s formula), or TpTe interval, was not observed in the exercise group compared to the rest group. T-wave inversions, although unspecific, have been linked to SCD and overall cardiovascular mortality (Yamazaki et al., 2005). A Finnish population-based cohort study by Laukkanen et al. displayed a 3.3-fold risk of SCD in subjects with T wave
inversions (Laukkanen et al., 2014). Inverted T waves in right precordial leads (V1 to V3) were not associated with adverse cardiac outcome in middle-aged subjects (Aro et al., 2012). Prolonged QT interval is associated with increased cardiovascular and SCD mortality in the general population (Zhang et al., 2011). Subjects with congenital LQTS type 1 have an increased risk of life-threatening arrhythmias during PE (Schwartz et al., 2001). In our study, the median QTc interval did not differ between the exercise group and rest group. The QTc interval was significantly shorter in the control population compared to both SCD groups. Prolonged TpTe interval is thought to result from transmural dispersion of ventricular repolarization (Watanabe et al., 2004), and TpTe interval has been found to be longer among SCD victims (Panikkath et al., 2011). However, we did not observe any difference between the exercise group and rest group in the mean value of TpTe interval.

### 6.2 Characteristics and prognosis of exercise-related sudden cardiac arrest

In our study, the overall incidence of exercise-related SCAs in Northern Ostrobothnia was 2.6 cases per 100,000 person years. In previous studies, the incidence of exercise-related SCA has varied from 0.6 to 2.1 cases per 100,000 person years (Berdowski et al., 2013; Edwards & Fothergill, 2015; Marijon et al., 2015). In Sweden, the incidence of exercise-related SCA was lower compared to our results (Torell et al., 2017). However, the characteristics of study populations and the definition of PE have varied between these studies. In these studies, PE has mainly included sports activities which do not take into account the effect of heavy physical labor. In a Chinese study, physical labor was the most common type of exertion related to SCD, with a proportion of over 50% (Wu et al., 2017). In our study, cycling (26%) was found to be the most common type of activity related to SCA, followed by heavy labor (21%). Cycling was also the second most common type of exertion in our study I. In Spain, with a warmer climate, cycling was the most common recreational trigger of exercise-related SCD (Suárez-Mier & Aguilera, 2002). In study I we did not categorize heavy labor as one specific type of exertion. Similarly to our previous findings, skiing and snow shoveling were also common triggers of exercise-related SCA. The most common types of physical activity in our study are not usually performed in public sporting facilities. Thus, the dissemination of AED to public facilities would likely have no
beneficial effect on these types of exercise-related SCA. We did not have information about bystander usage of AED in our data.

Subjects who suffered exercise-related SCA were younger compared to the rest group. A similar finding has been seen in previous studies (Berdowski et al., 2013; Edwards & Fothergill, 2015). Marijon et al. only included study subjects between the ages 35 and 65, and in their study no difference in mean age could be identified (Marijon et al., 2015). Younger subjects often have better physical fitness and they are able to perform physical activity more frequently and are more likely to achieve moderate-to-vigorous intensity, which might explain the age difference. Male gender was somewhat more frequent among exercise-related SCA, but this finding was not statistically significant. Study I and also numerous other studies have shown male dominance in exercise-related cardiac events (Giri et al., 1999; Marijon et al., 2011). Time to EMS arrival took on average 1.9 minutes longer when SCA occurred at rest; this finding did not, however, reach statistical significance. This finding is difficult to explain, because all cases were witnessed. Subjects with SCA at rest had more often prior congestive heart failure, diagnosed CAD and any prior cardiac disease. Especially congestive heart failure reduces the overall time spent being physically active, and therefore makes exercise-related SCA less likely. Physical activity is strongly recommended also for patients with heart failure (Yancy et al., 2013). It is also evident that sedentary subjects have the highest risk of adverse cardiac event during unaccustomed PE (Albert et al., 2000; Mittleman et al., 1993). We did not, however, have information about the habitual levels of physical activity or fitness levels of our study subjects. The underlying cause of SCA was mostly due to ischemic origin in both our study groups and no significant difference could be found in the prevalence of ischemic origin. A comprehensive medicolegal autopsy was performed on all SCA subjects who died before reaching hospital. This approach is more accurate than clinical evaluation alone.

