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CHARACTERISTICS OF UNDIAGNOSED CORONARY ARTERY DISEASE IN SUDDEN CARDIAC DEATH

AUTOPSY FINDINGS AND GENETICS

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Autopsy findings and genetics

Academic dissertation to be presented with the assent of the Doctoral Programme Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium 10 of Oulu University Hospital, on 17 June 2022, at 12 noon

Abstract

Sudden cardiac death (SCD) remains a major health problem worldwide, and a great proportion of victims do not have a previously diagnosed heart disease. Especially in older population, the majority of SCDs are caused by coronary artery disease (CAD); however, the burden of CAD among the young has also been noted. The aim of this thesis was to study the characteristics of SCDs associated with CAD, especially in younger victims and in those with no prior history of heart disease.

The study population consisted of 5,869 SCD victims from Northern Finland who underwent medicolegal autopsy between the years 1998–2017. In Study I, CAD was found to be the most common cause of SCD. At autopsies, a prior silent myocardial infarction (SMI) was detected in about 42% of the victims without a clinical history of CAD, and it was associated with myocardial hypertrophy and SCD during physical activity. A prior electrocardiogram was abnormal in 67% of the SCD victims with a previous SMI.

In Study II, 10% of the study population were found to be aged under 50 years and the most common cause of SCD among these young SCD victims was CAD. In about 90% of the cases SCD occurred in the absence of previously diagnosed CAD, but at least one known cardiovascular risk factor was present in over half of the victims. Despite the young age, advanced heart disease was a common finding at autopsies.

In Study III, the genetic background of cardiac hypertrophy was investigated in SCD victims with single-vessel CAD without a previously diagnosed heart disease. Possible disease-causing variants were detected in 8% of the study victims, while variants of uncertain significance existed in about 40% of the study victims. All detected variants were in myocardial structure protein coding genes.

In Study IV, temporal trends in the incidence and characteristics of SCDs were studied in subjects under 40 years of age. The incidence of SCD decreased during the years 1998–2017. Most SCDs in this age group were due to non-ischemic myocardial diseases, and the incidence of CAD-related SCD decreased.

The findings of this thesis increase the understanding of CAD-related SCDs, especially among younger population. In addition, Studies I and III provide novel information on the role of SMIs and genetics in the risk of SCD among victims without a previously diagnosed CAD.

Keywords: coronary artery disease, genetics, medicolegal autopsy, silent myocardial infarction, sudden cardiac death, young adults

Vähätalo, Juha, Diagnosoimattoman sepelvaltimotaudin tunnuspiirteet sydänperäisen äkkikuoleman yhteydessä. Ruumiinavauslöydökset ja genetiikka
Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Medical Research Center Oulu; Oulun yliopistollinen sairaala

Tiivistelmä

Sydänperäinen äkkikuolema on edelleen merkittävä terveysongelma maailmanlaajuisesti, ja suurella osalla uhreista ei ole aiemmin todettua sydänsairautta. Etenkin iäkkäillä suurin osa äkkikuolemista johtuu sepelvaltimotaudista, mutta sen taakka myös nuoremmilla on tiedostettu. Tämän väitöskirjatutkimuksen tavoitteena oli tutkia sepelvaltimotautiin liittyvien äkkikuolemien tunnuspiirteitä erityisesti nuoremmilla uhreilla sekä niillä, joilla ei ole aiemmin todettua sydänsairautta.

Tutkimusjoukkoon kuului 5869 sydänperäisen äkkikuoleman uhria Pohjois-Suomesta, joille tehtiin ruumiinavaus vuosina 1998–2017. Tutkimuksessa I sepelvaltimotaudin todettiin olevan yleisin äkkikuoleman syy. Ruumiinavauksissa aiemmin sairastettu hiljainen sydäninfarkti todettiin 42 %:lla uhreista, joilla ei ollut aiemmin diagnosoitua sepelvaltimotautia, ja se oli yhteydessä sydämen hypertrofiaan sekä äkkikuolemaan fyysisen rasituksen aikana. Ennen kuolemaa nauhoitettu sydänsähkökäyrä oli poikkeava 67 %:lla uhreista, joilla todettiin aiemmin sairastettu hiljainen sydäninfarkti.

Tutkimuksessa II havaitsimme, että 10 % tutkimusjoukostamme oli alle 50-vuotiaita ja sepelvaltimotautioli heillä yleisin äkkikuoleman syy. Noin 90 %:ssa tapauksista äkkikuolema esiintyi ilman aiempaa tietoa sepelvaltimotaudista, mutta yli puolella oli ainakin yksi tiedossa oleva sydän- ja verisuonisairauksien riskitekijä. Nuoresta iästä huolimatta pitkälle edennyt sydänsairauus oli yleinen löydös ruumiinavauksissa.

Tutkimuksessa III tutkimme sydämen hypertrofian geneettistä taustaa äkkikuoleman uhreilla, joilla oli yhden suonen sepelvaltimotauti ilman aiemmin diagnosoitua sydänsairautta. Löysimme todennäköisesti sydänsairautta aiheuttavia geenimuutoksia 8 %:lla tutkituista uhreista, ja 40 %:lla todettiin merkitykseltään epäselvä geenimuutos. Geenimuutokset todettiin sydänlihasproteiineja koodaavissa geeneissä.

Tutkimuksessa IV tutkimme alle 40-vuotiaiden äkkikuolemien ilmaantuvuuden ja tunnuspiirteiden ajallisia kehityssuuntia. Äkkikuolemien ilmaantuvuus väheni vuosina 1998–2017. Suurin osa äkkikuolemista tässä ikäryhmässä johtui ei-iskeemisistä sydänsairauksista, ja sepelvaltimotautiperäisten kuolemien ilmaantuvuus väheni.

Tämän väitöstutkimuksen havainnot lisäävät ymmärrystä sepelvaltimoperäisistä äkkikuolemista erityisesti nuoremman väestön keskuudessa. Lisäksi tutkimuksissa I ja II saatiin uutta tietoa hiljaisten sydäninfarktien ja genetiikan roolista äkkikuoleman riskissä uhreilla, joilla ei ole aiemmin diagnosoitua sepelvaltimotautia.

Asiasanat: genetiikka, hiljainen sydäninfarkti, nuoret aikuiset, oikeuslääketieteellinen ruumiinavaus, sepelvaltimotauti, sydänperäinen äkkikuolema

To my family

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Oulu, April 2022   Juha Vähätalo

List of abbreviations

AC   Arrhythmogenic Cardiomyopathy
ACS   Acute Coronary Syndrome
AI   Artificial Intelligence
ACMG   American College of Molecular Genetics
ARVC   Arrhythmogenic Right Ventricular Cardiomyopathy
BMI   Body Mass Index
CAD   Coronary Artery Disease
CI   Confidence Interval
CMRI   Cardiac Magnetic Resonance Imaging
CTA   Coronary Computed Tomography Angiography
CVD   Cardiovascular Disease
DCM   Dilated Cardiomyopathy
ECG   Electrocardiogram
EF   Ejection Fraction
ESC   European Society of Cardiology
fQRS   Fragmented QRS Complex
HCM   Hypertrophic Cardiomyopathy
HDL   High-Density Lipoprotein
ICD   Implantable Cardioverter Defibrillator
LDL   Low-Density Lipoprotein
LQTS   Long QT Syndrome
LVH   Left Ventricular Hypertrophy
MAF   Minor Allele Frequency
MI   Myocardial Infarction
NGS   Next Generation Sequencing
NYHA   New York Heart Association functional class
OR   Odds Ratio
PMF   Primary Myocardial Fibrosis
SCD   Sudden Cardiac Death
SD   Standard Deviation
SISu   The Sequencing Initiative Suomi
SMI   Silent Myocardial Infarction
VUS   Variant of Uncertain Significance

Original publications

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

I Vähätalo, J. H., Huikuri, H. V., Holmström, L., Kenttä, T. V., Haukilahti, M., Pakanen, L., Kaikkonen, K. S., Tikkanen, J., Perkiömäki, J. S., Myerburg, R. J., & Junttila, M. J. (2019). Association of Silent Myocardial Infarction and Sudden Cardiac Death. *JAMA Cardiology*, *4*(8), 796–802. doi: 10.1001/jamacardio.2019.2210

II Vähätalo J, Holmström L, Pakanen L, Kaikkonen K, Perkiömäki J, Huikuri H, Junttila J. (2021). Coronary artery disease as the cause of sudden cardiac death among victims < 50 years of age. *The American Journal of Cardiology*, 147, 33–8. doi: 10.1016/j.amjcard.2021.02.012

III Vähätalo JH, Holmström LTA, Pylkäs K, Skarp S, Porvari K, Pakanen L, Kaikkonen KS, Perkiömäki JS, Kerkelä R, Huikuri HV, Myerburg RJ, Junttila MJ. (2022). Genetic Variants Associated With Sudden Cardiac Death in Victims With Single Vessel Coronary Artery Disease and Left Ventricular Hypertrophy With or Without Fibrosis. *Frontiers in Cardiovascular Medicine*, Published Online First: 11 January 2022. doi: 10.3389/fcvm.2021.755062

IV Vähätalo J, Holmström L, Pakanen L, Kaikkonen K, Perkiömäki J, Huikuri H, Junttila J. (2022). Temporal Trends in the Incidence and Characteristics of Sudden Cardiac Death Among Subjects Under 40 Years of Age in Northern Finland During 1998-2017. *Cardiology*, Published Online First: 11 February 2022. doi: 10.1159/000522554

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1   Introduction

Cardiovascular disease (CVD) is one of the most significant and challenging health problems causing most of the morbidity and mortality worldwide (D. K. Arnett et al., 2019). In addition to health issues, CVD is a substantial burden in terms of economic costs: healthcare services and treatment, medications, and loss of productivity. Despite the advances in the management and treatment of CVDs during the past decades, future trends are worrying as the prevalence of obesity and unfavourable lifestyles seems to increase. Especially among young individuals, CVDs seem to be increasing in developed countries, possibly resulting in an epidemic of CVD in the near future (Andersson & Vasan, 2018).

Sudden cardiac death (SCD) has been estimated to account for about half of all cardiovascular deaths and 20% of total mortality in developed countries (Myerburg & Junttila, 2012; Wellens et al., 2014). Also, the burden of premature death from SCD has been observed to be greater than from any other single cause (Stecker et al., 2014). The fact that most SCD victims have never been diagnosed with a heart disease prior to the death makes it difficult to identify those at high risk of unexpected death (Wellens et al., 2014). However, SCDs are more commonly caused by coronary artery disease (CAD) (Isbister & Semsarian, 2019), and like CVDs, could therefore be prevented.

Although the majority of SCDs occur in older population, SCD of a young person is a shocking event for the family and society. The sudden deaths of young athletes, in particular, have received a lot of media attention and increased public concern. Among children and young adults, SCD is more often caused by hereditary myocardial diseases or arrhythmia disorders (Bagnall et al., 2016). In the vast majority of young patients, cardiac arrest is the first recognized manifestation of the underlying heart disease, although in some cases, at least some warning symptoms may have existed (Aro & Chugh, 2017).

Over the past decade, the magnitude of CAD as a cause of SCD also among younger individuals has been acknowledged (Arzamendi et al., 2011; Risgaard et al., 2014). CAD is no longer considered as a disease of the elderly population alone (Rubin & Borden, 2012), and given the increase in CVD and obesity among young people, the burden of CAD is likely to be more substantial in the future. Previously, studies of SCDs among the young have focused mainly on sports-related sudden deaths and non-ischemic causes of SCDs. In order to broaden our knowledge of CAD-related SCDs among younger population, develop risk assessment tools, and prevent unexpected deaths more efficiently in the future,

more studies on ischemic SCDs and their characteristics and temporal trends are needed.

The severity of CAD and cardiac hypertrophy increase the risk for fatal arrhythmias and sudden death, and the heart weight often increases along with the severity of CAD, i.e. the number of critically stenosed coronary arteries (Kaikkonen et al., 2009). However, some SCD victims, especially young people, have only one vessel CAD present at autopsies (Corrado et al., 1988). Therefore, it is likely that there are other influencing or contributing factors for SCD beyond the severity of the underlying heart disease. For example, the role of genetics and family history in the risk of SCD has increasingly been investigated (Bezzina et al., 2015; Faragli et al., 2016; Kaikkonen et al., 2006, 2009).

Like SCD, myocardial infarction (MI) may occur unexpectedly and with atypical or no symptoms at all (Arenja et al., 2013). According to estimates, clinically unrecognized MIs account for about half of all MIs (Kannel & Abbott, 1984; Pride et al., 2013; Sheifer et al., 2001). Myocardial scarring following MI may act as a substrate for arrhythmic events (Kwong et al., 2006) and eventually lead to SCD. The prevalence and role of unrecognized, or silent, MIs in the background of SCDs is still unclear.

The aim of this thesis was to determine the characteristics, temporal trends and autopsy findings of ischemic SCDs among young victims. Additionally, this thesis examines the genetics of cardiac hypertrophy among ischemic SCD victims with less advanced CAD, which is often present in younger victims, and the role of silent MIs in the background of CAD-related SCDs.

2   Review of the literature

2.1   Coronary artery disease

2.1.1 Disease process

Epicardial coronary arteries, starting from the base of the aorta, are located on the surface of the heart, supplying oxygen and nutrition to the heart muscle. Coronary artery disease (CAD) results from obstruction of the coronary arteries due to atherosclerosis, and significant occlusion can cause lack of oxygen (ischemia) in the heart muscle.

Atherosclerosis is a disease of the inner layer, intima, of large and medium-sized arteries, in which fibrofatty lesions develop in the arterial wall. It is mainly caused by accumulation of low-density lipoprotein (LDL) cholesterol in the intima. However, we currently understand the development as a complex phenomenon that also includes other risk factors, inflammation, and the immune system. Atherosclerosis in the coronary artery eventually leads to a constricting plaque and myocardial ischemia, especially during physical exertion. Also, sudden rupture or progressive erosion of a plaque can lead to an obstructive thrombus, even if the plaque itself does not produce a flow-limiting obstruction. These changes in the coronary arteries can lead to chest pain (angina pectoris), MI, fatal arrhythmias and (sudden) death. (Libby et al., 2019)

Traditionally, the severity of CAD and risk of cardiac events are viewed from the perspective of the number of occluded arteries and the degree of stenosis. Instead of considering CAD as a segmental or focal disease, we now understand that atherosclerosis is a diffusively distributed disease with outward or abluminally grown atherosclerotic lesions as well (Clarkson et al., 1994; Glagov et al., 1987). As a result, atherosclerosis may be present even without a significant stenosis in the coronary artery (Arnett E.N. et al., 1979).

Atherosclerosis develops with age in virtually everyone, and the disease process of CAD begins already in adolescence at the latest (Tuzcu et al., 2001). However, individual risk factors determine the rate of development.

2.1.2 Epidemiology

CAD remains a major public health problem both globally and in Finland, being one of the most common causes of death. However, in recent decades, the morbidity and mortality of working-age people has decreased dramatically due to advances in primary and secondary prevention. (Benjamin et al., 2018; Junttila et al., 2016; Nichols et al., 2013). Figure 1 represents mortality from CAD during the years 1969–2017. The North Karelia project in 1972 and 1997 dramatically reduced CAD mortality in Finland (Puska & Jaini, 2020). Favourable changes in CAD risk factors (reduction in smoking, for example) have been seen during the past decades. Also, the early detection and treatment of CAD have developed effectively. Interestingly, in Finland, CAD mortality among the working-aged population seems to be bi-seasonal, with one peak in winter and a second peak in June (Näyhä, 1981). The June peak in CAD mortality might be explained by the Finnish Midsummer festival, often associated with excessive alcohol consumption (Näyhä, 2021). There are also regional differences in Finland, morbidity and mortality due to CAD being higher in North-Eastern than in South-Western Finland (Nuotio et al., 2020). This so-called East-West divergence cannot be explained solely by the known risk factors for CAD; instead, genetic factors are suspected to play a role (Nuotio et al., 2020). Although morbidity has decreased, the ageing of the population is likely to increase the number of cases in the future. In addition, obesity and type 2 diabetes are increasing both globally and in Finland. This will be a serious challenge to social policy and health care in Finland, since as a result, favourable developments in CAD morbidity are slowing down. (Laatikainen et al., 2019).
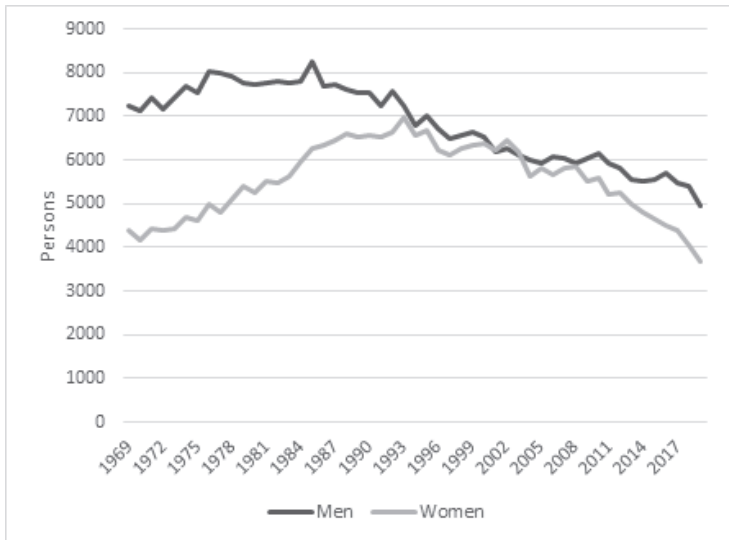
Fig. 1. Deaths caused by CAD in Finland between the years 1969 and 2017. Source: Statistics Finland.

2.1.3 Risk factors

High LDL concentration, low high-density lipoprotein (HDL) concentration, type II diabetes, high blood pressure, and smoking are risk factors for CAD that could be influenced. The magnitude of each individual risk factor, as well as the number of risk factors, influence the rate of atherosclerosis progression. Adverse lifestyle factors, such as unhealthy diet, physical inactivity, smoking and inability to maintain a healthy weight are significant risk factors for the development of atherosclerosis and CAD, as well as for the establishment of the aforementioned clinical conditions. Risk factors such as family history, genetics, age and gender cannot be influenced.

