

Coronary Artery Disease as the Cause of Sudden Cardiac Death Among Victims < 50 Years of Age



Juha Vähätalo, BM^{a,*}, Lauri Holmström, MD, PhD^a, Lasse Pakanen, MD, PhD^{b,c}, Kari Kaikkonen, MD, PhD^a, Juha Perkiömäki, MD, PhD^a, Heikki Huikuri, MD, PhD^a, and Juhani Junttila, MD, PhD^{a,d}

Coronary artery disease (CAD) is the most common cause of sudden cardiac death (SCD). Atherosclerosis increases with age, but also many victims of SCD in young and middle-aged population have CAD at autopsy. The purpose of this study was to determine the characteristics and autopsy findings of SCD due to CAD among victims of SCD under the age of 50. Fingesture is a population-based study consisting of consecutive series of victims of autopsy verified SCD in Northern Finland between the years 1998 to 2017 (n = 5,869). Histological examinations were part of all autopsies and a toxicology investigation was performed if needed. Analyses included information accumulated from death certificates, medical records, autopsy data, standardized questionnaire to the closest family members of the victims of SCD and police reports of the conditions of the death. Overall, 10.4% of all SCDs occurred among victims under the age of 50 years (610 victims). Most common underlying cause of SCD among these younger SCD victims was CAD (43.6%). The prevalence of CAD as the cause of SCD became more common in young SCD victims after the age of 35 years. The mean age of ischemic SCD victims was 44±5 years and most were men (89.5%). Most victims (90.2%) had no clinical diagnosis of CAD, however 33.8% had an autopsy evidence of silent myocardial infarction. SCD occurred during physical activity in 24.1%. Three-vessel disease was detected in 44.4% of the study victims. Cardiac hypertrophy (58.3%) and myocardial fibrosis (82.6%) were also common. At least 1 cardiovascular risk factor was present in 64.7% of SCD victims. In conclusion, most SCDs among victims < 50 years of age are due to CAD. © 2021 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>) (Am J Cardiol 2021;147:33–38)

Coronary artery disease (CAD) is the leading cause of sudden cardiac death (SCD),¹ resulting from either acute coronary syndrome or fatal arrhythmias due to myocardial fibrosis and/or scarring. Among young, nonischemic structural diseases and arrhythmia disorders are more prevalent.² While CAD is prevalent in older population, the magnitude of CAD as cause for SCD in younger subjects has also been acknowledged.^{3,4} Nevertheless, there are very little data on CAD in young populations since it is uncommon in these age groups. Compared with other causes of SCD in young population, CAD offers opportunities for effective prevention strategies. Since the burden of CAD related SCDs among young adults has remained unchanged, more

information is needed in order to develop effective risk prediction strategies and prevent unexpected CAD related SCD. In this autopsy-based, observational study, our aim was to determine the characteristics of ischemic SCD among young and middle-aged victims under the age of 50 years. Furthermore, we evaluated the proportion of CAD related SCD in different age groups, as well as studied the different prevalence of CAD-related SCD during the last 20 years. In Finland, all unexpected deaths undergo medico-legal autopsy based on Finnish law, which has made it possible to gather the unique and large Fingesture SCD cohort.

Methods

The study population was obtained from the Fingesture study (The Finnish Genetic Study of Arrhythmic Events), which consists of 5,869 autopsy-verified SCD victims from Northern Finland. Medico-legal autopsies were performed between the years 1998 and 2017 at the Department of Forensic Medicine of the National Institute of Health and Welfare and University of Oulu by experienced forensic pathologists, each performing more than 100 autopsies a year, using contemporary guidelines for the diagnosis of cause of death. Medico-legal autopsies are mandatory in Finland, when the death is not due to known disease, when the victim was not treated by a physician during his and/or

^aResearch Unit of Internal Medicine, Medical Research Center Oulu, University of Oulu and Oulu University Hospital, Oulu, Finland; ^bForensic Medicine Unit, Finnish Institute for Health and Welfare, Oulu, Finland; ^cDepartment of Forensic Medicine, Research Unit of Internal Medicine, Medical Research Center Oulu, University of Oulu, Oulu, Finland; and ^dBiocenter Oulu, University of Oulu, Oulu, Finland. Manuscript received November 25, 2020; revised manuscript received and accepted February 2, 2021.