The initial rhythm recorded by the first EMS unit was shockable in 77% of exercise-related SCAs and in 50% in the rest group. This finding has been fairly similar in previous studies as well (Berdowski et al., 2013; Edwards & Fothergill, 2015; Marijon et al., 2015). In our current study, asystole was the leading rhythm in cases with non-shockable initial rhythm. PEA was the initial rhythm in only 2.1% of exercise-related cases. The proportion of PEA was almost 7-fold in the rest group (14%), and this finding was statistically significant. PEA has been associated with better prognosis in out-of-hospital cardiac arrest compared to asystole as the initial rhythm (Andrew, Nehme, Lijovic, Bernard, & Smith, 2014).
In the entire study population the rate of bystander CPR (42%) was low, considering that only witnessed cases were included in the analysis. In our present data, bystander CPR was more likely initiated in exercise-related SCAs. This finding was compatible with previous studies (Berdowski et al., 2013; Edwards & Fothergill, 2015; Marijon et al., 2015; Torell et al., 2017). In the Netherlands, the overall rate of bystander CPR seemed to be significantly higher than in our study (Berdowski et al., 2013). It might be more difficult for the layperson to identify lifelessness in SCAs at rest, and this in turn delays CPR. In Denmark, targeted national initiatives have been able to increase the rates of bystander CPR and survival rates of out-of-hospital SCA during a 10-year study period (Wissenberg et al., 2013). Bystander CPR has been shown to improve survival and long-term outcome in SCA (Kragholm et al., 2017; Sasson, Rogers, Dahl, & Kellermann, 2010; Wissenberg et al., 2013). In Finland, further national initiatives should probably be set up to improve the abilities of citizens to recognize and act in SCA cases. For example, resuscitation training offered in learning institutions has been shown to increase the likelihood of bystander CPR (Wissenberg et al., 2013).

In our data, survival to hospital discharge was multiple times higher among exercise-related SCAs. Berdowski et al. presented a similar finding in subjects over the age of 35, and the effect was most evident in the oldest age group (age over 65 years) (Berdowski et al., 2013). Marijon et al., however, did not find a better survival rate in sports-related SCAs after adjustments for resuscitation variables (Marijon et al., 2015). In Sweden, the 30-day survival rate was almost 3-fold in exercise-related SCAs (Torell et al., 2017). A similar difference in survival to hospital discharge between our two study groups could be seen both in subjects under and over the age of 65 years. However, in the entire study population subjects over the age of 65 had lower survival to hospital discharge compared to subjects under the age of 65.

In our study, the risk of death prior to hospital discharge was still 7-fold among those with SCA at rest, even after adjustments for age, gender, bystander CPR, initial rhythm recorded and prior diagnosed cardiac disease in a multivariate regression analysis. There are probably several reasons for this. Subjects with SCA during rest might have had a more severe prior cardiac disease. Congestive heart failure was also clearly a more common finding in the rest group. Regular physical activity has widespread cardioprotective effects. Subjects who experienced SCA in association with physical activity were probably in better shape and therefore had higher probability of survival. This is, however,
speculative because we did not have information about the habitual physical activity and fitness levels of our study subjects.

6.3 The effect of changes in leisure-time physical activity on cardiac mortality in stable coronary artery disease

Physical inactivity and becoming physically inactive during the initial 2-year follow-up was related to increased risk of cardiac death and SCD, whereas the change from sedentary behavior towards at least irregular LTPA involved a risk that did not differ from maintaining at least irregular LTPA. In recent years, it has been discussed that very high levels of LTPA might generate an increased risk of cardiovascular mortality compared to moderate levels of LTPA (Arem et al., 2015; Mons et al., 2014) and the concept of a reverse J-shaped association has been presented. However, conflicting results have also been published (I. Lee & Paffenbarger Jr, 2000; Moholdt, Wisløff, Nilsen, & Slørdahl, 2008). In study IV, we noticed that the risk of cardiac death was somewhat linear when LTPA was assessed cross-sectionally both at the baseline and at 2 years, with the highest risk in inactive subjects. We could not identify higher risk of cardiac death in the most highly active subjects and therefore a reverse J-shape association was not observed. This contrasting observation might be due to different definitions and measurements of LTPA. Our finding confirms the safety of LTPA in our study population.