Cholesterol

At the population level, the most important health-promoting lipid levels are total plasma cholesterol below 5.0 mmol/l, LDL below 3.0 mmol/l and HDL more than 1.0 mmol/l in men and more than 1.2 mmol/l in women (Dyslipidemias: Current Care Guidelines, 2022). Elevated serum LDL cholesterol level is one of the major factors in the development of atherosclerosis, leading to lipid deposition in the

arterial wall and the initiation of an atheroma. Continued exposure leads to growth and progression of atherosclerotic plaques. (Mach et al., 2020). It has been suggested that LDL concentrations of about 0.5–0.8 mmol/l would be optimal for humans (Libby et al., 2019); however, the concentrations of blood cholesterol exceed by far the biological needs in most societies (Hopstock et al., 2017; Schreiner et al., 2016). Decreasing LDL cholesterol to very low levels (< 0.8 mmol/l) has been thought to be harmful since cholesterol has an important role, for example, in the function of cell membrane and in the biosynthesis of steroid hormones, bile acids and vitamins. However, aiming at very low LDL concentrations (< 0.8 mmol/l) seems to be safe and effective in reducing cardiovascular events (Giugliano et al., 2017). However, the net benefit and absolute risk reduction by achieving very low LDL levels depend on the cardiovascular risk at baseline and the cost-effectiveness should also be assessed. In familial hypercholesterolemia, serum LDL cholesterol levels may be markedly elevated, which can cause coronary artery stenosis already in childhood or early adulthood.

Along with lifestyle changes, the treatment of hypercholesterolemia is largely based on statins. The effect of a statin can be increased by combining it with ezetimibe. PCSK9 inhibitors are a new and highly effective drug group, but their use is limited by the high cost. It is generally agreed that lipid-lowering drugs should be administered to patients with clinical atherosclerotic CVD (secondary prevention), whereas the indications for primary prevention are somewhat controversial.

Currently, the decision on medication for primary prevention is largely based on a 10-year risk estimate of future cardiovascular disease/event using, for example, the SCORE or FINRISK calculator. However, these 10-year risk estimates do not take into account the cumulative lifetime risk of CVD, which might underestimate the remaining lifetime risk in young adults (Lloyd-Jones, 2010). A cohort study by Zhang et al. reported that greater exposure to cumulative LDL during young adulthood and middle age was associated with an increased risk of incident CAD events, suggesting that optimal LDL levels should be maintained even at younger ages (Y. Zhang et al., 2021). In addition, high non-HDL cholesterol levels have been shown to remain stable over time, suggesting that early lipid monitoring in young adults might be useful in identifying individuals at high long-term risk for CVD (Pencina et al., 2019). Pencina et al. proposed that two measurements of non-HDL between age 25 and 40 could be used to categorize individuals as high or low non-HDL for the next 25–30 years

(Pencina et al., 2019). Brunner et al. also reported that increasing concentrations of non-HDL cholesterol are associated with a higher 30-year CVD risk, especially in young individuals with a modest increase (Brunner et al., 2019).

HDL particles transport cholesterol away from atherosclerotic plaques, and low serum HDL levels has been associated with increased CVD risk. However, a causal role for low HDL on CAD risk remains unclear. Medications increasing HDL levels have not been shown to reduce atherothrombotic events in clinical trials. (Visseren et al., 2021)

Based on recent studies, plasma ceramides appear to contribute to the risk stratification of CAD (Laaksonen et al., 2016). Measuring plasma ceramide levels might be helpful in determining patient-specific risk levels to target preventive measures; however, more studies on clinical and cost-effectiveness are needed. Plasma ceramide levels can be reduced with, for example, statins and PCSK9 inhibitors. Currently, inhibitors of ceramide synthesis are the subject of drug development.

Diabetes mellitus

Diabetes is a common risk factor for atherosclerosis and CAD, increasing the risk for CAD by about a two-fold (Emerging Risk Factors Collaboration et al., 2010). Hyperglycemia accelerates the development of atherosclerosis. Diabetes and glucose abnormalities are associated with a poor prognosis in CAD patients (Lenzen et al., 2006; Ritsinger et al., 2015; Shahim et al., 2017). Thus, patients with both diabetes and CAD are considered to be at very high risk for cardiac events, and stricter targets for blood pressure and serum LDL level are recommended (Knuuti et al., 2020). The duration of diabetes has a strong effect on the risk of atherosclerotic diseases and cardiovascular mortality (Fox et al., 2004; Hu et al., 2001). The risk is already increased in those with impaired glucose tolerance or fasting glucose (Fuller et al., 1980; Haffner et al., 1999). Rawshani et al. reported that age at onset of type 1 diabetes was an important determinant of CVD, independently of diabetes duration, suggesting a need for more effective cardiovascular preventive measures in those with childhood onset diabetes (Rawshani et al., 2018). Diabetic autonomic neuropathy may underlie silent ischemia since patients with diabetes may not recognize MI (Sheifer et al., 2001). Therefore, the European Society of Cardiology (ESC) recommends resting electrocardiogram (ECG) in asymptomatic patients with diabetes to detect possible silent MIs, for example (Knuuti et al., 2020).

Hypertension

Hypertension is one of the most prevalent cardiovascular risk factors and accelerates atherogenesis through several mechanisms. For example, high blood pressure causes the smooth muscle cells of the artery wall to divide and thicken the wall, and changes in pressure and flow conditions induce endothelial dysfunction and contribute to make the atherosclerotic plaque unstable. In addition, left ventricular hypertrophy (LVH) resulting from hypertension may affect the coronary flow and increase myocardial oxygen demand, contributing to myocardial ischemia. Lowering high blood pressure can substantially reduce major cardiovascular risk and CAD (Knuuti et al., 2020).

The increasing burden of hypertension among young individuals, likely due to unhealthy lifestyle habits and obesity in Western societies, has been noted (Abrignani et al., 2019; Battistoni et al., 2015; Bendor et al., 2020). A systematic review and meta-analysis by Luo et al. concluded that young adults with high blood pressure may have a higher risk of cardiovascular events later in life (Luo et al., 2020). Arora et al. demonstrated an increase in acute MI hospitalizations attributable to young patients between 1995 and 2014 in parallel with cardiovascular risk factors, including hypertension (Arora et al., 2019).

Smoking

Long-term smoking contributes to the development of atherosclerosis in several ways. Tobacco smoke damages and increases inflammation of endothelial cells in coronary arteries, as well as increases cholesterol accumulation in the artery walls. Smoking is a strong risk factor of acute MI (Yusuf et al., 2004). The acute effects of smoking on endothelial function and thrombosis formation are quickly reversible after smoking cessation (Ding et al., 2019). Smoking cessation significantly decreases the risk of all-cause death in CAD patients (Critchley & Capewell, 2003). Smoking has been observed to be common in people with premature CAD, and has been associated with poor prognosis (Collet et al., 2019; Zeitouni et al., 2020). Especially among young individuals with CAD, the burden of smoking seems to be significant (Cole et al., 2003; Zimmerman et al., 1995). Marijuana's impact on the risk of CAD is less understood. However, cannabis smoking can cause a rise in heart rate and blood pressure in the acute setting as a result of sympathetic nervous system activation (DeFilippis et al., 2020).

Inflammation

Inflammation has been found to be a significant part of the development of atherosclerosis and destabilization of CAD; inflammation seems to have a role in the atherogenesis, may be an inciting mechanism in the acute coronary syndrome, and further injure the myocardium in MI. High-sensitivity C-reactive protein (hsCRP) and interleukin 6 (IL-6), for example, have been shown to be useful in clinical measuring of systemic inflammation and predicting cardiovascular events. (Lawler et al., 2021).

Patients with inflammatory rheumatic diseases are more likely to develop and die from CVD in comparison with the general population (Agca et al., 2017). For example, patients with rheumatoid arthritis have more than twofold risk for cardiovascular events compared with the general population, and the risk of CVD is even greater than in patients with diabetes (Agca et al., 2020; Aviña-Zubieta et al., 2008). In addition to common risk factors (obesity, dyslipidemia, hypertension, smoking, diabetes and insulin resistance, lack of exercise), chronic inflammation leads to acceleration of atherosclerosis and CAD. The European rheumatological society EULAR (European League Against Rheumatism) has made recommendations for CVD risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders (Agca et al., 2017). Active treatment of rheumatic disease with the intention of sustained remission as well as successful intervention in common cardiovascular risk factors are needed to reduce the burden of CAD.

Recently, a lot of research has been targeted at inflammation in order to prevent and treat CVDs (Ridker, 2018). Biomarkers like hsCRP and interleukin-6 can be used to identify CAD patients with so-called residual inflammatory risk who might benefit from anti-inflammatory therapies (Ridker, 2018). In the CANTOS study (Ridker et al., 2017), canakinumab, a therapeutic monoclonal antibody targeting interleukin-1 β, reduced cardiovascular events independently of lipid-level lowering in patients with a prior MI and a hsCRP level $\geqslant$ 2 mg/l. Monoclonal blockade of the interleukin-1 receptor (anakinra) and interleukin IL-6 receptor antagonist (tocilizumab) has been studied in acute coronary syndromes and on remodelling in the setting of heart failure (Abbate et al., 2013; Kleveland et al., 2016; Morton et al., 2015). In addition, colchicine in secondary prevention of atherosclerotic CVD is currently being studied in several trials (Lawler et al., 2021).

Several traditional risk factors of atherosclerosis and CAD are also involved in the activation of inflammatory pathways. Obesity with visceral adipose tissue and tobacco smoking are well known to cause systemic inflammation. Hypertension via angiotensin II can also activate inflammatory pathways. (Libby et al., 2019).

Non-modifiable risk factors

Age is a strong risk factor for CAD since coronary plaques develop slowly with age and may eventually become fragile. With age, different comorbidities such as hypercholesterolemia, hypertension and diabetes have more time to contribute to the development of atherosclerosis.

There are also gender differences in the progress of CAD since women develop CAD about ten years later than men. This has been thought to be largely explained by the different effects of sex hormones. For example, estrogens increase HDL cholesterol while androgens decrease it. These cardioprotective mechanisms of estrogens diminish in menopause. Lifestyle variations (such as smoking habits) also exist between genders, which may partly affect the gender differences. Approximately at the age of 70–79 years the differences between women and men in CAD morbidity and mortality have flattened. Previously, young women have been associated with poorer outcomes and higher mortality after MI (Cenko et al., 2018; Davis et al., 2015; Ricci et al., 2017). However, in a recent study among young Finnish patients, men were associated with poorer long-term cardiovascular outcomes after MI after baseline characteristics adjustment (Kerola et al., 2022). Similar results were observed among older (≥70 years) Finnish men with a higher long-term risk of major adverse cardiovascular events compared to women (Kerola et al., 2021). Special attention is recommended when examining women since symptoms are more likely to be atypical compared to men (Knuuti et al., 2020).

Genetics and family history (first-degree relative, number of affected relatives) are also well-known risk factors of CAD. Familial hypercholesterolemia, for instance, is a heritable disease which can lead to early and rapidly evolving atherosclerosis. Genetics may also partly explain susceptibility to risk factors such as hypertension and diabetes. The genetic risk for CAD appears to be very multifactorial, and many different genetic factors are being extensively investigated and have been associated with the risk of CAD. Genetic risk scores have been studied to improve CAD risk prediction. Genetic effects are more

significant in younger individuals and for early-onset CAD events. (Inouye et al., 2018; Schunkert et al., 2011; Tada et al., 2016; Zdravkovic et al., 2002)
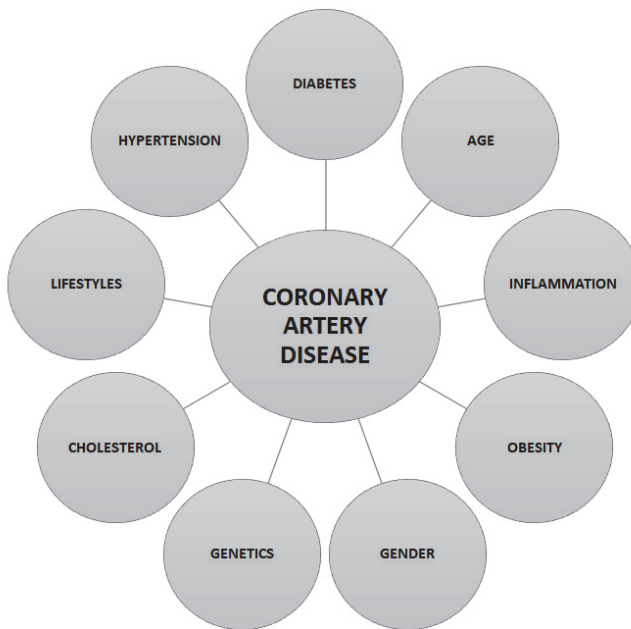
Fig. 2. Several risk factors have been associated with the development of CAD.

2.1.4 Diagnostics

Suspicion of CAD usually arises from typical symptoms of CAD (angina pectoris and/or dyspnea during physical exertion) and risk factors. Clinical evaluation, medical history and anamnesis must always precede further diagnostic testing. Resting ECG may reveal possible evidence of CAD, such as Q waves, ST-segment changes and T-inversions. After basic testing, clinical evaluation and differential diagnostics, the clinical likelihood of obstructive CAD is assessed according to, for example, characteristics of the symptoms and risk factors. Commonly applied risk charts are useful in assessing patients' overall risk of CVD. The FINRISK calculator, based on the Finnish population, calculates patient's risk of acute MI or acute disorder of cerebral circulation within the next ten years. Similarly, the ESC maintains SCORE risk tables. Information on coronary calcification can also be used to assess the risk of cardiovascular

outcomes and to guide medical therapy (Greenland et al., 2018; Knuuti et al., 2020). The presence of any coronary artery calcification in young adults has been associated with increased risk of fatal and non-fatal CAD (Carr et al., 2017). However, the clinical usefulness is limited taking into account that coronary calcium score does not detect non-calcified atherosclerotic lesion and the presence of coronary calcium is only a poor predictor of obstructive CAD (Knuuti et al., 2020). Coronary artery calcium scoring combined with machine learning of clinical variables may further improve prediction of the presence of obstructive CAD on coronary computed tomography angiography (CTA) (Al'Aref et al., 2020).

It is important to assess the clinical likelihood and pre-test probability of CAD in order to use diagnostic tests correctly. Patients are typically classified to have either low (< 15%), moderate to high (15–85%) or very high (> 85%) pre-test probability. Further studies should be performed judiciously in patients with low likelihood of CAD since the possibility of a false positive result is high. If necessary, using CTA, a negative test may rule out the disease. Similarly, in patients with very high likelihood of CAD, a negative result in non-invasive diagnostic tests does not rule out obstructive CAD and diagnosis can often be made on clinical basis. Thus, diagnostic testing is most useful in patients with moderate to high likelihood to determine whether the symptoms are due to obstructive CAD. (Knuuti et al., 2020).

Clinical exercise ECG

Traditionally, an exercise ECG has been the primary diagnostic test when an obstructive CAD is suspected. The benefits of the exercise ECG include practicality and good availability. Myocardial ischemia can be detected through ECG changes, and in addition, exercise ECG provides useful clinical information on symptoms, performance, prognosis, possible arrhythmias, blood pressure, and heart rate response to physical exertion. A few abnormalities on the resting ECG prevent interpretation of the ST segment changes during stress, e.g., left bundle branch block, LVH, paced rhythm, Wolff-Parkinson-White syndrome and $\geqslant 0.1$ mV ST-segment depression on resting ECG. However, according to the recent European guidelines (Knuuti et al., 2020), an exercise ECG is no longer recommended as an initial test to diagnose obstructive CAD. Taking into account the very limited power to rule in or rule out obstructive CAD, the usefulness of exercise ECG in diagnosing CAD appears to have limited diagnostic value

regardless of the level of pre-test probability (Knuuti et al., 2018). Nonetheless, if other imaging tests are not available, an exercise ECG may be considered as an alternative diagnostic test, keeping in mind the limitations of the test. In Finland, exercise test is still widely used due to its availability compared to other diagnostic methods.

Coronary computed tomography angiography (CTA)

CTA enables precise imaging of the anatomy of the coronary arteries using an intravenous contrast agent. CTA is increasingly being used to accurately detect obstructive coronary stenoses, mainly based on its sensitivity and reliability to rule out obstructive CAD, especially in patients low and moderate pre-test probability (Knuuti et al., 2018). One limitation of CTA is low specificity in identifying functionally significant stenoses, i.e. stenosis may be present but does not necessarily induce myocardial ischemia. Consequently, when stenosis is detected by CTA, functional testing is recommended to determine the significance of the stenosis (Knuuti et al., 2020). The identification of stenoses is hampered by excessive coronary calcification, poor image quality, rapid or irregular heart rate, and coronary stent. For example, the elderly are more likely to have non-diagnostic image quality due to possible extensive coronary calcification. Also, ionising radiation of CTA needs to be taken into account.

Functional non-invasive tests

In stress echocardiography or cardiac magnetic resonance imaging (CMRI), obstructive CAD can be diagnosed based on reversible wall motion abnormalities caused by myocardial ischemia. Single-photon emission CT, positron emission tomography, myocardial contrast echocardiography and contrast CMRI are based on ischemia-induced perfusion changes. Myocardial ischemia can also be provoked pharmacologically if physical exertion is not possible. The strength of functional non-invasive tests is high accuracy for the detection of flow-limiting coronary stenoses. On the other hand, lower-grade CAD without flow-limiting stenoses remains undetected. (Knuuti et al., 2020)

Although these diagnostic methods have good diagnostic performance, their use may be limited by availability, costs, personnel and practicality, for example. The most commonly used modalities in Finland are single-photon emission CT

and positron emission tomography (if available). Stress echocardiography and CMRI are rarely used in CAD diagnostics in Finland.

Invasive testing

Invasive coronary angiography may be used in patients with suspected CAD to confirm the diagnosis if non-invasive testing has not been sufficient or cannot be used, CAD has been previously diagnosed, patient's pre-test probability is very high, typical symptom(s) occur even during light exertion, or non-invasive assessment suggests high event risk and possible need for revascularization. In certain cases, invasive testing may include functional assessment, such as fractional flow reserve, since coronary stenoses may not always be hemodynamically relevant. Complications of the invasive procedure, e.g. bleeding, and patient suitability and possible advantages should be taken into consideration. For example, if the patient is not a candidate for revascularization or is not expected to benefit from the revascularization, i.e. functional status or quality of life is not expected to improve, ICA should not be performed.

2.1.5 Management and treatment

Management of CAD is largely based on the treatment of risk factors (see above) and the implementation of healthy lifestyle. The goal of pharmacotherapy and interventions is to improve prognosis by preventing cardiac deaths and MIs, relieve symptoms, reduce exercise-induced ischemia and improve quality of life. Efficient management of CAD requires a multidisciplinary approach and collaboration, patient information/education and encouragement of healthy lifestyle behaviours (healthy diet, physical activity, weight control). Percutaneous or surgical coronary revascularization is often needed in acute coronary syndrome or if the CAD patient continues to be symptomatic despite optimal medication, or if CAD has anatomical or functional high-risk features (such as a significant left main stenosis).