Sources of Funding: Aarne Koskelo Foundation, Finnish Foundation for Cardiovascular Research, the Finnish Medical Foundation, Instrumentarium Science Foundation, The Maud Kuistila Memorial Foundation, The Ida Montin Foundation, The University of Oulu Scholarship Foundation, Sigrid Juselius Foundation

*Corresponding author: Tel: (35) 840-653-7530.

E-mail address: juha.vahatalo@student oulu.fi (J. Vähätalo).

her last illness, or when death has been otherwise unexpected (Act on the Inquest into the Cause of Death, 459 of 1973, 7th paragraph: Finnish Law). The autopsy rates in Finland are the highest in Western societies.^{5,6} Sudden death was defined as witnessed death within 6 hours of the onset of symptoms or an unwitnessed death within 24 hours when the victim was last seen in a stable state of health. The Fingesture study included only sudden deaths determined to be caused by a cardiac disease. Victims with evidence of noncardiac cause, such as cerebral hemorrhage, pulmonary embolism as well as intoxications and other nonnatural causes were excluded from the study. The information on the SCD victims was gathered from autopsy reports, available medical reports, police reports and specific questionnaires for the relatives of the victim.

The study complies with the Declaration of Helsinki and was approved by the Ethics Committee of the University of Oulu and Finland's Ministry of Social Affairs and Health. National Supervisory Authority for Welfare and Health (Valvira) and National Institute for Health and Welfare approved the review of autopsy data by the investigators.

Causes of sudden death were determined by forensic pathologists in medicolegal investigations, which were based on police reports, available medical records, autopsy findings, and complementary analyses. Medicolegal autopsies were performed according to standard protocols and a specialized pathologist was consulted if necessary. Causes of death were reported according to the International Classification of Diseases, Tenth Revision code classifications (ICD-10). Histologic examination was part of all autopsies. Toxicology investigation, including ethanol, drugs and medications, such as psychotropics, for example, was performed if autopsy findings were insufficient to define a cause of death or if a toxic exposure was suspected. At

autopsies, thorough cardiac investigations were performed in all victims including macroscopic investigation and dissection of myocardium and coronary arteries, heart weight measurement, and several histological samples were obtained and analyzed. Classification of SCD as ischemic was based on 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. Left ventricular hypertrophy (LVH) was defined at autopsy by a heart weight > the predicted value based on body surface area (at least 420 g) with hypertrophic myocytes. More detailed methods for the classification of cause of death and diagnostic criteria have been reported earlier.⁷

Results

Among all SCD victims, a total of 610 victims (10.4%) were aged < 50 years in the Fingesture study. Of these victims 86.4% (n = 527) were male. CAD was the most common cause of SCD among the victims under 50 years of age (266 victims, 43.6%), followed by cardiomyopathy related to obesity (102 victims, 16.7%), alcoholic cardiomyopathy (67 victims, 11.0%) and primary myocardial fibrosis (63 victims, 10.3%). Distribution of the causes of SCD among victims under 50 years of age are presented in Figure 1.

Most ischemic SCDs occurred among victims between 45-50 years of age (n = 151, 56.8%) and fewer number among victims under 30 years of age (n = 2, 0.8%) (Figure 2). Starting from the age of 35 years, CAD was the most common single cause of SCD and after the age 40, CAD accounted for nearly half (47.1% to 49.8%) of all SCDs. The proportion of CAD-related SCDs among the