The beneficial effect of LTPA on all-cause and cardiovascular mortality in CAD patients is well documented (Moholdt et al., 2008; Wannamethee, Shaper, & Walker, 2000). However, in many previous population-based follow-up studies LTPA has been quantified by a single measurement at one time point (Apullan et al., 2008; Moholdt et al., 2008). This approach does not take into account naturally occurring changes in LTPA. In a study conducted in the United States, those subjects who became inactive during the 12 to 14 years of follow-up had the highest risk of all-cause and cardiovascular mortality (Wannamethee et al., 1998). In this study, subjects who became active or remained active had slightly lower all-cause and cardiovascular mortality in comparison to subjects who remained inactive, but this finding did not reach statistical significance. In a Harvard alumni data set, a similar reduction in all-cause and cardiovascular mortality was seen in study subjects who increased their physical activity to favorable levels during initial follow-up (11–15 years), but these findings were statistically insignificant (Paffenbarger Jr et al., 1993). Our present study used an evidently shorter-term
follow-up for the assessment of changes in LTPA, which may be more valuable for clinical practice. In contrast to Wannamethee et al., we noted the highest risk of cardiovascular mortality in subjects who remained inactive at both study points. Our finding might suggest cardioprotective value of previous LTPA during a relatively short time frame between the study points. However, becoming active seemed to decrease the risk of cardiac death to the level of patients who remained active over two years, supporting previous findings.

There are no previously presented data on changes in LTPA levels and further risk of SCD. It is well established that regular PE training decreases the risk of SCD, and one major mechanism is increased antiarrhythmic cardiac vagal activity and decrease in sympathetic activity (Billman, 2002; Lucini et al., 2002). Our study showed a novel but expected association between LTPA and its changes and the risk of SCD. Those who became at least irregularly active during initial follow-up had a similar risk of SCD compared to subjects with an active lifestyle at both study points. On the contrary, subjects who became inactive had an increased risk of SCD even after adjustments. A trend towards a J-shaped association between baseline LTPA and SCD was observed, with the lowest risk of SCD in active subjects. However, this finding could not be duplicated at the 2-year study point. We cannot establish the reason for this observation, but it may be that baseline LTPA represents only temporary exercise behavior after coronary angiography.

It is noteworthy that a larger part of the study participants became inactive than active during the initial 2-year follow-up, highlighting the problem of stable CAD patients becoming sedentary. This unfavorable development was noted in previous studies (Mons et al., 2014; Wannamethee et al., 1998). There are several possible explanations for this finding. Our study population consisted of mostly elderly people. The age was on average 70 years in subjects who became inactive during follow-up. Activity levels tend to naturally decrease with advancing age due to disease or infirmity. In our cases the heart disease could itself lower the activity levels by causing symptoms and reducing heart function. Unfortunately, there could also be fear of PE because of the diagnosis of CAD. Even in relatively young people permanent work disability is common after coronary revascularization despite the overall excellent survival (Lautamäki et al., 2016). The decreasing amount of LTPA indicates a need for targeted patient-centered counseling, which enables individual active participation in treatment and takes into account individual background of physical activity and comorbidities that might hinder LTPA (Kaakinen, Kyngäs, & Kääriäinen, 2013). It is thought that
offering information, encouragement, firm commitment and reminders are the key factors for sustaining changes in LTPA (Kanning, 2010).

6.4 Clinical implications

This thesis is first and foremost a series of clinical studies. SCD is still a common type of death, accounting for a significant share of years of potential life lost. Physical activity is an important part of our physical and mental well-being. According to the results presented in this serial study, we can conclude that subjects dying suddenly during PE are mostly males and the underlying cardiac disease is most often CAD. Among stable CAD patients physically active lifestyle was found to be safe and beneficial. When patients with several risk factors for CAD are about to start an unaccustomed physical training regime, we should actively search for a possible underlying cardiac disease and treat it before the increase in PE levels. In stable CAD patients, PE should be encouraged and sufficient levels of physical activity need to be supported at all levels of health care. However, in some cases heavy high-risk activities, such as snow shoveling, should be performed with caution. fQRS in anterior leads was found to be a common finding in the exercise group, especially in subjects with a prior diagnosis of CAD. When fQRS in anterior leads is seen in patients it can be used as part of the comprehensive risk assessment. This finding alone should, however, not lead to avoidance of PE.