Lifestyle modifications

The majority of CAD patients have unhealthy lifestyle, with about 38% of them being obese (body mass index [BMI] $\geqslant 30$ kg/m^2) and 66% being physically inactive (Kotseva et al., 2019), necessitating a great deal of effort to modify their

habits. The benefits of weight loss are likely to influence also other risk factors, particularly hypertension and diabetes. The importance of exercise and its favorable effects on cardiovascular risk factors and cardiovascular system physiology cannot be overstated (Knuuti et al., 2020). Smoking cessation is an integral part of CAD treatment, as discussed earlier. A versatile diet containing only little saturated fat, salt, alcohol, carbohydrates and red meat, as well as high in polyunsaturated fats, fiber, fish, fruit and vegetables is recommended (Knuuti et al., 2020).

Pharmacological management

Optimal anti-ischemic medication takes into account the patient's individual profile, such as severity of symptoms, comorbidities, interactions with other drugs, and potential adverse effects. Typically, beta-adrenergic blockers or calcium channel blockers are used as the first choice for anti-ischemic and symptom-relieving medication. Beta-blockers appear to have a prognostic effect in patients with recent MI or those with chronic heart failure with reduced ejection fraction. Short-acting nitrates (sublingual or spray nitroglycerin formulations) are prescribed to majority of CAD patients for immediate relief of angina or as preventative medication before physical activity. As a second-line treatment for angina relief, long-acting nitrate formulations (e.g. isosorbide mononitrate and isosorbide dinitrate) can be used. (Knuuti et al., 2020).

A very important part of CAD treatment is to prevent coronary thrombosis via antiplatelet drugs. Low-dose aspirin should be used in all patients with CAD and previous MI or revascularization for the prevention of ischemic events and mortality. In other patients with evidence of CAD low-dose aspirin may also be used. $P2Y_{12}$ inhibitors (clopidogrel, prasugrel and ticagrelor) also prevent effectively arterial thrombus formation. However, the use of $P2Y_{12}$ inhibitors is currently limited to certain specific situations such as acute coronary syndrome (ACS), and after percutaneous coronary intervention together with aspirin (dual antiplatelet therapy) to prevent stent thromboses or recurrent ischemic events after ACS. Furthermore, adding a low-dose rivaroxaban to aspirin for long-term secondary prevention may be considered in patients at moderate to high risk for ischemic events and at low risk of bleeding. Anticoagulant therapy is recommended in CAD patients with atrial fibrillation and who are at risk for thromboembolism, and in some cases in combination with aspirin (or clopidogrel). The use of antiplatelet drugs entails balancing between the

prevention of acute coronary events and increased risk of bleeding. Therefore, the optimal combination and the duration of antiplatelet treatment should be assessed individually in each patient. (Knuuti et al., 2020)

Comorbidities also guide drug therapy in CAD patients. Treating hypertension with beta-blockers and renin-angiotensin system blockers may prevent cardiac events after an acute MI (Law et al., 2009), and beta-blockers and calcium antagonists are useful in CAD patients with symptomatic angina. New diabetes drugs like sodium-glucose co-transporter-2 and glucagon-like peptide-1 receptor agonists have been shown to reduce cardiovascular events, in addition to other beneficial effects (Brown et al., 2021).

Revascularization

The aim of revascularization is to relieve symptoms in patients with angina and/or to improve prognosis. Coronary artery revascularization is performed either by balloon dilatation and stent implantation, or in some cases, treatment with drug eluting balloon, in the area of blockage or by surgical coronary artery bypass grafting. The decision on the need and choice between percutaneous coronary intervention and bypass surgery is based on factors such as the severity, location and number of stenoses, symptoms, comorbidities such as diabetes, surgical risk, left ventricular function and possible aortic and valvular diseases. Guidelines recommend revascularization in stable disease mainly in patients who remain symptomatic despite optimal medical therapy and in whom it may improve prognosis (Knuuti et al., 2020; Neumann et al., 2019). In stable CAD with moderate or severe ischemia, initial invasive strategy did not reduce the risk of ischemic events or death compared with initial conservative strategy (D. J. Maron et al., 2020).

2.2 Sudden cardiac death

In SCD, a sudden arrest of cardiac function leads to hemodynamic collapse and eventually to death. SCD is generally defined as unexpected, natural death in the absence of non-cardiac causes, commonly within 1 hour of the onset of the symptoms or within 24 hours of the person last having been seen in a stable state of health (Isbister & Semsarian, 2019). Ventricular tachyarrhythmias (tachycardia/fibrillation) are considered to cause the majority of sudden deaths, triggered by acute coronary events, for example (Huikuri et al., 2001). SCDs are

often the first manifestation of the underlying cardiac condition; almost half of the victims have no previously diagnosed heart disease (Wellens et al., 2014). Autopsy is crucial in determining the sudden death as of cardiac origin. Determination of the cause of death that is based only on clinical data and medical records is less reliably and may skew registers and study results, for example (Basso et al., 2017; Tseng et al., 2018).

2.2.1 Epidemiology

Despite the great effort being put into attempting to prevent and treat cardiac diseases, SCD remains one of the leading causes of death in Western societies, accounting for about 15–20% of all deaths (Albert et al., 2003; Hayashi et al., 2015). It has also been estimated that about half of all cardiac deaths occur suddenly (Huikuri et al., 2001). Our more accurate understanding of the epidemiology of SCD is quite limited. Partly because of the variability between study methods and definitions, the incidence estimates of SCD vary widely among studies (Kong et al., 2011; Tseng et al., 2018). The incidence in Western societies varies between 50–100 per 100,000 while lower rates are seen in Asia (Wong et al., 2019). The estimated annual incidence of SCD in Finland is between 1 and 2 deaths per 1,000 person-years (Junttila et al., 2016), accounting for roughly 5,000–10,000 cases each year. While the overall incidence of SCD in general population is low, the highest absolute number of SCDs occur in this presumably low-risk population (Myerburg et al., 1998). As prevention and interventions of CVD have improved, the incidence of SCD has declined in recent decades, with variations depending on gender and cardiac history (Agesen et al., 2021; Shuvy et al., 2019). However, in the population from Northern Finland, the overall incidence of SCDs did not appear to have changed considerably (Junttila et al., 2016).

The majority of SCD occur among adults, with incidence increasing markedly with age (Hayashi et al., 2015; Isbister & Semsarian, 2019). This can be explained, at least in part, by the fact that atherosclerosis and CAD become more prevalent with age. However, the proportion of deaths that are sudden seems to be higher among younger population (Krahn et al., 2004). Despite the statistically uncommon event among young individuals, SCDs among the young tend to be more dramatic and reach public awareness more effectively through the news. Besides, studies among the young have focused mainly on the sudden deaths of young athletes instead of general population (Bagnall et al., 2016).

There are also disparities in the rates of SCD between men and women as well as between ethnicities. The incidence of SCD is higher among men than among women (Albert et al., 2003; Haukilahti et al., 2019). Women have been shown to be older than men at the time of SCD, and SCDs among women occur on average about ten years later than among men (Haukilahti et al., 2019; Kannel et al., 1998). The incidence and risk of SCD also appears to be higher among African Americans compared to Caucasians (Deo et al., 2018; Zhao et al., 2019), but the mechanisms underlying these racial differences are somewhat unclear. Differences in income and education between races might be a key determining factor (Zhao et al., 2019).

2.2.2 Etiology and mechanisms

Coronary artery disease is the most common underlying cause of SCD (about 70 to 75% of all SCDs), followed by non-ischemic cardiomyopathies, valvular heart diseases, primary arrhythmic syndromes, and inflammatory cardiac diseases (Hayashi et al., 2015; Isbister & Semsarian, 2019); Semsarian, 2019). Among young victims, inherited structural heart diseases and primary arrhythmogenic disorders are more prominent (Bagnall et al., 2016). The proportion of non-ischemic causes for SCD has been found to be higher among women (Haukilahti et al., 2019; Hayashi et al., 2015).

The mechanism behind cardiac arrest and SCD is mainly ventricular tachyarrhythmias, more commonly ventricular tachycardia leading to ventricular fibrillation and later to asystole (Huikuri et al., 2001). However, according to recent studies, the prevalence of pulseless electrical activity and asystole has increased (Hulleman et al., 2012; Myerburg et al., 2013), likely due to the decreasing trend of ischemic heart disease as a cause of sudden cardiac arrest (Kauppila et al., 2018). Bradyarrhythmias are also common mechanisms leading to SCD especially in patients with advanced heart disease (Huikuri et al., 2001). The onset of fatal arrhythmia requires a substrate, predisposing and triggering factors. The substrate may be a functional conduction defect or anatomical, such as myocardial fibrosis or scarring from a previous infarction (Huikuri et al., 2001). The most common predisposing factor is acute myocardial ischemia along with electrolyte disturbance, pharmacologic effects and change in autonomic nervous system function. An arrhythmia may be triggered by ventricular premature beat as a result of, for example, certain medications, structural heart

disease, alcohol intake or increased level of adrenaline that can be caused by exercise, mental stress, caffeine or tobacco.
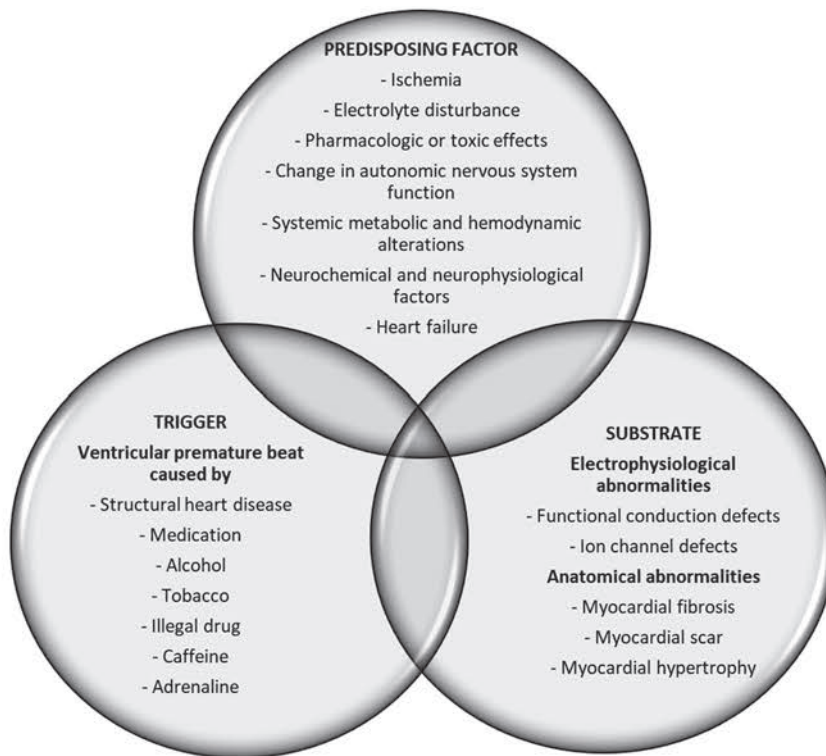
Fig. 3. Cardiac arrest is a result of a trigger for arrhythmia, a transient predisposing factor and an arrhythmia maintaining substrate.

2.2.3 Risk factors

Since CAD accounts for the majority of SCDs, the main risk factors for SCD are mostly the same as in coronary heart disease: male sex, older age, cigarette smoking, hypertension, hypercholesterolemia, diabetes mellitus, obesity, and family history (Adabag et al., 2010). In addition, obstructive sleep apnea, which is often associated with the conditions above, has been shown to increase the risk of SCD (Gami et al., 2013). Unfavourable lifestyles (such as poor diet, low physical activity, smoking) naturally increase the risk of SCD by facilitating the development of traditional cardiovascular risk factors (obesity, diabetes,

hypertension, dyslipidemia) (Chiuve et al., 2011; Obrova et al., 2022). Metabolic syndrome has also been associated with an independent increase in the risk of SCD (Kurl et al., 2016). Other risk factors include LVH, left ventricular dysfunction, poor functional status, history of heart failure, elevated heart rate, an abnormal ECG, and abnormal autonomic markers (Adabag, Luepker, et al., 2010).

Cardiac hypertrophy with varying amounts of myocardial fibrosis is a well-known risk factor for SCD, increasing the risk for fatal arrhythmias in patients with or without CAD (Ang et al., 2007; Ghali et al., 1992; Hookana et al., 2011; Manyari, 1990; Marian, 2008). LVH is a common finding at autopsies in both ischemic and non-ischemic SCD victims (Hookana et al., 2011; Kaikkonen et al., 2009). In patients with CAD, LVH is more commonly caused by hypertension; however, it is also prevalent among normotensive CAD patients (Ang et al., 2007). Other causes for LVH include aortic valve stenosis, cardiomyopathies, infiltrative myocardial diseases, physiological adaptation to exercise and obesity. Determining the cause of cardiac hypertrophy at autopsy is not entirely unequivocal and is often multifactorial. However, certain criteria can be utilized to assess the most likely cause (Hookana et al., 2011). Increased left ventricular mass may reduce the coronary flow and increase the need for oxygen, potentially resulting in ischemia and arrhythmias (Laukkanen et al., 2014).

Myocardial fibrosis is present in several myocardial diseases and also replaces injured cardiac cells, for example, after ischemia, inflammation, pressure overload and chemical exposure. The purpose of fibrotic placement is to maintain structure and function of the heart after myocyte death. However, myocardial fibrosis affects the contraction and conduction of the heart and has been associated with a poor prognosis in patients with heart failure (Assomull et al., 2006; Wu et al., 2008). Myocardial fibrosis may be a substrate for fatal arrhythmias and has been shown to predict appropriate implantable cardioverter defibrillator (ICD) therapy (Iles et al., 2011). Furthermore, myocardial fibrosis may be a better predictor of arrhythmic events than a reduced left ejection fraction (Zegard et al., 2021). While magnetic resonance imaging is widely used in clinical practice to detect myocardial fibrosis, it is not practical for large-scale population screening. Instead, standard 12-lead ECG may also reveal fibrotic accumulation in the myocardium (Holmström et al., 2020)   .

A lot of research has focused on abnormalities on a 12-lead ECG as predictors for SCD. An abnormal ECG can reveal or raise suspicion of an underlying structural or genetic heart disease, as well as primary arrhythmogenic

disorders. Inherited arrhythmia syndromes usually have typical ECG patterns with or without provocative testing. Some depolarization (pathologic Q waves, prolonged QRS duration, fragmentation of the QRS complex, LVH) and repolarization (prolongation of the QT interval, T-peak to T-end interval, early repolarization) have been shown to be associated with increased risk for SCD (Narayanan & Chugh, 2015). A single ECG abnormality, however, is unlikely to predict the SCD risk alone. That is why using multiple EGC markers instead of one could be more efficient. Such electrical risk score stratifications combining ECG risk markers have already been studied (Aro et al., 2017; Holkeri et al., 2020)   .

While traditional risk factors for SCD have been widely studied, the role of genetics and personalized risk prediction are increasingly being investigated (Faragli et al., 2016; Myerburg & Junttila, 2012) Junttila, 2012). The significance of family history for the risk of SCD is substantial (Bezzina et al., 2015; Faragli et al., 2016; Kaikkonen et al., 2006). In the future, genetic profiling will likely have an increasingly important role in the assessment of arrhythmogenic risk (Bezzina et al., 2015). Genetic variants may be disease-causing, as in genetically based disorders (long QT syndrome [LQTS], Brugada syndrome, for example), or predispose to fatal arrhythmias in complex diseases like CAD (Wellens et al., 2014). The development of genetic testing methods has led to an increasingly large amount of genetic data and variants. Risk scores could also be useful in the genetics of SCD.

Mental disorders have been linked to a higher risk of cardiovascular death, but the exact pathways and pathophysiological mechanisms remain unclear. However, in a case-control study including a consecutive series of victims of SCD, the use of psychotropic drugs, antipsychotics and antidepressants was associated with increased risk of SCD (Honkola et al., 2012). These results may provide a potential mechanism behind the association between cardiac mortality and psychiatric disorders. Among patients with stable CAD, mental stress-induced myocardial ischemia has been associated with an increased risk of adverse cardiovascular events (Vaccarino et al., 2021).

Alcohol consumption is likely to increase the risk of SCD especially in individuals with myocardial structural abnormalities that may provide an anatomic basis for the maintenance of fatal ventricular arrhythmias. However, there is no clear evidence of the causality between alcohol intake and SCD. It is well known that alcoholic cardiomyopathy can develop as a result of chronic heavy drinking (Mirijello et al., 2017). However, according to some studies, light-

to-moderate alcohol use may increase cardiovascular health, reduce the risk for SCD, increase blood HDL cholesterol levels, and decrease blood LDL cholesterol levels and the risk for thrombosis (Cooper et al., 2000; Klatsky, 2009; Klatsky et al., 2005; Suzuki et al., 2009). However, these studies may overestimate the protective effects because of selection bias (Naimi et al., 2017). In addition, the protective effects disappear in heavy drinkers, partly due to the harmful increase in blood pressure levels (Foerster et al., 2009). Recently, elevated blood alcohol levels have been observed in both ischemic and non-ischemic SCD victims in autopsy studies (Kauppila et al., 2021; Perkiömäki et al., 2016). Along with the long-term effects of alcohol on myocardial remodelling and increasing the vulnerability to fatal arrhythmias, acute alcohol intake is thought to have an effect on cardiomyocyte electrophysiology, which could increase the risk for SCD (Sutanto et al., 2020). In addition, tachycardia-induced ischemia, electrolyte disturbances and metabolic alterations may have a role in the arrhythmogenesis.

2.2.4 Risk prediction and prevention

Despite the rather widely studied SCD risk factors and stratifications, our ability to recognize individuals at high risk of dying suddenly remains severely limited (Wellens et al., 2014) because of the phenomenon known as SCD paradox. It is well known that individuals with severe heart disease and multiple risk factors are at high risk for sudden death; however, the majority of SCDs occur in lower-risk population (Myerburg et al., 1998). Progress has been made in population profiling of SCD risk among high-risk subgroups; however, individuals with risk factors without known disease and low risk subgroups account for a large proportion of the SCD burden. Most SCD victims do not have a low ejection fraction (Stecker et al., 2006), and not all patients with a low ejection fraction are at high risk for SCD (Buxton et al., 2007; Goldenberg et al., 2008). The challenge in the future is to identify individuals at high risk among these assumed low risk populations and assess individual risk more accurately.

Instead of risk profiling individuals based on a single risk marker, the risk assessment should be viewed from a multifactorial and dynamic perspective. Generally, different risk factors are considered as static rather than dynamic variables (Goldberger et al., 2011; Myerburg et al., 2009). For example, the risk of SCD is highest in the first 30 days after MI and declines over time after the infarction (Solomon et al., 2005). Also, the risk of sudden death has been shown to vary regarding to the time of the day, day of the week, and season of the year

(Arntz et al., 2000). For example, there seems to be an association between cold spells and SCD, particularly in ischemic SCDs (Ryti et al., 2017). SCD can be due to several different pathophysiological events such as plaque rupture, change in repolarization caused by electrolyte shifts or autonomic inputs, and each of these events may be associated with different risk factors, making the risk stratification for SCD extremely challenging (Goldenberg et al., 2008).