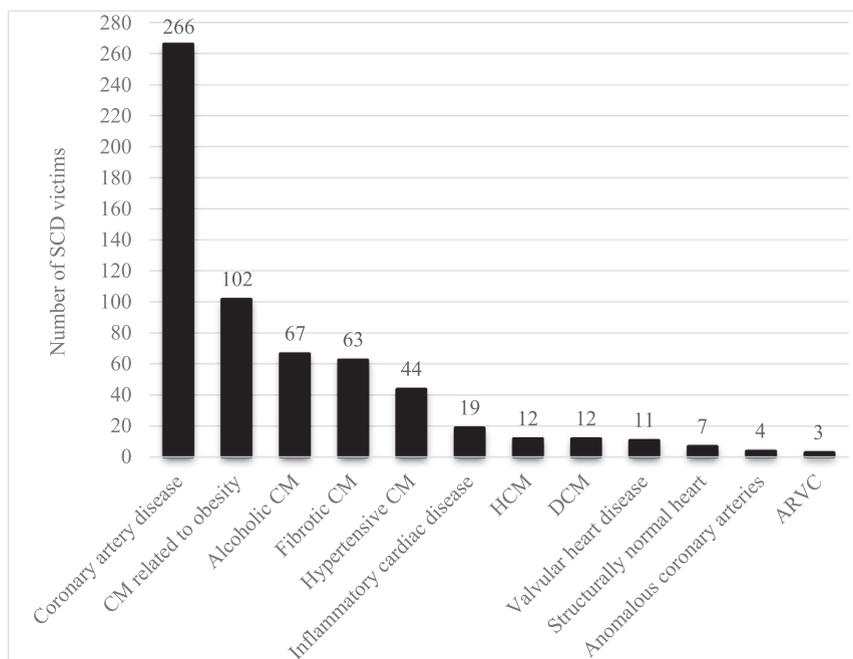


Figure 1. Distribution of the causes of sudden cardiac death in victims aged under 50 years between years 1998-2017 in Northern Finland. SCD = sudden cardiac death; CM = cardiomyopathy; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; ARVC; arrhythmogenic right ventricular cardiomyopathy.

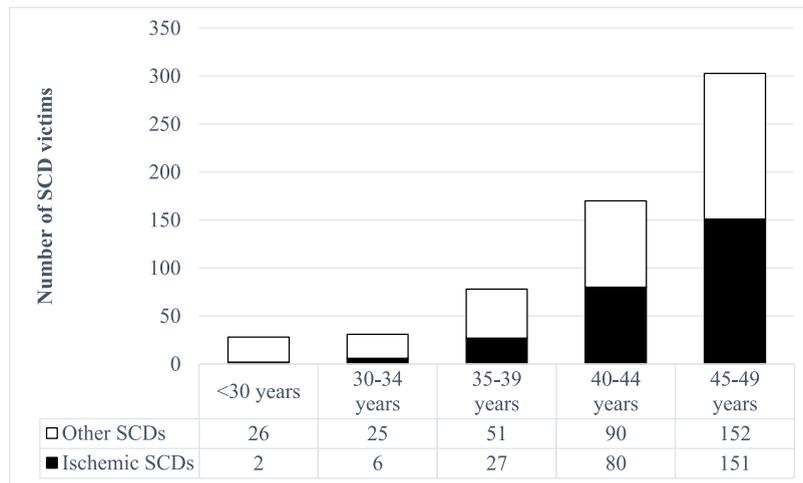


Figure 2. The proportions of ischemic sudden cardiac deaths (SCDs) to other cause of SCDs among victims under 50 years old.

victims under 50 years of age decreased during past 20 years from about 50 % to 35 % (Figure 3).

The demographics and clinical characteristics of the ischemic SCD victims aged under 50 years are presented in Table 1. The mean age of the study victims was 44.2 ± 4.5 years and 89.5% (238 victims) of the victims were males. In 90.2% ($n = 231$), CAD had not been diagnosed prior to SCD. Over a half of the victims (64.7%, 172 victims) had ≥ 1 cardiovascular risk factor (diabetes mellitus, hypertension, dyslipidemia, smoking, or obesity [considered as body mass index ≥ 30 kg/m²]). One fourth (26.8%) of victims (71 victims) were known to have a history of abundant use of alcohol and 84 out of 110 victims (76.4%) had a history of smoking. Over a third (38 out of 110 victims, 34.5%) were known to have a family history of SCD. One-fourth of victims (24.1%, 64 victims) SCD occurred during physical activity.