6.5 Study limitations

A few limitations can be noted in all of the present studies and they need to be discussed. Even though the FinGesture study population with comprehensive medicolegal autopsies is unique, there are a few limitations regarding this data. In subjects with advanced cardiac disease the general physician is allowed to issue a death certificate for victims of SCD without a complete medicolegal autopsy, and these cases are missing from the study population. There are also differences in the definition of SCD. In FinGesture, all deaths took place within a 6-hour time frame after the onset of symptoms or 24 hours after the subject was seen in a normal state of health. In many cases the subject was found dead and the exact mechanism of SCD is difficult to assess. However, we used only witnessed cases in all present studies. Medicolegal autopsy does not reveal the exact mechanism by which SCD occurred but it is the best possible way to identify the underlying
cardiac abnormality. There were only 0.3% of cases with no cardiac abnormalities at autopsy, and there were probably arrhythmic deaths that were classified as something else than SCD and were not included in the study population. The FinGesture study population, however, consisted of mainly older subjects, which might explain the very low amount of autopsy-negative cases. This finding has already been presented and discussed in the same study population (Hookana et al., 2011). The information about medications and prior diagnosed cardiac diseases was collected from available medical records and next of kin. There might be some inaccuracy in this information, and the actual usage of medications could not be assessed.

The circumstances at the time of death in studies I and II were described in comprehensive death certificates and police reports. Questionnaires to next of kin were also used. In study III, the physical activity at the time of SCA was assessed according to the information from emergency units, death certificates and police reports, questionnaires to next of kin, and medical records documented by treating physicians. The level of physical activity at the time of the event was assessed according to the type of exertion. Therefore, the estimate of METs of physical activity is rough. We do not know the actual intensity of the physical activity at the time of death. The MET of certain type of exertion is also related to the capacity of the individual and might vary considerably. There was most likely inaccuracy in classification between low-intensity and moderate-intensity activity. We excluded unwitnessed deaths, which means that SCDs and SCAs taking place unwitnessed during sleep were excluded. While making the diagnosis of SCD more accurate, this might lead to an unusually high proportion of exercise-related cases. We also lacked the information about the habitual levels of physical activity of the victims. Therefore no estimate of the transient risk caused by PE can be made. In study III, the absolute amounts of SCA during exercise and at rest were small, which diminishes the ability to extrapolate the presented findings. There are probably cases of resuscitation that were not included in the EMS study population, so we cannot draw accurate estimates about the overall incidence of exercise-related SCA in our study area. In study III we did not gather information about the neurological outcome after SCA, so we do not know the condition in which the subjects were at hospital discharge.

In study II, the ECGs were taken on average around three years prior to the SCD and we do not have any information about possible dynamic changes during this time frame. However, this time difference between the ECG recording and the event is significantly shorter than in many previously published prospective
cohort studies. We only had 40 cases of exercise-related SCD with a previously recorded ECG in study II, which makes it more difficult to find statistically significant changes. It also diminishes the ability to generalize our present findings.

We used subjective self-reporting measurement for the level of LTPA. Even though this method is easily applied in follow-up studies, current subject-friendly methods for objective measurement of LTPA would have been more precise. The questions used in LTPA measurements did not provide detailed information about the intensity and mode of LTPA. Due to the small number of SCDs, the conclusions regarding the risk of SCD need to be evaluated cautiously. The comprehensive baseline clinical examinations were not repeated after the initial follow-up. Therefore, we cannot make a more detailed analysis of other health factors (such as echocardiography and lipid profiles) related to changes in LTPA.