Artificial intelligence (AI) and machine learning provide a promising and interesting tool for predicting SCDs in the future. Machine learning could identify, for example, potential novel risk markers for sudden arrhythmic death on the ECG or other clinical features and detect patients at significant risk from a large population of patients. By analysing a large number of variables at once, machine learning may uncover previously unknown associations which would not otherwise be noticed by clinicians. For example, AI has been used to detect HCM and DCM based on ECG (Ko et al., 2020; Shrivastava et al., 2021) and to demonstrate various meteorological and chronological variables associated with the incidence of out-of-hospital cardiac arrest (Nakashima et al., 2021). Very large data sets are often needed for AI to perform successfully, making research challenging.

Preventing the development of the underlying cardiac disease is the most effective strategy to prevent SCD. Since CAD is the number one predisposing condition to SCD, a great proportion of prevention strategies should focus on primary and secondary prevention of CAD. These include optimization of blood pressure, cholesterol, glucose, weight, smoking, diet and physical activity, pharmacologic intervention and revascularization (Morin et al., 2017). Secondary prevention strategies for SCD apply to patients with prior cardiac arrest or sustained ventricular tachyarrhythmia. ICDs are effective in the treatment of potentially life-threatening ventricular arrhythmias; however, selection of patients who benefit from ICD therapy remains challenging. Currently, the selection of patients for primary prophylactic ICD implantation is mainly based on either ischemic or non-ischemic patients with impaired left ventricular ejection fraction ($\leq$ 35%) with symptoms in New York Heart Association (NYHA) functional class II–III despite $\geq$ 3 months of optimal medical treatment, and the patient is expected to survive longer than one year with good functional status. (McDonagh et al., 2021). Secondary prevention with an ICD is recommended in patients who have had a ventricular arrhythmia causing hemodynamic instability in the absence of reversible causes, and who are expected to survive longer than one year with good functional status (McDonagh et al., 2021). More precise criteria are

presented in the ESC guidelines (McDonagh et al., 2021). There is a need for better identification of those who would benefit from ICD implantation. For example, traditional ECG variables together with other risk variables could be used for more accurate patient selection (Pelli et al., 2020, 2021).

2.2.5 Coronary artery disease and sudden cardiac death

Although the proportion of SCDs caused by CAD has decreased in recent decades (Junttila et al., 2016), CAD still accounts for the majority of SCDs, especially in Western societies. It is noteworthy that about two thirds of all SCDs caused by CAD occur either as a first clinical manifestation of the underlying disease or in subjects who have been diagnosed with CAD but are considered low risk (Myerburg, 2001)   .

The conventional risk factors for atherogenesis and CAD are widely studied; however, broad population profiling does not seem to be useful in individual SCD risk prediction due to low absolute event rates (Myerburg & Junttila, 2012) Junttila, 2012). Currently, the most common risk prediction strategies used on individual subjects are clinical markers of the extent of underlying coronary atherosclerosis, myocardial injury, ejection fraction and heart failure. A variety of non-invasive risk markers such as clinical characteristics (e.g. clinical heart failure), electrophysiological markers (e.g. QRS duration) and autonomic markers (e.g. heart rate variability) have been studied to improve the power for identifying individual risk, but none of these indicators has emerged as a clinically dominant method (Myerburg & Junttila, 2012).

SCD occurs in CAD patients typically (1) during or after acute MI, (2) provoked by ischemia, and (3) in the presence of myocardial structural alterations like fibrosis/scar. Some, but not all, of the patients with CAD have plaque rupture with or without associated thrombosis and/or MI at the time of SCD. The mechanism for SCD is most commonly polymorphic ventricular tachycardia/fibrillation triggered by acute ischemia or infarction, for example, and monomorphic ventricular tachycardia degenerating into ventricular fibrillation resulting from myocardial scar. (Hayashi et al., 2015).

To date, it is understood that acute coronary syndromes and SCDs are often due to dynamic variations in the vascular pathophysiology. Disease severity is still an important factor in SCD; however, plaque characteristics and their alteration by inflammation, plaque fracturing, and fissuring lead to a complex pathophysiology of transient events that cause sudden cardiac arrest. Also,

myocardial pathophysiology may be dynamic, resulting from transient ischemic changes, for example (Myerburg & Junttila, 2012).

Silent myocardial infarction

Despite the decrease in mortality due to advances in the treatment of CAD (Ibanez et al., 2018), two groups of acute MI patients seldom benefit from this progress: patients in whom acute MI results in SCD and patients with silent MI (Arenja et al., 2013). MI with atypical, milder or no symptoms at all are characterized as unrecognized or silent (SMI).

It has been estimated that about one half of all MIs are clinically unrecognized (Kannel & Abbott, 1984; Pride et al., 2013; Sheifer et al., 2001). Myocardial scarring acts as a substrate for fatal ventricular arrhythmias and the extent of the scar has been shown to be a strong predictor of cardiac events (Kwong et al., 2006). The prognosis of patients with SMI is comparable to or even worse than of patients with a recognized MI (Kwong et al., 2006; Pride et al., 2013; Valensi et al., 2011). Acharya et al. reported that patients with SMI detected by CMRI had higher risk of all-cause mortality, nonfatal MI and heart failure (Acharya et al., 2018). Also in the ARIC study, SMI detected by ECG was shown to be a risk factor for heart failure (Qureshi et al., 2018). The early recognition of SMIs is critical for initiating secondary prevention measures, and these patients are also likely to be more motivated to change their possible harmful behaviours, such as quit smoking. ECG abnormalities like pathological Q waves, fragmented QRS complexes (fQRS), prolonged QRS duration and inverted T waves have been shown to determine the presence of myocardial scarring (Aro et al., 2011; Das et al., 2006, 2010; Michael et al., 2007; Teodorescu et al., 2011). However, Q waves detected in the asymptomatic general population seem to overestimate the actual SMI prevalence and therefore need to be confirmed by imaging tests, whereas among individuals with greater risk of CVD, the positive predictive value is higher (Ramos et al., 2016). The current knowledge of the prevalence and association between SMI and SCD is limited.

Prevention of ischemic sudden cardiac deaths

Primary prevention of SCD in patients with CAD is based on risk stratification and pharmacologic/lifestyle intervention, revascularization and ICD therapy. As in the management of CAD, optimization of blood pressure, cholesterol, glucose,

weight, smoking, diet, and physical activity through lifestyle interventions should be the focus of primary prevention of ischemic SCDs. Pharmacological interventions including β -blockers, angiotensin-converting enzyme inhibitors, and statins reduce the risk of SCD in patients with impaired left ventricular function and CAD. However, according to prospective, randomised trials, antiarrhythmic agents for the suppression of ventricular arrhythmias seem to have a neutral or negative impact on mortality. In selected populations, including patients with impaired ventricular function, ICD has been shown to reduce SCD and improve total mortality. Secondary prevention of SCD comprises interventions in patients who have survived a previous cardiac arrest or prolonged ventricular tachyarrhythmia. In such patients, ICD has demonstrated to be superior to antiarrhythmic drug therapies. (Estes, 2011).

2.3   Sudden cardiac deaths among the young

Death is inevitable, and what better way to die than suddenly. This statement is applicable to the elderly, but sudden death in a young person not only is a tragedy for the victim but also has a devastating effect on parents, spouses, and the victim's children. (Marcus & Chugh, 2011).

Although rather infrequent in the young, SCDs in this apparently healthy population have substantial socioeconomic implications due to loss of life years. The definition of "young" varies between different studies. In this thesis, the term "young" is defined as population under 50 years of age.

2.3.1 Epidemiology and etiology

The prevalence of SCD among the young is age-dependent. The first spike in the prevalence of SCD occurs in early infancy (mostly because of sudden infant death syndrome). In early childhood the prevalence comes down and begins to rise again in adolescence. (Ackerman et al., 2016). The incidence rate varies between 0.93 and 8.6 per 100,000 persons depending on the age cut-off and study methods determining the cause of death (Ackerman et al., 2016; Zachariasardóttir et al., 2017).

    Gender differences can also be seen among the young SCD population. SCD is shown to be more prevalent in young males (Meyer et al., 2012; Pilmer et al., 2014; Winkel et al., 2014). More research is needed to determine whether there

are differences between ethnicities in the incidence of SCD. Certain subgroups, such as those with neurological or mental illnesses, may have a greater incidence of SCDs (Holst et al., 2013; Mellor et al., 2014; Risgaard et al., 2015).

The etiology of SCD in young individuals differs slightly from the older population. Among young population, SCDs are more often caused by structural heart disease like HCM or primary arrhythmogenic disorders like LQTS (Bagnall et al., 2016). However, studies have shown that CAD is also the most common cause of SCD in victims under 40–50 years of age (Arzamendi et al., 2011; Risgaard et al., 2014). After the age of 25 years, CAD becomes the major cause of out-of-hospital cardiac arrest in young adults (Meyer et al., 2012; Waldmann et al., 2019).

Coronary artery disease

In general, coronary heart disease is thought to be primarily a disease of the elderly, and therefore, it is not as well characterized in young individuals. It is generally accepted that development of atherosclerosis and CAD begins already in adolescence at the latest.

The magnitude of CAD as cause for SCD in younger population has also been recognized (Corrado et al., 1988; Rubin & Borden, 2012). In a Canadian study consisting of 97 victims under 40 years of age, CAD was the main cause of SCD from the age of 20 years (Arzamendi et al., 2011). Similar results have been observed in a Danish study among victims under 50 years of age (n=439) (Risgaard et al., 2014). Bagnall et al. reported unexplained SCD being the predominant finding in Australian and New Zealand population among victims under 35 years of age, followed by CAD (n=490) (Bagnall et al., 2016).

Ischemic SCDs, compared to other causes for SCD, among young population have been associated with older age, higher BMI, higher rate of smoking habit, hypertension, hypercholesterolemia and family history of CAD (Arzamendi et al., 2011). Also, an association between non-atherosclerotic coronary disease and myocardial ischemia and SCD has been observed, especially in younger population and male patients (Hill & Sheppard, 2010). Non-atherosclerotic coronary diseases include spontaneous dissection of coronary artery, coronary artery vasculitis, anomalous coronary arteries and coronary artery spasm.

It has been shown that young persons who experienced CAD-SCD had cardiac symptoms such as angina pectoris (62%) and dyspnea during the last year before death, and almost half of them had contacted the healthcare system

(Jabbari et al., 2013). Physicians often struggle to identify the individuals at high risk of MI, given the low chance that chest pain is caused by acute coronary syndrome in persons aged under 40 years.

Cardiomyopathies

Heritable cardiomyopathies include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and left ventricular non-compaction cardiomyopathy (LVNC). HCM is a heterogeneous monogenic heart disease, classified as non-dilated LVH in the absence of any other cardiac or systemic disease that could produce the extent of wall thickening in evidence (Maron & Maron, 2013). Among children and young adults (age < 30 years) HCM is the most common underlying cause for SCD. DCM is defined as left ventricular dilatation and left ventricular systolic dysfunction with an associated increase in mass and volume, without abnormal loading conditions like hypertension or valvular diseases (Jefferies & Towbin, 2010). ARVC is a heritable myocardial disease affecting mainly the right ventricle, characterized as loss of myocytes and replacement by fibrofatty tissue (Corrado et al., 2017). In LVNC, prominent left ventricular trabeculae impair the contractility of the myocardium (Arbustini et al., 2016).

Myocarditis

Myocarditis is more commonly due to viral infections, whereas bacteria, fungi and sarcoidosis are less frequent causes. Fatal arrhythmias in acute phase are due to myocardial inflammation resulting in ion channel dysfunction and alteration of intracellular signalling. Myocardial scarring and fibrosis caused by prior myocarditis may predispose to re-entrant ventricular arrhythmias. Myocarditis is a significant cause for SCDs especially among younger victims and young athletes, accounting for approximately 10% of deaths, depending on the study population and methods/classifications used. Men appear to be at higher risk of developing fatal myocarditis. (Ali-Ahmed et al., 2020; Kytö et al., 2007; Lynge, Nielsen, Gregers Winkel, et al., 2019)

Primary arrhythmogenic disorders

Primary arrhythmogenic disorders, also called channelopathies, include LQTS, short QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia. These disorders are difficult to identify since structural changes are rarely present and postmortem autopsies are "negative". The incidence of SCDs among the young may actually be underestimated since it is possible that primary arrhythmogenic disorders can predispose to events such as road accidents and drownings. (Semsarian et al., 2015).

Congenital coronary artery anomalies (CCAA)

Coronary anomalies are relatively uncommon and usually detected incidentally during coronary angiography or postmortem autopsy. The majority of CCAAs are considered as benign with no hemodynamic or prognostic implications. However, malignant lesions may predispose to fatal complications, such as MI and SCD. Especially among young, competitive athletes, the relevance of CCAAs has been acknowledged, being the second most common cause of SCD (Angelini et al., 2002; Hill & Sheppard, 2014).

2.3.2 Screening and prevention SCDs among young people

The most reliable symptom that predicts high risk for SCD is a prior aborted or resuscitated sudden cardiac arrest. A significant proportion of ICD implantations in young patients are due to previous sudden cardiac arrest or prolonged ventricular arrhythmia. Other symptoms associated with the risk of SCD include chest pain, palpitations, seizure and syncope, especially during physical exertion. However, such symptoms are unspecific since they may occur in healthy children as well. (Ackerman et al., 2016). Skjelbred et al. also found that, for example, most young SCD-CAD victims are symptomatic, with chest pain as the most prevalent single symptom (Skjelbred et al., 2021).

Screening could be effective in individuals with a family history of hereditary cardiac disease or SCD, providing a more focused and widely accepted way compared to systematic screening directed at the general population (Aro & Chugh, 2017; Ranthe et al., 2013). This often requires that the deceased have undergone appropriate post-mortem examinations with autopsy and genetic investigations (Bagnall et al., 2016; Sanchez et al., 2016).

Screening of asymptomatic individuals has been proposed as a strategy to reduce the incidence of SCD in young people. However, due to a lack of evidence, screening of young asymptomatic non-athletes is not currently supported by guidelines. More research is needed to assess the cost-effectiveness of different screening programs. However, in European guidelines, pre-participation screening in athletes is recommended with clinical evaluation, personal or family history taking and a baseline 12-lead ECG. (Priori et al., 2015).

SCD of a young person during sports is a devastating event and causes public concern. The absolute rate of SCD in sports, however, remains rather low. The exact frequency of SCD in young athletes is unknown, incidence rates varying from 1 per 917,000 to 1 per 3,000 depending on the population observed. Currently, the effectiveness of pre-participation screening in lowering the rate of SCDs in young athletes is yet to be shown. The pre-participation screening has a poor detection rate and the effectiveness of the management of the diseases identified in asymptomatic people is uncertain. In addition, the harms of pre-participation screening should not be ignored. Additional cardiovascular testing and false positive test results may cause psychological harm, avoidance of exercise and unnecessary restrictions from competitive sports and employment opportunities, for example. Most people with Wolff-Parkinson-White syndrome or HCM, for example, live normal lives even if the disease has not been detected. (van Brabandt et al., 2016). The study by Malhotra et al. showed that six of the eight SCDs among young soccer players occurred in athletes who had completely normal results on cardiovascular screening (Malhotra et al., 2018).

In most sports-related SCDs, symptoms like syncope, chest pain, dyspnea, dizziness, and palpitations seem to be present prior to death. Therefore, raising awareness of the symptoms among athletes has been proposed in order to identify individuals at risk of sports-related SCDs. (Stormholt et al., 2021).

Wider dissemination of bystander-initiated cardiopulmonary resuscitation and development of public-access defibrillator programmes are likely to improve survival and outcomes of cardiac arrest among the young (Bardai et al., 2011; Chugh, 2011; Iwami et al., 2015). The presence of automated external defibrillators has a significant influence on survival after sudden cardiac arrest in sport centres (Aschieri et al., 2018).

3   Purpose of the present study

The overall aim of the present study was to increase the knowledge of CAD-related SCDs, especially among young and middle-aged population and victims without a previously observed CAD, by studying the characteristics, autopsy findings, ECG abnormalities and genetics of the victims. The specific aims of the study were:

1. To determine the prevalence of SMI among ischemic SCD victims without a previously diagnosed CAD and to detect ECG abnormalities associated with SMI-related SCD.
2. To describe the characteristics and autopsy findings of ischemic SCDs among young and middle-aged victims under the age of 50 years.
3. To investigate the genetic basis of myocardial hypertrophy in ischemic SCD victims with less advanced CAD and without a prior diagnosis of CAD.
4. To study the temporal trends in the incidence and characteristics of SCD in young patients during the last twenty years.

4 Material and methods

4.1 Study population

The study population was derived from the Finnish study of Genotype and Phenotype Characteristics of Sudden Cardiac Death (Fingesture), consisting of consecutive victims of SCD in Northern Finland between 1998 and 2017. All cases were autopsy verified. Postmortem examinations were performed by experienced forensic pathologists (each performing more than 100 autopsies per year) at the Department of Forensic Medicine of the University of Oulu and National Institute for Health and Welfare in Oulu, Finland. In Finland, medicolegal autopsy is mandatory if the death is not due to a known disease, the deceased had not been treated by a physician during his/her last illness, or when the death was otherwise unexpected (Act on the Inquest into the Cause of Death, 459/1973, 7th paragraph: Finnish Law). Due to this legislation and guidelines, Finland has the one of the highest autopsy rates in Western societies and the quality of postmortem investigations is set at a high standard (Lahti, 2005; Saukko, 1995). The Fingesture study includes only sudden deaths considered to be of cardiac origin; victims with evidence of non-cardiac cause (such as pulmonary embolism or cerebral haemorrhage) were excluded from the study. Sudden death was defined as either witnessed death within 6 hours of the onset of symptoms or as unwitnessed death within 24 hours of the time the deceased individual was last seen in a good state of health.

The determination of the cause of death was determined by a forensic pathologist and was based on autopsy data, available medical records and medication, questionnaires to closest family members, and police reports at the scene where the sudden death victim was found dead. Medicolegal autopsies were performed according to standard protocols and histologic examination was part of all autopsies. If autopsy findings were insufficient to define a cause of death or if a toxic exposure was suspected, toxicology investigation was performed. Toxicological samples are screened and quantified for legal and illegal drugs, as well as poisonous substances (Launiainen & Ojanperä, 2014). Specialised pathologist was consulted if necessary. The underlying cause of death was reported according to the International Classification of Diseases, Tenth Revision code classifications (ICD-10). The medicolegal autopsy procedures included thorough cardiac investigations, i.e. macroscopic investigation and dissection of

the myocardium and coronary arteries, heart weight measurement, and several histological samples.

SCD was classified as ischemic if there was evidence of an acute coronary complication, defined as an acute intracoronary thrombus, plaque rupture or erosion, intraplaque hemorrhage or critical stenosis (>75%) in major coronary artery or chronic atherosclerotic lesions with healed scar or fibrosis. If no evidence of CAD was detected, SCD was determined as non-ischemic. The classification of non-ischemic causes and detailed diagnostic criteria have been reported earlier (Hookana et al., 2011).