The autopsy findings of the study victims are shown in Table 2. The mean body mass index of the study victims was 27.5 ± 5.4 kg/m², 66 victims were obese (24.8%). The mean total heart weight of the study victims (454 ± 117 g) was beyond normal heart weight (<420 g) and over half of the victims had LVH (58.3%, 155 victims). CAD affecting all 3 main coronary arteries was present in

44.4% of the victims (118 victims). In total, 71 victims (28.2%) had a single-vessel disease, determined by occlusion of a single epicardial coronary artery. The most commonly affected major coronary artery was left anterior descending artery in 90.1% of the victims. The coronary artery status between different age groups is presented in Figure 4. More than 75% stenosis measured in the cross-sectional area was detected in 56.8% of the study victims (151 victims). Myocardial scar was detected in 38.7% of all victims and in 33.8% of victims without history of CAD indicating a prior silent myocardial infarction (MI). Fibrosis of the myocardium was present in 82.6% of the victims with varying magnitude. Alcohol in blood or urine was detected in 32.1% of the victims of whom toxicology investigation was performed (212 victims, 79.7%).

Discussion

In the present study consisting of all autopsy-verified SCD victims in Northern Finland during the years 1998-2017, we investigated the burden of CAD-related SCDs among victims aged under 50 years. Of the total of 5,869 SCD victims from the Fingesture study, we found 610

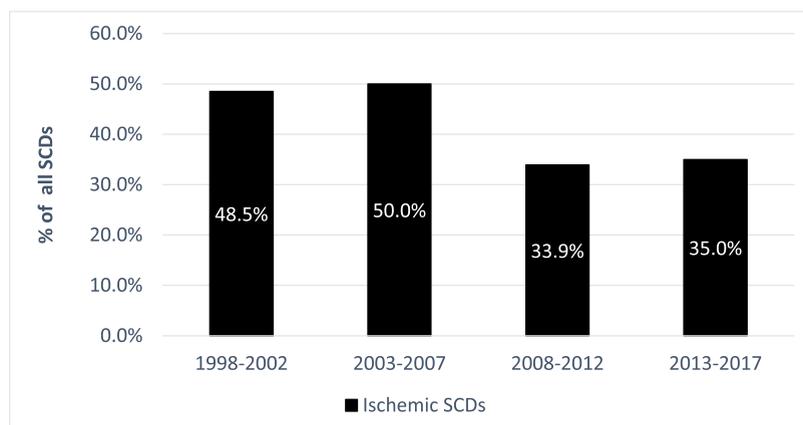


Figure 3. Temporal trends in the prevalence of ischemic sudden cardiac deaths (SCDs) among victims under the age of 50 years during 1998 to 2017.

Table 1

Clinical characteristics of ischemic sudden cardiac death in victims under 50 years of age

Characteristic	(n=266)
Age (years)	44.2 ± 4.5
Men	238 (89.5%)
Prior	
Coronary artery disease	25/256 (9.8%)
Acute myocardial infarction	16/258 (6.2%)
Hypertension	60/254 (23.6%)
Diabetes mellitus	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 center, 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 (percent). CVD = cardiovascular disease; DM = diabetes mellitus, SCD = sudden cardiac death, obesity = body mass index ≥30 kg/m².

victims under the age of 50 years. As seen in previous studies on SCDs among young victims,^{8,9} CAD was the most common cause of SCD in the present study (266 victims, 44%) and at least to our knowledge, this study provides the largest autopsy population of young and middle-aged ischemic SCD victims so far.