6.6 Summary and future aspects

In summary, the present studies show that physical activity has beneficial effects on cardiovascular mortality, and subjects who suffer SCA during exercise have a markedly better prognosis. However, some subjects might have an excessive risk of adverse events during exercise, especially men with underlying CAD performing heavy unaccustomed physical exertion, such as snow shoveling. We also offered some ECG variables as new tools to identify patients at an increased risk of exercise-related SCD. These findings further highlight the importance of prevention and early diagnosis of CAD.

In study I, skiing and snow shoveling were common types of exertion related to SCD. In the future, it would be interesting to study the effect of cold weather and cold spells on the incidence of exercise-related SCD. Cold spells have been linked to excessive cardiac mortality and SCDs (Ryti et al. 2017), and this extreme weather phenomenon is likely to enhance the trigger effect of PE. The FinGesture study population is growing irresistibly and the number of exercise-related SCDs is at the moment around 600. Further analysis of this population is going to be interesting to see trends and obtain more detailed information on exercise-related SCDs. The study population in study II was rather small, with only 40 cases of exercise-related SCD with a previously recorded ECG available. This study population is also increasing in number, and in the future we might be able to identify more ECG variables as markers of increased risk of exercise-related SCD. Finally, it is important to encourage physical activity in CAD.
patients, and the ARTEMIS study population will hopefully show us further beneficial effects of LTPA.
7 Conclusions

The aim of this thesis was to clarify the relation between physical activity and cardiac events, especially SCD, in the general population in northern Finland. We wanted to find potential detectable risk factors to prevent such events during exercise. On the other hand, we also wanted to study the beneficial effects associated with habitual physical activity.

In study I, the results showed a considerable male dominance among exercise-related SCDs. CAD was clearly the most common underlying cardiac abnormality in these cases. In addition, we noted that cross-country skiing, cycling, and snow shoveling were common triggers of SCD. According to these findings, prevention and timely diagnosis of CAD are pivotal also in reducing the risk of exercise-related adverse events. As a result, clinicians might be able to detect subjects at excessive risk of exercise-related adverse events during heavy exercise and advocate low-to-moderate rather than heavy intensity activities.

Study II tried to identify ECG variables that are more often present among exercise-related SCDs. We found that fQRS in anterior leads was more common among exercise-related SCDs compared to SCD occurring at rest. This finding was especially distinct when there was a prior diagnosis of CAD. Widened QRS complex and Q waves in anterior leads were also common findings among exercise-related cases. These findings offer new tools for identifying subjects, especially CAD patients, at higher risk of exercise-related SCD.

In study III, we focused on exercise-related out-of-hospital SCA. Subjects suffering exercise-related SCA in the general population tended to have relatively good survival rates. They were also younger, previously healthier and the initial rhythm was more often shockable. Cycling and heavy physical labor were the most common types of physical activity related to SCA. It was also noteworthy that bystander CPR was initiated in only 30% of witnessed cases, indicating that national initiatives should be taken to improve the rates of bystander CPR.

In study IV, we showed that patients with stable CAD clearly benefit from LTPA. Even minor changes in LTPA over two years were related to a subsequent reduction in cardiac death and SCD. The presented findings also highlighted the importance of dynamic risk profiling over time instead of single measurement in identification of patients with increased risk of adverse cardiac outcome. Sedentary CAD patients should be encouraged to embrace a more active lifestyle. All in all, LTPA is an essential part of treatment of CAD patients.
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45*(8), 1354-1363.
Original publications

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


* Equal contribution.

The original publications are reprinted with permission from Taylor & Francis (I), John Wiley and Sons (II) and Elsevier (IV). Study III is published in open access journal.

Original publications are not included in the electronic version of the dissertation.


1473. Lantto, Ulla (2018) Etiology and outcome of PFAPA (periodic fever, aphthous stomatitis, pharyngitis and adenitis) syndrome among patients operated with tonsillectomy in childhood

1474. Hintsala, Heidi (2018) Cardiovascular responses to cold exposure in untreated hypertension


1481. Kelloniemi, Annina (2018) Novel factors regulating cardiac remodeling in experimental models of cardiac hypertrophy and failure


Tomi Toukola

PHYSICAL EXERCISE AND SUDDEN CARDIAC DEATH

CHARACTERISTICS AND RISK FACTORS