In Study II, we acquired the information on the victims' previous smoking status and possible family history of SCD through letters sent afterwards to the victims' closest relatives.

The study complies with the Declaration of Helsinki and was approved by the Ethics Committee of Northern Ostrobothnia Hospital District. The Finnish National Institute for Health and Welfare and the Regional State Administrative Agency of Northern Finland approved the review of medicolegal death investigation data. The Ethics Committee decided to waive the consent from relatives since medicolegal autopsy does not require consent according to the Finnish law.

4.2   ECG measurements

All standard 12-lead ECGs were recorded at a calibration of 1 mV/10 mm and a paper speed of 50 mm/s with the subject resting in supine position. If multiple ECG recordings were available, we used the most recent one. ECGs were analysed by two independent researchers who were blinded to the cause of death. The ECG abnormalities were divided into three categories: anterior (V1-V3), lateral (I, aVL, or V4-V6), and inferior (II, III, or aVF). Fragmented QRS was determined by at least one additional R wave or notching of R or S wave meeting the criteria that have been set previously (Das et al., 2006). QRS duration was measured as the mean duration from all leads and was considered as prolonged if it was $\geq$ 110 ms. Pathologic Q waves were defined as Q waves $\geq$ 30 ms and $\geq$ 0.1 mV deep in at least two contiguous leads. Inverted T waves were defined as T-wave amplitude $\leq$ -0.1 mV in at least 2 contiguous leads.

4.3 DNA Sequencing

For the genetic studies, DNA was isolated from formalin-fixed paraffin-embedded tissue samples taken at autopsy. The TruSight Cardio gene panel kit was used for library preparation. The gene panel kit comprised 174 genes with associations with inherited cardiac conditions most affected by a genetic predisposition (http://support.illumina.com/downloads/trusight-cardio-product-files.html) (Illumina, San Diego, CA. The samples were bead purified with Agencourt AMPure XP beads (Beckman Coulter Life Sciences, Indianapolis, IN).

   The quality of the samples selected for NGS was confirmed with quantitative polymerase chain reaction-based formalin-fixed paraffin-embedded quality control kit (Illumina), and the samples passing quality control (i.e., with a quantitative polymerase chain reaction $\triangle$ Cq value $\leqslant 2.3$) were selected for gene panel sequencing with NextSeq550 platform (Illumina). Within the BaseSpace Genomics computing environment (Illumina), BWA Enrichment (BWA Genome Aligner Software and the GATK Variant Caller) was used for sequence alignment and variant calling; VariantStudio for annotation, filtering, and classification of the variants; and Integrative Genomics Viewer for data visualization to exclude falsely annotated variants and sequencing artefacts. The *in silico* prediction tools PolyPhen and SIFT were used to predict the effect of amino acid alterations on protein function within BaseSpace. The data from the DNA sequencing was deposited in the European Variation Archive.

4.4 Variant analysis

For variant analysis, we selected all variants with a possible effect on protein (missense, frameshift, stop gained/lost, initiator codon, in-frame insertion, in-frame deletion, and splice-site alterations). These variants were further filtered according to their prevalence in dbSNP or Exome Aggregation Consortium database by excluding variants which had minor allele frequency (MAF) of more than 0.01 among Finnish control subjects. Pathogenicity of the variants was assessed based on consensus guidelines by the American College of Medical Genetics (ACMG) (Richards et al., 2015). Variants considered as benign were excluded from the study and variants classified as non-benign were further classified as pathogenic/likely pathogenic or as variants of uncertain significance (VUS), based upon the ACMG guidelines by combining data from previous literature, Human Gene Mutation Database (HGMD), ClinVar database, *in silico*

prediction tools (SIFT, PolyPhen) and population frequency databases (gnomAD, The Sequencing Initiative Suomi (SISu)).

4.5   Statistical analysis

All necessary analyses were performed with the Statistical Package for Social Studies version 24.0 (IBM). Continuous variables were demonstrated as mean standard ± deviation (SD). Two-sided t tests for contiguous variables and χ2 tests for categorical variables were used to compare study groups. P-values less than 0.05 were considered statistically significant and all p-values were 2-sided. In Study III, statistical significance, odds ratios (OR) and 95% confidence intervals (CI) were estimated using χ2 tests with two-sided p-value (Fisher's Exact Test if a specific variant was detected in multiple study subjects). As a control group, we used the SISu database including data on genetic variants from 10,490 exome sequenced Finnish citizens. For incidence calculations in Study IV, we used the reference population in the geographical area of Northern Finland (Statistics Finland, www.stat.fi) for every 5-year period, and χ2 test was used to compare incidence rates between the first and last study period.

5   Results

5.1   Association of silent myocardial infarction and sudden cardiac death (Study I)

In Study I, the aim was to study the prevalence of SMI scars in individuals who experienced SCD without a previously diagnosed CAD and to identify possible ECG abnormalities related to SMI-associated CAD. The study population was derived from the Fingesture study. A total of 4,392 victims (74.8%) of the Fingesture study population had CAD as a cause of SCD and 3,122 victims (71.1%) had no diagnosis of CAD prior to death. We excluded 244 individuals (5.6%) who had no information available on whether they had been diagnosed with CAD prior to SCD. Also, two individuals were excluded due to insufficient autopsy data. At autopsies, 42.4% of the patients (1,322 victims) without a previously diagnosed CAD (3,122 victims) had a myocardial scar consistent with an SMI. In the present study, we compared autopsy findings, clinical characteristics, and ECG markers associated with SMI between ischemic SCD victims with and without evidence of SMI. Figure 4 represents the study design.

5.1.1 Clinical features and conditions of death

The victims with SMI were more commonly male (83.4% vs 75.5%, p<0.001) and were slightly older (67 ± 11 years vs 66 ± 12 years, p < 0.001) in comparison with victims without SMI. Victims with SMI also had greater mean heart weight in both men and women, had more commonly LVH, and had greater heart weight-to-body surface area ratio. No difference between study groups was detected in the prevalence of prior hypertension, diabetes mellitus, dyslipidemia, angina pectoris or exercise dyspnea. Victims in the SMI group experienced SCD more frequently during physical activity (18.2% vs 12.4%, p<0.001) and outdoors (20.0% vs 14.9%, p = 0.001). However, in the non-SMI group, SCDs in the sauna were more common (4.3% vs 1.6%, p = 0.032). Most SCDs in both study groups took place during daytime, between noon and 6 PM. Table 1 shows the characteristics of those with and without SMI.
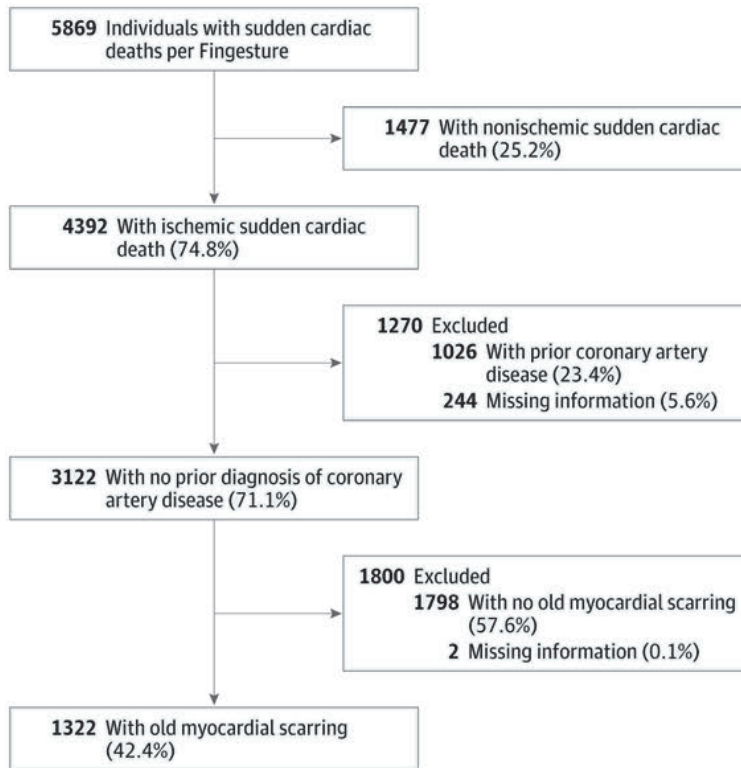
Fig. 4. Study population derivation from the Fingesture study. Reused with permission of the publisher (American Medical Association) from the original article.

Table 1. Clinical characteristics, autopsy findings and conditions of SCD in victims without a history of coronary artery disease. Reused with permission of the publisher (American Medical Association) from the original article.

Characteristic	Victims with SMI, n=1322	Victims without SMI, n=1798	P value
Age, years	66.91 ± 11.1	65.52 ± 11.6	0.001
≥50 years	1244 (94.1)	1646 (91.5)	0.081
Male	1102 (83.4)	1357 (75.5)	<0.001
BMI, kg/m^2	26.92 ± 5.07	26.68 ± 5.61	0.223
<20	87 (6.6)	196 (10.9)	0.001
20.00-24.9	395 (29.9)	517 (28.8)	0.645
25.0-29.9	525 (39.7)	641 (35.7)	0.027
≥30	315 (23.8)	444 (24.7)	0.205
Total heart weight, grams	482.9 ± 108.6	437.8 ± 105.9	<0.001
Men	497.2 ± 107.0	454.7 ± 105.0	<0.001
Women	411.3 ± 85.69	386.1 ± 91.24	0.001
LVH	938 (71.0)	965 (53.7)	<0.001
Heart weight / BSA	251.6 ± 43.6	230.4 ± 41.1	<0.001
Total occlusion of coronary artery	519 (39.3)	291 (16.2)	<0.001
Diabetes mellitus	249 (18.8)	312 (17.4)	0.071
Hypertension	523 (39.6)	688 (38.3)	0.682
Angina	81 (6.1)	104 (5.8)	0.719
Dyslipidemia	149 (11.3)	200 (11.1)	0.919
Dyspnea	45 (3.4)	53 (2.9)	0.482
Heart failure	95 (7.2)	88 (4.9)	0.065
Circumstances at death			
Unwitnessed; dead on initial contact	1104 (83.5)	1551 (86.3)	0.176
During physical activity	241 (18.2)	223 (12.4)	<0.001
In hospital, health centre or ambulance	84 (6.4)	125 (7.0)	0.548
Outdoors	265 (20.0)	268 (14.9)	0.001
Sauna	21 (1.6)	78 (4.3)	0.032
Time of death	n=824	n=908	
12 AM–6 AM	149 (18.1)	193 (21.3)	0.103
6 AM–12 PM	248 (30.1)	251 (27.6)	0.265
12 PM–6 PM	279 (33.9)	279 (30.7)	0.165
6 PM–12 AM	148 (18.0)	185 (20.4)	0.222

Values are expressed as mean ± SD or number of subjects (per cent). BMI = body mass index; BSA = body surface area, SMI = silent myocardial infarction; LVH = left ventricular hypertrophy.

5.1.2 ECG analyses

ECGs recorded prior to SCD were available in 187 victims with SMI and 251 victims without SMI (a total of 438 ECGs). Inverted T-waves (16.6% vs 8.4%, p = 0.011) and pathologic Q waves (12.8% vs 6.8%, p = 0.045) were more commonly found in the SMI group compared to the non-SMI group. Fragmented QRS complex in at least 2 contiguous leads was a common finding in both groups. The prevalence was somewhat higher in the SMI group than in the non-SMI group; however, the difference was not statistically significant (54.5% vs 45.8%, p = 0.082). There was no significant difference in mean QRS duration (99 ± 19 ms vs 97 ± 18 ms, p = 0.277) or in the prevalence of prolonged QRS duration ⩾ 110 ms between the groups (18.2% in the SMI group and 14.3% in the non-SMI group, p = 0.294). Abnormal ECG (at least one of the following: T-wave inversion, Q wave, fQRS, QRS ⩾ 110 ms) was detected in 66.8% of victims with SMI and in 55.4% of victims without SMI, respectively (p = 0.018). ECG abnormalities in relation to SMI are presented in Table 2.

Table 2. Potential electrocardiographic markers of SMI among victims of SCD without a history of coronary artery disease. Reused with permission of the publisher (American Medical Association) from the original article.

Variable	Victims with SMI, n=187	Victims without SMI, n=251	P value
Fragmented QRS complex	102 (54.5)	115 (45.8)	0.082
Anterior	34 (18.2)	38 (15.1)	0.435
Inferior	85 (45.5)	94 (37.5)	0.096
Lateral	36 (19.3)	51 (20.3)	0.810
Q wave	24 (12.8)	17 (6.8)	0.045
Anterior	10 (5.3)	5 (2.0)	0.066
Inferior	14 (7.5)	10 (4.0)	0.138
Lateral	2 (1.1)	5 (2.0)	0.704
Inverted T-wave	31 (16.6)	21 (8.4)	0.011
Anterior	3 (1.6)	7 (2.8)	0.527
Inferior	13 (7.0)	5 (2.0)	0.013
Lateral	22 (11.8)	14 (5.6)	0.023
QRS, ms	98.6 ± 19.0	96.7 ± 18.3	0.277
≥110 ms	34 (18.2)	36 (14.3)	0.294
Any ECG abnormality	125 (66.8)	139 (55.4)	0.018

Values are expressed as mean ± SD or number of subjects (per cent). SMI = silent myocardial infarction; ECG = electrocardiogram.

5.2 Coronary artery disease as the cause of sudden cardiac death among victims < 50 years of age (Study II)

The Fingesture study consisted of a total of 610 victims (10.4%) aged under 50 years and the majority of them were male (86.4%, 527 victims). SCD was most often due to CAD in 43.6% of the victims (266 victims). Other underlying causes included cardiomyopathy related to obesity (16.7%, 102 victims), alcoholic cardiomyopathy (11.0%, 67 victims) and primary myocardial fibrosis (PMF) (10.3%, 63 victims). Inflammatory cardiac disease was found in 19 victims (3.1%), whereas both HCM and DCM were the underlying cause for SCD in 12 victims (2.0%) Figure 5 represents distribution of the causes of SCD among the study victims.
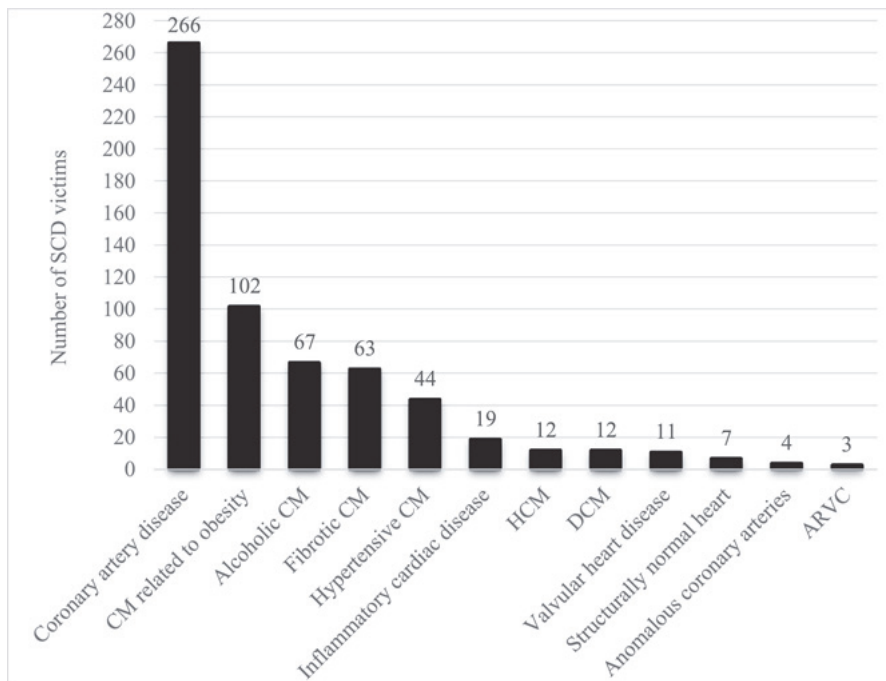
Fig. 5. Distribution of the causes of sudden cardiac death in victims aged under 50 years between the years 1998–2017 in Northern Finland. SCD = sudden cardiac death; CM = cardiomyopathy; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; ARVC; arrhythmogenic right ventricular cardiomyopathy. (Under CC BY-NC-ND 4.0 license from Publication II © 2021 Authors).

5.2.1 Demographics of ischemic SCDs among young population

In the last 20 years, the proportion of CAD as the cause of SCD has decreased in victims under 50 years of age. Since the beginning of the Fingesture study, the proportion of ischemic SCDs among the young has dropped from around 50% to 35% (Figure 6). The proportion of CAD-related SCDs increased with age, being highest among victims between 45 and 50 years of age (56.8%, 151 victims) (Figure 7). CAD became the most prevalent single cause of SCD after the age of 35 years and accounted for almost half of all SCDs after the age of 40. Only two SCDs were determined to be caused by CAD in victims under the age of 30.
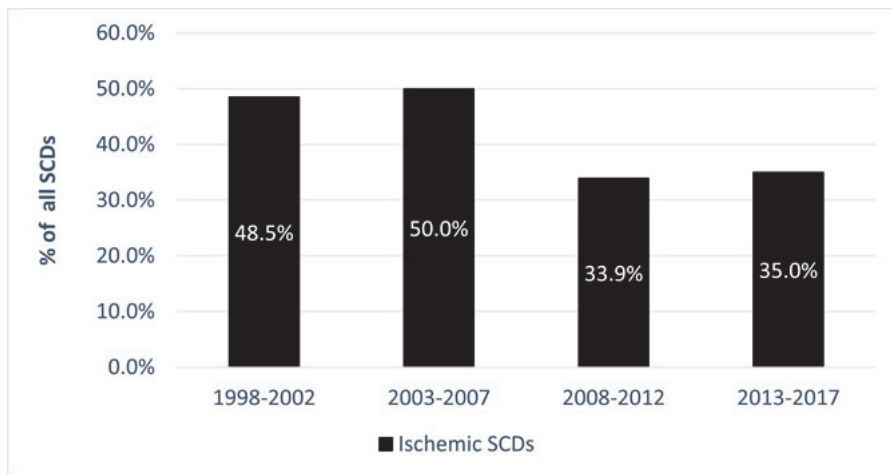
Fig. 6. Temporal trends in the prevalence of ischemic sudden cardiac deaths (SCDs) among victims under the age of 50 years from 1998 to 2017. (Under CC BY-NC-ND 4.0 license from Publication II © 2021 Authors).