The proportion of ischemic SCDs increased regularly with increasing age-groups, being lowest in victims under 30 years (7.1%) and highest among victims aged from 45 to 50 years (49.8%). Over a period of 20 years, the proportion of ischemic SCDs compared with other causes has decreased in our SCD cohort among young and middle-

Table 2

Autopsy findings of ischemic SCD victims under 50 years old

Characteristic	n=266
BMI (kg/m ²)	27.5 ± 5.4
≥30	66 (24.8%)
Heart weight (g)	453.5 g ± 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%)
LAD	64 (90.1%)
CX	1 (1.4%)
RCA	6 (8.5%)

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

aged population. Similar trend has also previously been observed in overall SCD population.¹⁰ The decrease in the SCD caused by CAD may be due to improved primary prevention strategies, such as lifestyle changes and statin therapy, during the past decades.

SCD is more often the first manifestation of the underlying heart disease, especially in CAD^{1,11} and among younger victims,¹² which was also seen in our study. It is noteworthy that most ischemic SCDs among young and middle-aged victims occurred without a previously diagnosed CAD (90.2%). As expected, ischemic SCD victims aged under 50 years were mostly men, even more commonly than in the previous study among Danish CAD-SCD victims (90% vs 76%).¹³ Among women, SCD and coronary heart disease occur at significantly older age and SCD is more often caused by non-ischemic heart diseases.¹⁴

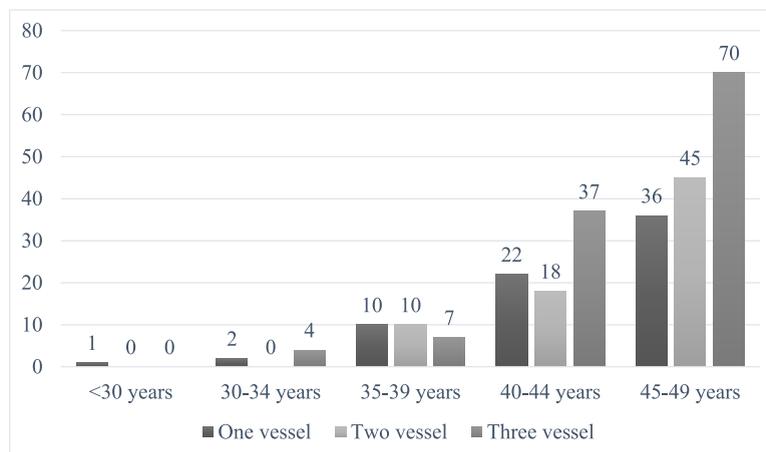


Figure 4. The number of affected coronary arteries between different age groups among ischemic sudden cardiac death victims under 50 years of age.

At least one cardiovascular risk factor was present in over half of the victims (64.7%), emphasizing the importance of early screening and cardiovascular preventive measures also in the young population. Similar observations have been made in sudden cardiac arrest (SCA) victims aged under 35 years.¹⁵ Since CAD comprises a great deal of SCDs among the young and is a preventable disease, prevention strategies should focus on lowering cardiovascular risk factors also in the younger populations. Smoking is one of the most important risk factors for both CAD and SCD.^{16,17} Significant proportion, about 1/3 of the study victims were known to be smokers. In addition to contributing to the development of atherosclerosis in long-term use, smoking has acute effects on endothelial function and thrombosis formation.¹⁶ Along with established cardiovascular risk factors, about one-third of the victims had a family history of SCD, which is a well-known risk factor for dying suddenly during an acute coronary event.¹⁸

Approximately one-fourth of study victims were known to have a history of abundant use of alcohol. While alcohol consumption may have some beneficial influences like increase in blood HDL-cholesterol levels, the protective effect disappears in heavy drinkers due to increase in blood pressure levels.^{19,20} Additionally, heavy use of alcohol increases probability of myocardial disease related to alcohol, which would undoubtedly have additive risk for life-threatening arrhythmias during an ischemic event.²¹ Acute alcohol intake may also induce electrical instability in ischemic heart disease and increase the risk of arrhythmias and SCD.¹⁹ About one-third of the victims also had alcohol detected in their blood or urine sample in post-mortem examinations. As noted in the earlier study,¹⁹ further studies are needed to investigate the actual role of acute alcohol intake on SCDs.