	<30 years	30-34 years	35-39 years	40-44 years	45-49 years
□ Other SCDs	26	25	51	90	152
■ Ischemic SCDs	2	6	27	80	151
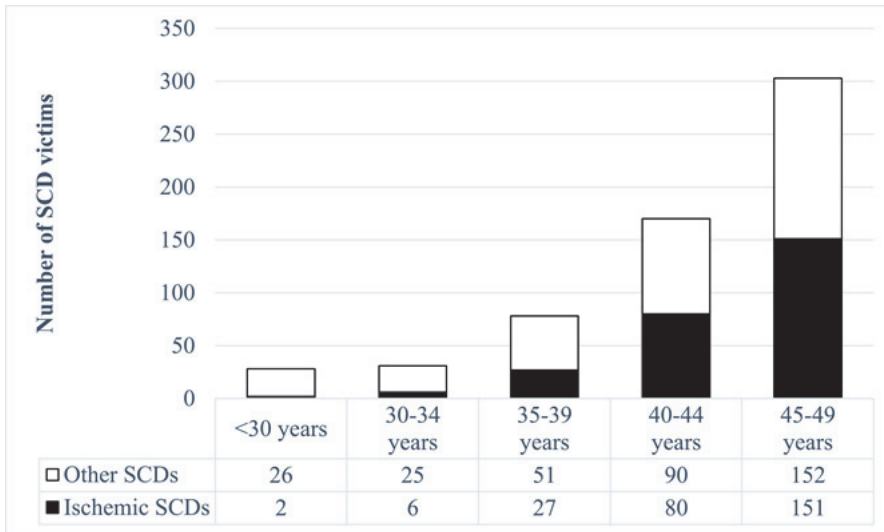
Fig. 7. The proportions of ischemic sudden cardiac deaths (SCDs) to other cause of SCDs among victims under 50 years old. (Under CC BY-NC-ND 4.0 license from Publication II © 2021 Authors).

5.2.2 Characteristics of the young ischemic SCD victims

The mean age of the SCD victims in the present study was 44 ± 5 years. Ninety per cent were male (238 victims). Approximately 90% of the SCDs occurred in victims without a previously diagnosed CAD. A family history of SCD was reported in over a third of the ischemic SCD victims (34.5%, 38 out of 110 victims). A great part of the study victims had known cardiovascular risk factors, with at least one risk factor (diabetes, dyslipidemia, hypertension, smoking, or obesity [defined as BMI $\geqslant$ 30 kg/m2]) present in more than half of the study victims (64.7%, 172 victims). Approximately 76% of the victims (84 out of 110 victims) were known to be smokers and 27% (71 victims) were known to have a tendency to alcohol abuse. About one fourth of study victims experienced SCD during physical exercise (24.1%, 64 victims). The highest number of SCD events occurred in the afternoon between 12 pm and 6 pm and the lowest number at night. The clinical features of the victims and circumstances during SCD are presented in Table 3.

Table 3. Clinical characteristics of ischemic SCD victims under the age of 50. (Under CC BY-NC-ND 4.0 license from Publication II © 2021 Authors).

Characteristic	Victims (n=266)
Age, years	44 .2 ± 4.5
Male	238 (89.5)
Prior	
Coronary artery disease	25/256 (9.8)
Acute myocardial infarction	16/258 (6.2)
Hypertension	60/254 (23.6)
Diabetes	49/255 (19.2)
Dyslipidemia	31/255 (12.2)
Angina pectoris	25/255 (9.8)
Dyspnea	9/255 (3.5)
Heavy alcohol ingestion	71/265 (26.8)
Smoker	84/110 (76.4)
≥1 CVD risk factor (DM, hypertension, dyslipidemia, obesity, smoker)	172 (64.7)
Family history of SCD	38/110 (34.5)
Conditions of death	
During physical activity	64 (24.1)
In hospital, health centre, or ambulance	22 (8.3)
Outdoors	49 (18.4)
Time of death	n=186
12 AM–6 AM	33 (17.7)
6 AM–12 PM	49 (26.3)
12 PM–6 PM	68 (36.6)
6 PM–12 AM	36 (19.4)

Values are expressed as mean ± SD or number of victims (per cent). CVD = cardiovascular disease; DM = diabetes mellitus, SCD = sudden cardiac death, obesity = body mass index ≥30 kg/m2.

5.2.3 Findings in medico-legal autopsy examinations

The autopsy findings are presented in Table 4. Approximately one fourth of the study victims were obese (66 victims, 24.8%), and the mean body mass index was 28 ± 5 kg/m^2. The mean heart weight of the victims was 454 ± 117 g, which is higher than the usual heart weight in general population (less than 420 g). LVH was present in over half of the victims (58.3%, 155 victims). Scarring of the myocardium was observed in 38.7% of all victims and in 33.8% of those who had no prior history of CAD, indicating a previously occurred SMI. Varying amount of fibrosis was present in 82.6% of the study victims. Three-vessel CAD was a

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common finding among the study victims (44.4%, 118 victims). About 28% of the victims had only a single epicardial coronary artery affected, the most prevalent being the left anterior descending artery in 90% of the victims. Figure 8 shows the distribution of coronary artery status between different age groups. In 56.8% of the study victims, there was more than 75% stenosis (assessed in the cross-sectional area) in the affected coronary artery(ies). Toxicological examination was performed in 212 victims (79.7%), and alcohol in blood or urine was detected in 32.1% of the victims tested.

Table 4. Autopsy findings of ischemic sudden cardiac death victims under the age of 50. (Under CC BY-NC-ND 4.0 license from Publication II © 2021 Authors).

Characteristic	Victims (n=266)
BMI (kg/m2)	27.5 ± 5.4
≥ 30	66 (24.8)
Heart weight, g	453.5 ± 117.0
LVH	155 (58.3)
Myocardial scar	103 (38.7)
Prior silent myocardial infarction	78/231 (33.8)
Degree of myocardial fibrosis	n=265
Substantial	24 (9.1)
Patchy, moderate	109 (41.1)
Patchy, mild	86 (32.5)
None	46 (17.4)
Blood/urine ethanol concentration > 0‰	68/212 (32.1)
Significant occlusion of coronary artery (reduction in the cross-sectional area > 75%)	151 (56.8)
Number of coronary arteries narrowed	
3	118 (44.4)
2	73 (27.4)
1	71 (28.2)
Occluded coronary artery	
LAD	64 (90.1)
CX	1 (1.4)
RCA	6 (8.5)

Values are expressed as mean ± SD or number of victims (per cent). BMI = body mass index; LVH = left ventricular hypertrophy; LAD = left anterior descending; CX = Circumflex; RCA = right coronary artery.
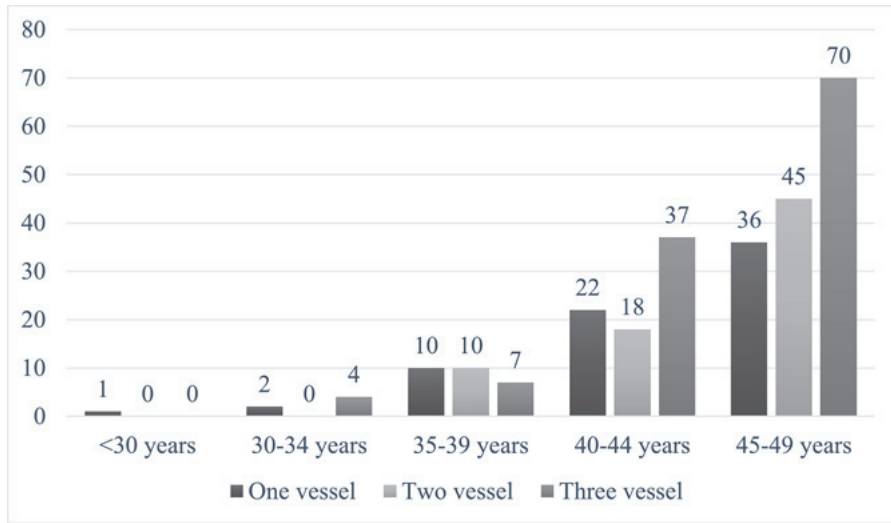
Fig. 8. The number of affected coronary arteries in different age groups among ischemic sudden cardiac death victims under 50 years of age. (Under CC BY-NC-ND 4.0 license from Publication II © 2021 Authors).

5.3 Genetic variants associated with sudden cardiac death in victims with single vessel coronary artery disease and left ventricular hypertrophy with or without fibrosis (Study III)

5.3.1 Clinical and autopsy characteristics of the study victims

In the Fingesture study, 4,392 out of 5,869 victims (74.8%) had CAD as an underlying cause of SCD, with 3,122 victims (71.1%) having no prior history of CAD. In 244 victims without a previously diagnosed CAD, single-vessel disease and cardiac hypertrophy were observed without macroscopic or microscopic evidence of cardiomyopathies. In this study, we analysed DNA from 95 victims with single-vessel CAD and cardiac hypertrophy with no history of previously diagnosed CAD and whose DNA was found to be suitable for further analysis after passing quality control. The mean age of the study population was 64 ± 10 years and most were men (88.4%, 84 victims). The mean heart weight was 515 ± 87 g (range 421–820 g) and the mean BMI 29 ± 5 kg/m^2. Left anterior descending was the most commonly occluded artery among the study victims (84.2%, 80

victims). About one fifth of the victims had a myocardial scar observed at autopsy (23.2%, 22 victims). The clinical features, autopsy findings and circumstances at death are described in Table 5.

Table 5. Clinical characteristics, autopsy findings and circumstances at death in ischemic SCD victims with single-vessel CAD and cardiac hypertrophy in the absence of previously diagnosed CAD. (Under CC BY 4.0 license from Publication III © 2022 Authors).

Characteristic	Victims (n=95)
Age, years	63.6 ± 10.3
Male	84 (88.4)
Hypertension	25 (26.3)
Diabetes mellitus	12 (12.6)
Dyslipidemia	8 (8.4)
Angina	4 (4.2)
Dyspnea	5 (5.3)
Abundant use of alcohol	32 (33.7)
Circumstances at death	
Unwitnessed; dead on initial contact	89 (93.7)
During physical activity	5 (5.3)
In hospital, health centre, or ambulance	3 (3.2)
BMI (kg/m2)	29.0 (5.3)
Total heart weight, g	514.5 ± 87.3
	(421-820 g range)
Occluded coronary artery	
LAD	80 (84.2)
CX	4 (4.2)
RCA	11 (11.6)
Myocardial scar	22 (23.2)

Values are expressed as mean ± SD or number of victims (per cent). BMI = body mass index; LAD = left anterior descending; CX = Circumflex; RCA = right coronary artery.

5.3.2 Detected variants

Among the study victims, we observed potentially disease-related variants (pathogenic, likely pathogenic or VUS) in 43 individuals (45.3%) in 22 different genes. The gene panel used in the study and the genes in which the variants were detected are shown in Figure 9. Pathogenic or likely pathogenic variants were present in 8 victims (8.4%). In eight individuals (8.4%), at least two potentially significant variants were detected. A total of five variants were classified as

pathogenic or likely pathogenic and 38 variants were classified as VUS. All the potentially disease-related variants were observed in cardiac structure-related genes while no significant variants were identified in ion channel-coding genes. However, variants in *RYR2* have previously been associated with cardiomyopathies and catecholaminergic polymorphic ventricular tachycardias (CPVTs). At autopsies, 10 victims (23.4%) with potentially disease-related variant(s) had a healed myocardial scar.

| Hypertrophic cardiomyopathy | ACTC1, **ACTN2**, **ANKRD1**, CALR3, CAV3, **CSRP3**, JPH2, **MYBPC3**, **MYH6**, **MYH7**, MYL2, MYL3, **MYLK2**, MYO6, MYOZ2, MYPN, **NEXN**, PDLIM3, PLN, PRKAG2, TCAP, TNNC1, TNNI3, TNNT2, **TPM1**, TRIM63, VCL |

| Dilated cardiomyopathy | **ABCC9**, **ACTN2**, ACTC1, **ANKRD1**, BAG3, **CRYAB**, **CSRP3**, DES, DMD, **DSG2**, EYA4, GATAD1, **LAMA4**, **LDB3**, LMNA, **MYBPC3**, **MYH6**, **MYH7**, MYPN, **NEXN**, PLN, RBM20, SCN5A, SGCD, TAZ, TCAP, TMPO, TNNC1, TNNI3, TNNT2, TPM1, **TTN**, VCL, ZBTB17 |

| Arrhythmogenic cardiomyopathy | DES, **DSC2**, **DSG2**, DSP, JUP, LMNA, **PKP2**, PLN, RYR2, SCN5A, TGFB3, TMEM43 |

| Left ventricular non-compaction cardiomyopathy. | **DTNA**, **LDB3**, LMNA, MIB1, **MYBPC3**, **MYH7**, PRDM16, TAZ, TNNT2, **TPM1** |

| Metabolic disorders and syndromes with cardiac diseases and congenital heart defects | ALMS1, BRAF, CBL, COX15, CRELD1, DNAJC19, DOLK, FXN, GAA, GLA, HFE, HRAS, JAG1, KRAS, LAMP2, MAP2K1, MAP2K2, NKX2-5, NODAL, NOTCH1, NRAS, PTPN11, RAF1, SCO2, SDHA, SHOC2, SMAD4, SOS1, TBX3, TBX20, TBX5, TTR, ZIC3 |

| Arrhythmic disorders (Long QT syndrome, Brugada, Catecholaminergic polymorphic ventricular tachycardia etc.) | AKAP9, ANK2, CACNA1C, CACNA2D1, CACNB2, CALM1, **CASQ2**, CAV3, DPP6, GJA5, GPD1L, HCN4, KCNA5, KCND3, KCNE1, KCNE2, KCNE3, KCNH2, KCNJ2, KCNJ5, KCNJ8, KCNQ1, NPPA, RANGRF, **RYR2**, SCN1B, SCN2B, SCN3B, SCN4B, SCN5A, SNTA1, TRDN, TRPM4 |

| Dyslipidemia | ABCG5, ABCG8, APOA5, APOB, APOC2, APOE, CETP, GPIHBP1, LDLR, LDLRAP1, LMF1, LPL, PCSK9, SREBF2 |

| Aortopathies / Ehlers-Danlos syndrome | ACTA2, COL3A1, COL5A1, COL5A2, EFEMP2, ELN, FBN1, FBN2, MYH11, MYLK, SLC2A10, SMAD3, TGFB2, TGFB3, TGFBR1, TGFBR2 |

| Muscular dystrophies/myopathies | ACTA1, BAG3, EMD, FHL1, FKRP, FKTN, LAMA2, RYR1, SEPN1, SGCB, SGCD, SGCG, SLC25A4, TMEM43 |

| Other | APOA4, CBS, CREB3L3, CTF1, FHL2, GCKR, HADHA, HSPB8, ILK, KLF10, LTBP2, MURC, PRKAR1A, SALL4, TXNRD2, ZHX3 |

Fig. 9. Cardiac structure and function related genes sequenced in the panel, classified by related diseases. Variants detected in the present study are highlighted. (Reprinted [adapted] under CC BY 4.0 license from Publication III © 2022 Authors).

Pathogenic and likely-pathogenic variants

Typical features for pathogenic and likely pathogenic variants are low population frequency (especially in Finland in the present study), previous identification among patients with inherited cardiac disease in published literature, location in the gene where it can be assumed to disrupt gene function, and prediction to be damaging by *in silico* algorithms or *in vitro* studies. In this study, we observed one pathogenic and four likely pathogenic variants among the victims. The pathogenic and likely pathogenic variants detected in the present study are shown in Table 6.

A splice site variant (c.523+1G>A) in the desmosomal gene *DSG2*, which is generally associated with arrhythmogenic cardiomyopathy (AC), was classified as pathogenic. A similar splice site variant (c.523+2T>C) has previously been described in three unrelated AC patients (Fressart et al., 2010).

Two variants in generally HCM-related genes (*MYBPC3* and *MYH7*) were classified as likely pathogenic. Ala833Thr in *MYBPC3* (two victims) and Glu1039Gly in *MYH7* (three victims) were detected in multiple study victims. Ala833Thr in *MYBPC3* have previously been observed in familial HCM (Mörner et al., 2003) and classified as likely pathogenic in a PMF study (Junttila et al., 2018). The difference in the prevalence of affected carriers was statistically significant when compared to the Finnish control group (SISu) (2/95 vs 46/10,480; p = 0.016, OR = 4.9, 95% CI 1.2–20.4). However, ClinVar had conflicting interpretations of pathogenicity. Glu1039Gly in *MYH7* has also been detected in SCD victims with PMF (Junttila et al., 2018), and a similar mutation next to this codon (Leu1038Pro) has been linked to DCM (Møller et al., 2009). However, the variant was classified as VUS in ClinVar. The prevalence of carriers was significantly higher in comparison with the Finnish control group (SISu) (3/95 vs 18/10,489; p = 0.0008, OR = 19.0, 95% CI 5.5–65.5). Mutation Val56Met disrupts conserved region in DSG2 gene and has been described in an AC patient (Syrris et al., 2007), yet ClinVar represented conflicting interpretations of pathogenicity. Pro121Leu in the conserved region of *DTNA* has been detected in a family with left ventricular non-compaction syndrome (Ichida et al., 2001).

Variants of uncertain significance

A total of 39 study victims (41.1%) carried variants classified as VUS. Five variants were observed in multiple victims, indicating possible pathogenicity:

Thr358Ile in *DSC2* (n=3), Lys259Glu in *TPM1* (n=3), Arg100His in *CSRP3* (n=2), Ala936Val in *MYH6* (n=2) and Arg634His in *DSC2* (n=4). The detected variants have previously been associated with AC (Ser140Phe in *PKP2,* Thr1373Ala in *DSP* and Thr358Ile in *DSC2*) (Dalal et al., 2009; Gerull et al., 2004; Lahtinen et al., 2011; Rasmussen et al., 2014), HCM (Arg100His in *CSRP3*) (Andersen et al., 2009), DCM (Ser140Phe in *PKP2*, Gly154Ser in *CRYAB* and Ala2294Gly in *DSP*) (Elliott et al., 2010; Garcia-Pavia et al., 2011; Pilotto et al., 2006) and PMF (Ala292Ser in *CASQ2*, Arg31Gln in *DTNA*, Arg2518Trp in *RYR2*, Gly154Ser in *CRYAB* and Arg1037Gln in *LAMA4*) (Junttila et al., 2018). Ala2499Thr, Arg3597Gly and Asp1862Ala in *RYR2* have not been previously described.

5.4 Temporal trends in the incidence and characteristics of SCD among subjects under 40 years of age in Northern Finland during 1998–2017 (Study IV)

A total of 160 victims (2.7%) in the Fingesture study were aged under 40 years of age, with a total incidence of 2.9/100,000/year (based on an average of 289,933 inhabitants under 40 years of age in the geographical region of Northern Finland in 1998–2017). During the past 20 years, the incidence of SCD decreased as follows: 4.0/100,000/year (n = 50) in 1998–2002, 3.7/100,000/year (n = 45) in 2003–2007, 2.5/100,000/year (n = 36) in 2008–2012, and 1.5/100,000/year (n = 29) in 2013–2017 (p < 0.001). The prevalence of men (81%) and obesity (40%) remained quite stable during the study period (p = 0.58 and p = 0.79, respectively). Among the study victims, CAD was the most common underlying cause for SCD (46 victims, 29%), followed by obesity-related hypertrophic myocardial disease (38 victims, 24%), PMF (30 victims, 19%), hypertensive myocardial disease (10 victims, 6.3%), myocarditis (8 victims, 5%) and HCM (6 victims, 4%). About 3% of the victims had a structurally normal heart at autopsy (5 victims). SCDs caused by CAD were more frequent in those aged 35 to 40 (38 victims, 83%). Also, the incidence and proportion of CAD-related SCDs decreased during 1998–2017: 1.5/100,000/year in 1998–2002 (38%), 1.2/100,000/year in 2003–2007 (33%), 0.6/100,000/year in 2008–2012 (22%), and 0.2/100,000/year in 2013–2017 (14%) (p < 0.001).

Table 6. Pathogenic and likely pathogenic variants among the study victims. (Reprinted [adapted] under CC BY 4.0 license from Publication II © 2022 Authors).

Mutated gene	Nucleotide change	Effect on protein	Predicted effect	N	GnomAD > 3000 Finnish controls MAF	SISu > 10,000 Finnish controls MAF	Clinical features and autopsy findings of the victims
DSG2	c.523+1G>A		Affects canonical splicing	1	Not Detected	<0.0001	Male, in his 70s, BMI 25, heart weight 446 g, no fibrosis, LAD occluded
MYBPC3	c.2497G>A	Ala833Thr	Missense	2	0.0023	0.0022	1: Male, in his 50s, BMI 22, heart weight 450 g, mild fibrosis, LAD occluded 2: Female, in her 70s, BMI 27, heart weight 598 g, moderate fibrosis, LAD occluded, myocardial scar
MYH7	c.3116A>G	Glu1039Gly	Missense	3	0.0011	0.0009	1: Male, in his 60s, BMI 31, heart weight 540 g, moderate fibrosis, LAD occluded 2: Male, in his 70s, BMI 28, heart weight 535 g, substantial fibrosis, LAD occluded 3: Male, in his 60s, BMI 29, heart weight 575 g, mild fibrosis, CX occluded, myocardial scar
DTNA	c.362C>T	Pro121Leu	Missense	1	Not Detected	<0.0001	Female, in her 40s, BMI 28, heart weight 430 g, no fibrosis, LAD occluded
DSG2	c.166G>A	Val56Met	Missense	1	0.0006	0.0004	Male, in his 50s, BMI 31, heart weight 580 g, moderate fibrosis, LAD occluded, myocardial scar

BMI = body mass index; CX= Left circumflex coronary artery, GnomAD = The Genome Aggregation Database, LAD = Left anterior descending coronary artery, MAF = Minor allele frequency, SISu= The Sequencing Initiative Suomi.

6 Discussion

6.1 Prevalence and characteristics of silent myocardial infarction among sudden cardiac death victims without a prior diagnosis of coronary artery disease

In the Fingesture study, only a small proportion of ischemic SCD victims had a previously diagnosed CAD prior to death, which is not unexpected given that SCD is, unfortunately, often the initial presentation of the underlying heart disease, especially in victims with CAD (Hayashi et al., 2015; Myerburg & Junttila, 2012; Wellens et al., 2014). However, since medicolegal autopsies are performed only in individuals with unexpected or sudden death in Finland, the study population may not include all deaths caused by known heart disease. At autopsies, a myocardial scar was detected in about 42% of the individuals without a known CAD, indicating a previously unrecognized MI. Compared to a study conducted in the United States (24 of 71 individuals [34%]) (Adabag et al., 2010), the prevalence of SMI was even higher in this study (1,322 of 3,122 individuals [42%]). However, the study population of the previous study was significantly smaller and only those aged 25 to 60 were included, which likely lowered the proportion of SMIs identified. Furthermore, divergence between autopsy procedures and geographical differences may partly explain the variations in results.

The rather high number of individuals who experienced SCD with SMI might be due to the wide range of MI symptoms that patients perceive. Some patients may have experienced unrecognized or abnormal symptoms of MI and failed to identify and report the severity of their symptoms. It is also possible that autonomic nervous system and cardiac receptors differ between people. In patients with diabetes, diabetic neuropathy may impair the ability to recognize angina (Sheifer et al., 2001). According to Øhrn et al. (2016), patients who suffer undiagnosed MIs have higher pain tolerances. It is also suggested that SMI is associated with smaller infarct size than clinical MI, which has a less harmful effect on myocardial function (Cheng et al., 2021). Thus, the clinical symptoms and manifestations may also remain minor.

In the present study, individuals with SMI experienced SCD more often during physical activity. Previously, myocardial scarring has been associated with SCD during physical exercise (Toukola et al., 2015). Myocardial scar provides a

substrate for re-entrant ventricular arrhythmias that can be triggered by exercise-induced myocardial ischemia. Presumably, individuals with SMI did not limit their physical exertion at the onset of possible symptoms since they were unaware of their heart disease. Furthermore, they were unlikely to receive medication aimed at preventing CAD. Cold weather has also been associated with increased risk of MI and ischemic SCD (Mohammad et al., 2018; Ryti et al., 2017). In the present study, SCD occurred more commonly outdoors in the victims with scars. Pathological pathways between cold weather and SCD have been hypothesised, including various physiological, vascular and thrombogenic factors (Ryti et al., 2017). It is possible that myocardial scarring further predisposes to ventricular arrhythmias in the presence of cold-induced pathological conditions.

In Study I, almost one fifth of the victims with SMI had a history of diabetes, although the prevalence of diabetes was not higher than in those without SMI. However, in general, SMI seems to be more prevalent among diabetic patients (Arenja et al., 2013; Scirica, 2013; Valensi et al., 2011). Diabetic patients also have high prevalence of asymptomatic myocardial ischemia (Sheifer et al., 2001). It is known that diabetic neuropathy may impair the ability to identify a possible MI. This neurologic dysfunction, on the other hand, is more common in advanced diabetes, which may explain the discordant results. Additionally, it is possible that infarctions are more likely to be detected among patients with diabetes because of their intense health surveillance and medical control (Sheifer et al., 2001). Some of the SCD victims in the present study may have had undetected diabetes; however, diagnosing type 2 diabetes postmortem is challenging.

Cardiac hypertrophy was a more common autopsy finding among SCD victims with prior SMI. Also, both in men and women, the mean heart weight tended to be higher among victims with SMI. Myocardial hypertrophy after infarction can act as a compensatory response to maintain stroke volume after the myocyte loss (Pfeffer & Braunwald, 1990), and the extent of hypertrophy depends, at least in part, on the size of the infarction. LVH is an important risk factor of SCD (Zehender et al., 1995), and combined with myocardial scarring, can make the prognosis even worse. Previous studies have observed an association of cardiac hypertrophy with healed infarct at autopsy (Burke et al., 1996; Kaikkonen et al., 2009), as well as their effect on vulnerability toward cardiac arrhythmias and SCD (Davies et al., 1989; Scott & Briggs, 1972; Warnes & Roberts, 1984).

Current findings are in line with previous studies (Arenja et al., 2013; Valensi et al., 2011; Z. M. Zhang et al., 2016): the prevalence of SMI increases with age,

and SMI is more commonly found among men. The Atherosclerosis Risk in Communities study has previously demonstrated race and gender differences in the incidence and prognostic significance of SMI (Z. M. Zhang et al., 2016). The diagnosis of SMI was determined solely by ECG in the previous SMI study, whereas in the Fingesture study, autopsy data were combined with ECG findings. These findings, along with observations in previous studies, highlight the importance of personalised risk assessment for SMI.

SCD victims with SMI had more commonly at least one abnormality on ECG (fQRS, prolonged QRS, Q wave, or T-wave inversion), indicating possible scarring of the myocardium. Individuals with SMI had more often inverted T waves and pathologic Q waves compared to individuals without SMI. In the present study, fQRS was the most common ECG marker related to a myocardial scar in the SMI group. In a previous study conducted among the Fingesture SCD population, fQRS was associated with exercise-related SCD (Toukola et al., 2018), and as discussed earlier, individuals with SMI experienced SCD more often during physical exercise in the present study. The fQRS seems to be a sensitive marker of myocardial scarring, albeit with a slight compromise in specificity (Das et al., 2006). Taking into account the prevalence of ECG abnormalities in individuals with SMI, some previously unrecognized MIs might have been detectable in an ECG recording, despite the fact that the methods are not highly specific. Instead of using only one ECG abnormality to detect myocardial scars, it would be more beneficial to use several markers or ECG risk scores. The baseline ECG is likely to be normal in patients who experience SCD as a first manifestation of the underlying CAD and in the absence of prior MI Junttila et al., 2012). In this study, ECGs were only available in 187 subjects with SMI, so no definite conclusions can be drawn from the data. Rather, they provide encouragement for more research into this topic.

In the future, diagnosing unrecognized MIs with modern methods could be more effective compared to a standard ECG. Although imaging techniques, such as CMRI, have a higher sensitivity for detecting and quantifying myocardial scarring (Kwong et al., 2006), CMRI screening is likely to be impractical and ineffective in terms of costs. Therefore, it could be reasonable to screen high-risk populations with ECG in order to identify patients who should be examined further. For example, identifying individuals for CMRI screening with echocardiographic strain analyses after ECG screening would be an option for lowering the costs of SMI screening in high-risk groups for CAD. Promising correlations between strain measurements and CMRI fibrosis have previously

been reported (Hoffmann et al., 2014). Furthermore, as observed in an Icelandic study, individuals with SMI detected by CMRI have a similar mortality rate as individuals with previous clinical MI (Acharya et al., 2018). Just as after a clinical MI, secondary prevention strategies should be initiated once a prior SMI has been diagnosed.

6.2 Ischemic sudden cardiac deaths in victims under 50 years of age

Study II examined the prevalence of CAD as the cause of SCD in young and middle-aged people under the age of 50 years. The study population was derived from the Fingesture study consisting of 5,869 SCD victims in Northern Finland during the years 1998–2017, of whom 610 (10%) were aged under 50 years. SCD was most often due to CAD in this age group, as previously described in SCD studies of young victims (Arzamendi et al., 2011; Risgaard et al., 2014). To our knowledge, Study II represents the largest autopsy cohort of young and middle-aged individuals who experienced ischemic SCD.

As expected, the lowest proportion of ischemic SCDs was observed in victims under 30 years (7%), increasing regularly with increasing age, and being highest in victims aged from 45 to 50 years (50%). In comparison to other causes of SCD in the study population, the proportion of ischemic SCDs decreased from 1998 to 2017. Similar observations have been made earlier in general SCD population (Junttila et al., 2016). This trend might be due to improved primary prevention strategies including statin treatment, lifestyle changes and the development of invasive treatments for acute coronary syndromes in the past decades. However, as the prevalence of obesity and type 2 diabetes seems to increase alarmingly in Western societies, this trend might change in the near future.

Particularly in CAD and among younger population, SCD occurs more frequently without a previously diagnosed heart disease (Aro & Chugh, 2017; Myerburg & Junttila, 2012; Wellens et al., 2014). Also in the present study, approximately 90% of the young and middle-aged victims had no prior diagnosis of CAD. The prevalence of males among the study victims was even greater than reported previously in Danish CAD-SCD population (90% vs 76%) (Zachariasardóttir et al., 2017). The male predominance is explained by the fact that in women, CAD occurs about 10 years later than in men (Duda-Pyszny et al.,

2018), and women have been shown to experience SCD at older age and more often due to non-ischemic heart diseases (Haukilahti et al., 2019).

Over one half of the young ischemic SCD victims had at least one known cardiovascular risk factor. This finding highlights the importance of early screening and detecting cardiovascular risk factors in the young population as well. The prevalence of established cardiovascular risk factors in sudden cardiac arrest victims under the age of 35 was also surprisingly high (58%) in a previous study (Jayaraman et al., 2018). Attention should also be paid to cardiovascular preventive measures in young adults in order to prevent them from dying suddenly. Although CAD is the leading cause of SCD among young people, it is a preventable disease, which provides a chance to influence the burden in the future. About a third of the victims were known to be smokers, which has been estimated to be one of the most important risk factors for SCD and development of CAD (Aune et al., 2018; Ding et al., 2019). Smoking has long-term effects on atherosclerosis as well as acute effects on endothelial function and thrombus formation (Ding et al., 2019). A family history of SCD has also been reported to predispose to SCD during an ischemic event (Kaikkonen et al., 2006). In Study II, approximately one third of the study victims had a family history of SCD. Especially ischemic SCDs have been shown to have a strong familial background (Hookana et al., 2012). It should also be noted that, on the other hand, almost half of the victims did not have any known cardiovascular risk factors, making it difficult to predict or prevent ischemic SCDs among the young population.

A known history of extensive alcohol consumption was present in about one fourth of the study victims. Although alcohol has been shown to have some beneficial effects, such as increase in blood HDL cholesterol levels, the disadvantages outweigh the benefits in heavy use (Foerster et al., 2009). Abundant use of alcohol predisposes to myocardial diseases, which could certainly increase the likelihood of fatal arrhythmias during an ischemic event. In the postmortem examinations, alcohol was detected in the blood or urine samples of more than a third of the study victims. This is a significant observation, since acute alcohol consumption can cause electrical instability in those with ischemic heart disease, which can eventually lead to fatal arrhythmias (Perkiömäki et al., 2016). However, more research is needed on this topic. Other toxic substances and drugs were not investigated further in this study.

Sudden cardiac arrests and SCDs in sports and among young athletes have received a lot of media and public attention, despite the fact that the incidence of SCD in young athletes is actually quite low (Schmied & Borjesson, 2014).

However, the estimates of incidences vary widely between studies due to differences in research methodologies and subpopulations of the athletes studied (Schmied & Borjesson, 2014). The risk of SCD during sports increases with age, likely due to development and progression of CAD (Marijon et al., 2011). In Study II, about a fourth of the individuals experienced SCD during physical activity, a higher proportion than previously observed (24% vs 12%) (Zachariasardóttir et al., 2017). This is not surprising given the high prevalence of male gender, LVH and myocardial scarring in the study population, all of which have been linked to SCD during physical exercise (Toukola et al., 2015).

Autopsies performed in the present study revealed a considerable number of victims with severe CAD, despite the young age of the study population. Almost half of the study victims had three-vessel CAD, and findings like myocardial fibrosis (83% of the victims) and hypertrophied hearts (58% of the victims) were both prevalent. In comparison to earlier observations (Zachariasardóttir et al., 2017), the prevalence of three-vessel disease (44% vs 21%) and cardiac hypertrophy (58% vs 40%) was notably higher. The presence of three-vessel CAD and cardiac hypertrophy are both features that significantly enhance the risk of fatal arrhythmias (Kaikkonen et al., 2009). Myocardial fibrosis is an integral component in most diseases of the myocardium, impairing heart muscle contractility and the electrical conductive system, and is linked to previous cardiovascular events (Ambale-Venkatesh et al., 2019). About a third of the study victims without a prior diagnosis of CAD had an old myocardial scar detected at autopsy, indicating a previously unidentified MI. In Study I, SCD victims with SMI were associated with male gender, LVH and exercise-related sudden death, which were also common features among the subjects of the present study. Young adults with prior MI have a substantially increased long-term mortality compared to individuals with no prior MI (Cole et al., 2003).

Although it is known that CAD begins to develop at a young age, the autopsy findings of the present study suggest that severe CAD may be seen in young individuals as well. This emphasises the need for early detection of CAD among the young. CAD is not well understood in young people since it is predominantly a disease of the elderly. However, young individuals with CAD have been shown to have an even weaker prognosis than the older population (Rubin & Borden, 2012), which is why more effort should be made to identify CAD earlier among the young. As previously reported (Jayaraman et al., 2018), the results in this study also underline the role of early screening for cardiovascular risk factors. Currently, despite its practicality and cost-effectiveness, the role of 12-lead ECG

is very modest in identifying CAD. ECG, on the other hand, might be effective in detecting previous MIs, as seen in Study I. SMIs were rather prevalent in the study population, and detecting them would be critical because of the elevated risk of fatal arrhythmias.

The study population was derived from the geographical area of Northern Finland, and it is reasonable to speculate whether premature CAD is related with the genetic heritage of Northern Finland. Finns have a unique genetic background, and medical singularity called the Finnish Disease Heritage is well known phenomenon (Norio, 2003). The role of heredity in the development of CAD has been noted, and in Finland, for example, the genetic differences between geographical areas seem to be significant (Locke et al., 2019).

6.3   Genetics of myocardial hypertrophy and fibrosis in sudden cardiac death victims with single vessel coronary artery disease

According to genetic studies performed in Study III, rare variants in cardiomyopathy-associated genes were prevalent in ischemic SCD victims with single-vessel CAD and myocardial hypertrophy without anatomical or histological signs of hereditary cardiomyopathies. We observed no significant variants in ion channel coding genes among the study victims; all the variants were found mainly in myocardial structure coding genes associated with DCM, AC, HCM and LVNC. Nonetheless, mutations in the RYR2 gene are linked to both catecholaminergic polymorphic ventricular tachycardias and AC (Roux-Buisson et al., 2014).

The observations in the present study suggest that at least in some ischemic SCD patients, variants in myocardial structural coding genes may play a role in the development of myocardial hypertrophy and/or fibrosis, as well as contribute to the risk of fatal arrhythmias, particularly when the severity of CAD does not appear to fully explain the cause of SCD. Still, it is also possible that myocardial hypertrophy with or without fibrosis may be only a bystander in certain cases where an acute coronary event results in sudden death. At autopsies, approximately 23% of the study victims were observed to have a myocardial scar. A healed myocardial scar can cause myocyte hypertrophy in non-infarcted areas remote from the scar (Yuan et al., 1999), which may be associated with a risk of arrhythmias. A genetic predisposition to hypertrophy and fibrosis may further increase the vulnerability to fatal arrhythmias. In the study population, the

myocardial hypertrophy and fibrosis are most likely caused by multiple different factors, including also ischemic modulation and varying levels of treated or untreated hypertension. Nonetheless, the fact that many study victims carried the potentially cardiac disease-causing genetic variant is intriguing. In the future, we should perhaps broaden our perspective of the pathophysiology underlying the risk of sudden death instead of the current approach of classifying each heart disease as a separate entity.