SCDs among athletes, especially among young, have attracted a lot of public attention, even though the incidence of SCD in young athletes is very low.²² In this study, we observed a higher proportion of ischemic SCDs during physical activity, compared with the previous study (24% vs 12%).¹³ However, this is not surprising considering the characteristics and autopsy findings of our study victims. Young and middle-aged ischemic SCD victims were mostly men and autopsy findings like LVH and myocardial scarring were common, all of which have been associated with SCD during physical activity.²³

Despite the young age of our study victims, substantial amount of young and middle-aged ischemic SCD victims had significant CAD at autopsy. Three-vessel CAD was detected in nearly half of the victims and myocardial fibrosis (82.6% of the victims) and hypertrophied hearts (58.3% of the victims) were common findings among the study victims. The prevalence of three-vessel disease was surprisingly high in comparison with the previous observations (44% vs 21%), as well as the prevalence of cardiac hypertrophy (58% vs 40%).¹³ Both three-vessel CAD and cardiac hypertrophy independently increase the risk of fatal arrhythmias.²⁴ Myocardial fibrosis is a common finding in most myocardial diseases, affecting both the contractibility of cardiac muscle and electrical conductive system and is associated with prior cardiovascular events.²⁵ In addition,

an old myocardial scar was found in approximately one-third of the victims without a known CAD, indicating a previous, unrecognized MI. In our previous study,²⁶ silent MIs in SCD victims were associated with male gender, LVH and sudden death during exercise. Patients with unrecognized MI may have even worse prognosis than those with recognized MI^{27,28} and a prior MI has been shown to predict a significantly higher mortality in young adults.²⁹

It is generally accepted that the disease process of CAD begins already in adolescence at the latest. However, these autopsy findings suggest that CAD may be highly advanced even at young age, a notion that enhances the need for early recognition of coronary disease among young. Since CAD is primarily a disease of older population, it is not as well characterized in young subjects. The long-term mortality in young adults with CAD has been shown to be even higher than in older population,⁴ which emphasizes the need for better detection of CAD in the young to improve the prognosis. Along with previous studies,¹⁵ the present study highlights the role of screening cardiovascular risk factors at earlier ages. Although the standard 12-lead electrocardiogram (ECG) is an inexpensive and practical study, its role in detecting CAD is minor. However, ECG could be useful in detecting prior MIs,²⁶ which were common among our study victims and would be crucial to find out because of the increased risk for fatal arrhythmias.

The present study does not prove any causal relationship between clinical characteristics or autopsy findings and SCD, since the design of our study was descriptive. The history of previously diagnosed CAD, cardiovascular risk factors and symptoms like angina and dyspnea were based on available medical records at the time of post-mortem examinations and therefore, the accurate occurrence rate of diagnosed conditions and symptoms may remain unclear. Also, the information about the family history of SCD and smoking were gathered afterwards via letters for the closest family members of the victims. Unfortunately, we did not receive response letters from all relatives, and, for example, the length of the past smoking status was not specified.

In conclusion, CAD was the most common underlying cause of SCD among victims under 50 years of age in our autopsy population. Substantial amount of ischemic SCDs among young and middle-aged victims occurred without previously diagnosed CAD and still, many victims had advanced underlying heart disease and a previously undetected MI at autopsy.

Authors Contributions

Study design and conception: Juhani Junttila, Heikki Huikuri, Juha Perkiömäki. **Acquisition, analysis or interpretation of data:** Juha Vähätalo, Lauri Holmström, Lasse Pakanen, Kari Kaikkonen, Juha Perkiömäki, Heikki Huikuri, Juhani Junttila. **Drafting of the manuscript:** Juha Vähätalo & Juhani Junttila. **Statistical analysis:** Juha Vähätalo & Lauri Holmström. **Critical revision of the manuscript for important intellectual content:** Lauri Holmström, Lasse Pakanen, Kari Kaikkonen, Juha Perkiömäki, Heikki Huikuri, Juhani Junttila. **Obtained**

funding: Juha Vähätalo & Juhani Junttila. **Supervision:** Juhani Junttila & Heikki Huikuri

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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