In Study III, likely disease-causing variants were discovered in genes associated with AC, HCM, DCM and LVNC. The study victims, however, did not have postmortem results that were consistent with these particular cardiomyopathies. In the postmortem examinations, all the SCDs were determined to be caused by CAD, in the presence of LVH and fibrosis of various degrees. Inherited cardiomyopathies can have a variety of phenotypic expressions (Caselli & Pelliccia, 2019; DeWitt et al., 2019; Junttila et al., 2018), and, for example, fibrosis may be the only or early expression of an underlying structural cardiac disease (Junttila et al., 2018). As also demonstrated in the present study, hereditary structural disorders may have overlapping features (Junttila et al., 2018). We found many variants in the same genes as reported in SCD victims with PMF (Junttila et al., 2018). The classification of variants may vary considerably between observers, and also in this study, ClinVar did not support a causal relationship between cardiomyopathy and three of the five pathogenic or likely pathogenic variants. Nevertheless, it can be hypothesized whether these gene variants predisposed to myocardial fibrosis, for example.

Between gene mutations and cardiomyopathies, phenotypic manifestations and the age at the onset of the myocardial disease are quite diverse. Mutations in *MYBPC3*, for instance, appear to have incomplete disease penetrance and are linked to late-onset disease (Christiaans et al., 2010; Niimura et al., 2002). Different gene defects and variants can have a wide range of disease severity and penetrance rates, even within the same gene (Maron et al., 2012). Individuals with the same gene mutation might have different phenotypes as well. Despite the fact that no autopsy findings associated with specific cardiomyopathies were discovered in any of the study victims, it is plausible to speculate that the gene defect(s) may contribute to the development of cardiac hypertrophy.

It is well known that cardiac hypertrophy and increased left ventricular mass are associated with an increased risk for fatal arrhythmias and SCD (Kaikkonen et al., 2009; Laukkanen et al., 2014). As seen in CAD patients, it may have an independent mechanism for ventricular arrhythmias (Reinier et al., 2011). The

increased left ventricular mass increases oxygen demand, lowers coronary flow and vasodilatory reserve, and affects left ventricular muscle contractility (Antony et al., 1993; Laukkanen et al., 2014). As a result, it is reasonable to suggest that the risk of SCD was possibly higher among the study subjects compared to individuals with single-vessel CAD in the absence of hypertrophy. A variant in myocardial structural coding genes was found in nearly half of the study victims, which might have, at least in some cases, caused or predisposed to myocardial hypertrophy. We used a panel consisting of 174 myocardial genes in the genetic studies: however, it is possible that some of the study victims had undetected variants in other genes.

Many variants whose significance remained unclear were detected among the study victims. In general, the challenge of the increasing number of variants classified as VUS has been acknowledged (Bertier et al., 2016). The number of genetic testing and research is increasing since, for example, the introduction of NGS technology has made it possible to sequence large gene panels in a reasonably quick and cost-effective manner. The genetic studies use often the ACMG guidelines for gene variant interpretation and reporting. The variant assessment in some genetic diseases like CPVT may be suboptimal since the guidelines have not been validated for specific conditions (Giudicessi et al., 2019). Although a gene variant is not considered pathogenic, it is reasonable to consider potential disease-modifying and contributing effects on the risk of sudden death, especially in the context of CAD.

The aberrant myocardial structure is thought to act as a substrate for arrhythmias in cardiomyopathies. The arrhythmias may also occur in the early stages of myocardial diseases and even without phenotypic features of cardiomyopathies, indicating that underlying gene defects may have additional arrhythmogenic pathways (Bezzina et al., 2015). The risk profile for SCD in the study victims with CAD may include elements from both CAD and structural gene defects.

It has been hypothesised that patients with double (or compound) gene mutations may have more severe heart disease and higher risk of SCD (Maron et al., 2012; van Driest et al., 2004). Two or more potentially relevant structural gene variants were detected in 8.4% of the study victims, and it is reasonable to argue that patients with multiple variants are more likely to develop fatal arrhythmias. In addition, several VUS variants could contribute to the risk of cardiac disease and arrhythmias, even though one variant alone could be insignificant.

Previously, the conventional risk factors for CAD and SCD have received a lot of attention. Recently, the role and value of genetics and the importance of personalised risk prediction in identifying those at high risk for SCD have been acknowledged (Faragli et al., 2016). Heredity has been shown to have a significant effect on the risk of SCD (Kaikkonen et al., 2009), and genetic profiling is expected to play an increasingly important role in the evaluation of arrhythmogenic risk in the future (Bezzina et al., 2015; Faragli et al., 2016). Current findings suggest that variants in myocardial structure coding genes may be linked to the risk of SCD in patients with single vessel CAD and cardiac hypertrophy, supporting the notion that more intensive secondary prevention efforts for CAD among such patients are needed. Furthermore, these observations highlight the need of primary prevention (e.g., lifestyle changes, cholesterol and blood pressure control), especially in those who have variants in myocardial structure coding genes in the absence of clinical CAD. As a result, screening victims' families with the profiles described in this study might be useful to identify people at high risk for SCD and thus lower their CVD risk.

The accuracy of establishing the cause of death may be improved by postmortem genetic analysis, for example, when an autopsy reveals a structurally normal heart or when the severity of cardiac disease does not seem to completely explain the cause of sudden death (Sanchez et al., 2016). When CAD is discovered at autopsy, especially in middle-aged and older people, genetic investigations are not needed to determine the cause of death. Current results, however, raise a question of whether rare variants in myocardial structure coding genes may play a role in the development of myocardial disease in patients with less advanced CAD. The usefulness of this finding in areas such as diagnostics is yet to be defined.

6.4 Temporal trends in sudden cardiac deaths among victims under 40 years of age in Northern Finland

In Study IV, the incidence of SCD in the young population seemed to be decreasing during the study period, which is in line with previous reports (El-Assaad et al., 2017; Lynge, Nielsen, Blanche, et al., 2019). The majority of SCDs were due to non-ischemic myocardial diseases, such as obesity-related hypertrophic myocardial disease, PMF, and hypertensive myocardial disease. As observed in the general population (Junttila et al., 2016), the proportion and hence, the incidence of CAD as an underlying cause of SCD has declined in

individuals under the age of 40 over the past two decades. Obesity as a comorbidity of SCD, on the other hand, remained rather steady across the 20-year period. The lower proportion of mortality owing to CAD as a result of advances in the prevention and treatment of CAD as well as an increase in the mean age of those dying from CAD might explain the decrease in the incidence of SCD in the young population. It has also been observed that asystole and pulseless electrical activity are becoming more common as the first recorded rhythm in sudden cardiac arrest, probably due to a decrease in the occurrence of CAD as an underlying cause (Kauppila et al., 2018). Due to widespread media attention of unexpected deaths in sports and among younger populations, defibrillators are now widely available in sports venues and shopping malls. As a result, the current procedures and treatments for sudden heart attacks are likely to be more successful. The survival rate of patients experiencing out-of-hospital cardiac arrest has improved in Finland according to the Finnresusci study (Hiltunen et al., 2012).

A lot of advancements have been made in the primary prevention of CAD and lifestyle changes, but acquired cardiac diseases remain a substantial burden. For example, the proportion of obesity-related hypertrophic myocardial disease was rather high in the present study. Obesity is an escalating global epidemic and a well-known risk factor for CVD. In a previous British study among young and obese individuals who experienced SCD, unexplained LVH was a common finding in autopsies (Finocchiaro et al., 2018). Obesity-related cardiomyopathy is a largely preventable condition when compared to other frequently studied inherited cardiac diseases that cause SCD in young people. In approximately 20% of the cases, SCD was determined to be caused by PMF, which is a common autopsy finding among young people who experience SCD and may represent a varied phenotypic or early pathologic manifestation of cardiomyopathies (Junttila et al., 2018).

6.5   Clinical implications and future directions

The major challenge of predicting and preventing SCDs is that a significant proportion of them occur among people who have not been previously diagnosed with heart disease. In the studies of this thesis, we focused on investigating some special features of ischemic SCDs in victims without a prior clinical CAD. We also focused on younger population who more often experience SCD as an initial manifestation of heart disease. In the Fingesture study, about 70% of ischemic

SCDs occurred without a prior diagnosis with CAD, and the proportion was even greater among the younger population (90%). These findings reflect the burden of undiagnosed CAD among the general population and considering the prevalence of SMIs and highly advanced CAD already at young age, even severe and complicated coronary heart diseases are missed in our daily clinical practice.

If we want to reduce the burden of SCDs in the future, a lot of effort should be made to prevent the development of atherosclerosis and CAD. A great proportion of SCDs could be prevented also among the younger population, considering the proportion of CAD and other acquired cardiac diseases as an underlying cause. The prevalence of obesity has been increasing in both adults and children (The GBD 2015 Obesity Collaborators, 2017; Wang et al., 2021), and by 2030, about 80% of American adults, 39% of children and 46% of adolescents are predicted to be obese/overweight, respectively (Wang et al., 2021). According to the FinHealth study from 2017, almost half (47%) of the young men and just over a third (35%) of the women aged 18–29 were overweight or obese (Jääskeläinen et al., 2019). Furthermore, the global burden of diabetes has been increasing (Lin et al., 2020), and of particular concern is the increase in the prevalence and incidence of young-onset type 2 diabetes (Magliano et al., 2020). Given these worrying health trends, it is somewhat contradictory that we observed a descending proportion of CAD-related SCDs among the young in the Fingesutre autopsy cohort. Still, it is likely that the prevalence of CAD is not decreasing, on the contrary. Instead, perhaps CAD is more effectively detected and treated also among the younger population, and therefore individuals experience SCD less frequently. There has also been a significant reduction in smoking among young adults since the early 2000s (Jääskeläinen et al., 2019). However, hypertension and obesity-related myocardial diseases expressing cardiac hypertrophy might increase their relative proportion as an underlying cause for SCD in the future.

Lifestyle interventions and managing traditional risk factors are likely to improve prognosis not only in acquired cardiac diseases but also in hereditary cardiomyopathies. For example, it can be hypothesised whether the individuals expressing rare gene variants associated with cardiomyopathies in Study III could have avoided sudden death if they had not developed CAD. Potentially pathogenic gene variants have also been observed among SCD victims with acquired non-ischemic myocardial diseases (Holmström et al., 2021). Taking also into account the well-studied role of family history in the risk for SCD, the relatives of SCD victims could benefit from more intensive treatment of

conventional risk factors. Genetic studies also increase our understanding of the development of myocardial disease and the mechanism of SCD, especially in acquired multifactorial heart diseases. Postmortem genetic analyses may be beneficial in determining the cause of death more accurately when the severity of cardiac disease does not seem to completely explain the sudden death. With increasing data from SCDs caused by CAD, developing a risk-score tool for CAD patients could be useful in the future.

In Study I we determined the prevalence of SMIs among ischemic SCD victims without a previously diagnosed CAD and observed some characteristics of victims associated with a prior undetected MI scar. SMIs were also detected in Study II in about a third of the young victims without a prior history of CAD. This information can be used for better understanding of the mechanisms preceding CAD-related SCD and to whom preventive strategies could be targeted. Considering the prevalence and prognosis of SMI, some form of screening, such as ECG recordings during health care visits, could be beneficial for high-risk patients with cardiovascular risk factors. More research is needed to clarify the benefits and effectiveness of screening.

6.6   Study limitations

There are some limitations in the studies of this thesis that must be addressed when evaluating the overall results. First, the six-hour definition for SCD was used in the Fingesture study, which differs from general guidelines using the 1-hour definition (Al-Khatib et al., 2018; Priori et al., 2015). The 1-hour definition for SCD is quite strict, considering that the term "onset of symptoms" is rather indefinite, and would have missed many subjects with SCD. Because all of the studies are descriptive in nature, the results do not establish a causal relationship between clinical features or autopsy findings with SCD. There may have been variation between forensic pathologists in interpreting autopsy findings and determining the cause of death. In the Fingesture study, however, medico-legal autopsies were performed by only a few experienced forensic pathologists. Additionally, strict criteria for diagnoses and meticulous guidelines were used in postmortem investigations. Unfortunately, we did not have individual data of coronary plaque histology (other than categorical evaluation of stenosis percentage), which would have been interesting to evaluate. We collected the data on the victims' diseases, risk factors, history of CAD and symptoms from accessible medical records at the time of postmortem examinations; the exact

prevalence of these conditions might therefore differ from the reported observations. Also, possible symptoms prior to SCD or at the onset of cardiac arrest are difficult to assess, and some people with SCD may have understated their premonitory symptoms.

In Study I, premortem ECGs were not available in all SCD victims. Furthermore, no ECG abnormalities were found if SMI occurred between the most recent ECG recording and SCD. The autopsy data revealed only the presence of a scar in the myocardium but not its size. Nevertheless, autopsy verification of SMI is superior to ECG analyses used in earlier research on this topic.

In Study II, the information on family history of SCD and smoking was acquired afterwards through letters to the victims' closest relatives; however, response letters were not received in all cases. In addition, the duration of the previous smoking status was not clarified.

In Study III, DNA was extracted from formalin-fixed paraffin-embedded tissues, which has some well recognized limitations. However, NGS coverage was sufficient in all cases, and Sanger confirmation was not required. The causal association between identified variants and structural heart diseases is yet to be established, as in most NGS studies. Several VUSs were detected among the study population whose role in the pathophysiology of SCDs remains to be clarified. It is also possible that some variants have not been detected since the NGS method used cannot identify mutations in intron regions, large deletions, or copy number variations, for example. Because none of the subjects in the present study had a known heart disease, it is possible that they had underlying hypertension that contributed to the development of LVH.

7   Conclusions

The aim of this thesis was to study the clinical features, autopsy findings and genetics of ischemic SCD in young and middle-aged population and in victims without a history of CAD.

In Study I, we found that many individuals who experienced SCD as a result of CAD had had a previously undetected MI. Previous SMI was associated with older age, male gender, myocardial hypertrophy and SCD during physical activity. Premortem ECG was abnormal in two thirds of the individuals who had had a SCD after an SMI. Further studies are required to recognize and prevent SMIs and to find out whether targeted ECG screening for SMI might yield clinical benefit.

In Study II, CAD was found to be the most prevalent underlying cause for SCD also among people under the age of 50. Over the past two decades, the proportion of SCDs resulting from CAD among young people has decreased. A significant number of ischemic SCDs among young people occurred in individuals who had not previously been diagnosed with CAD. Despite their young age, highly advanced heart disease and SMIs were common autopsy findings in the study victims. Preventing SCDs among the young should focus on detecting and treating cardiovascular risk factors at an earlier age since the majority of the victims had conventional risk factors.

In Study III, variants in myocardial structure coding genes were frequently detected in SCD victims with single-vessel CAD and LVH without a prior diagnosis of CAD. Detected variants have previously been associated with HCM, DCM, AC, LVNC and CPVT, although none of the study victims presented typical autopsy findings related to these inherited cardiomyopathies. The findings of Study III raise a hypothesis of whether these gene variants could contribute to the risk of fatal arrhythmias and SCD, especially in patients with less advanced CAD.

In Study IV, we observed a descending trend in the incidence of SCD among people aged under 40 years in Northern Finland over the past twenty years. The majority of SCDs in this population were caused by non-ischemic myocardial diseases, with obesity-related cardiomyopathy and PMF accounting for a significant proportion. Furthermore, the incidence of SCDs associated with CAD appears to be declining among the younger population. The preventative initiatives among the young should be focused on non-ischemic heart diseases, particularly cardiomyopathy associated with obesity and hypertension. The

treatment of CAD, on the other hand, will also be crucial in the future in order to reduce the absolute numbers of SCDs in the young population.

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Original publications

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

I   Vähätalo, J. H., Huikuri, H. V., Holmström, L., Kenttä, T. V., Haukilahti, M., Pakanen, L., Kaikkonen, K. S., Tikkanen, J., Perkiömäki, J. S., Myerburg, R. J., & Junttila, M. J. (2019). Association of Silent Myocardial Infarction and Sudden Cardiac Death. *JAMA Cardiology*, *4*(8), 796–802. doi: 10.1001/jamacardio.2019.2210

II Vähätalo J, Holmström L, Pakanen L, Kaikkonen K, Perkiömäki J, Huikuri H, Junttila J. (2021). Coronary artery disease as the cause of sudden cardiac death among victims < 50 years of age. *The American Journal of Cardiology,* 147, 33–8. doi: 10.1016/j.amjcard.2021.02.012

III Vähätalo JH, Holmström LTA, Pylkäs K, Skarp S, Porvari K, Pakanen L, Kaikkonen KS, Perkiömäki JS, Kerkelä R, Huikuri HV, Myerburg RJ, Junttila MJ. (2022). Genetic Variants Associated With Sudden Cardiac Death in Victims With Single Vessel Coronary Artery Disease and Left Ventricular Hypertrophy With or Without Fibrosis. *Frontiers in Cardiovascular Medicine*, Published Online First: 11 January 2022. doi: 10.3389/fcvm.2021.755062

IV Vähätalo J, Holmström L, Pakanen L, Kaikkonen K, Perkiömäki J, Huikuri H, Junttila J. (2022). Temporal Trends in the Incidence and Characteristics of Sudden Cardiac Death Among Subjects Under 40 Years of Age in Northern Finland During 1998-2017. *Cardiology*, Published Online First: 11 February 2022. doi: 10.1159/000522554

1663. Erikson, Kristo (2022) The brain as an end organ in sepsis?

1664. Karvonen, Elina (2022) Glaucoma screening in the Northern Finland Birth Cohort Eye Study

1665. Tuisku, Virve (2022) Improving lung cancer care using real-world data

1666. Roivainen, Petri (2022) Kiireettömien ensihoitotehtävien hoidon tarpeen arviointi puhelinsairaanhoitajan toteuttamana

1667. Nurkkala, Juho (2022) Commencement of nutrition support during critical illness and after major surgery

1668. Kamakura, Remi (2022) A novel system for delivery of nutritional compounds to regulate appetite

1669. Björnholm, Lassi (2022) Early predictors of white matter microstructure in the adult brain

1670. Lehtilahti, Maria (2022) Charcot-Marie-Tooth Disease : molecular epidemiology in Northern Ostrobothnia

1671. Niemelä, Jarmo (2022) Malignant biliary obstruction and percutaneous transhepatic biliary drainage : the impact of cholangitis and chemotherapy on survival

1672. Jääskeläinen, Anniina (2022) New prognostic factors and long-term prognosis of different breast cancer subtypes

1673. Oikarainen, Ashlee (2022) Effects of an educational intervention on mentors' competence in mentoring culturally and linguistically diverse nursing students

1674. Hiltunen, Anniina (2022) NHLRC2 in embryonic development, neurodevelopment, and neurodegeneration : modelling a novel FINCA disease in mouse

1675. Niiranen, Laura (2022) Metabolic regulation during seasonal adaptation

1676. Hökkä, Minna (2022) Palliative care nursing competencies and undergraduate nursing students' views of palliative care education

1677. Sissala, Niina (2022) The effects of maternal hypoxia on pregnancy outcome, lipid and glucose metabolism and gestational diabetes

1678. Oulasmaa, Lauri (2022) Predictive factors for exposure to severe hospital-treated physical and sexual assaults : a study of former psychiatric adolescent inpatients in Northern Finland

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