From the Department of Clinical Sciences,
Danderyd Hospital
Karolinska Institutet, Stockholm, Sweden

Evaluation and prognostic significance of premature ventricular contractions in patients without structural heart disease

Raffaele Scorza, MD

Karolinska Institutet

Stockholm MMXXIII

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2023

ISBN 978-91 -8016-883-0

Evaluation and prognostic significance of premature ventricular contractions in patients without structural heart disease

Thesis for Doctoral Degree (Ph.D.)

By

Raffaele Scorza

The thesis will be defended in public at Danderyd Hospital, Stockholm, 17th of February 2023 at 09.00

Principal Supervisor:
Viveka Frykman, MD, PhD
Karolinska Institutet
Department of Clinical Sciences,
Danderyd Hospital
Division of Cardiovascular Medicine

Co-supervisors
Professor Mårten Rosenqvist, MD, PhD
Karolinska Institutet
Department of Clinical Sciences,
Danderyd Hospital
Division of Cardiovascular Medicine

Associate Professor Leif Friberg, MD, PhD
Karolinska Institutet
Department of Clinical Sciences,
Danderyd Hospital
Division of Cardiovascular Medicine

Opponent:
Associate Professor Fredrik Holmqvist, MD, PhD
Lund University
Department of Clinical Sciences
Division of Cardiology

Examination Board:
Associate Professor Jonas Schwieler, MD, PhD
Karolinska Institutet
Department of Medicine
Division of Cardiology

Associate Professor Håkan Walfridsson, MD, PhD
Linköping University
Department of Department of Health, Medicine and Caring Sciences
Division of Diagnostics and Specialist Medicine

Professor Maria Eriksson, MD, PhD
Karolinska Institutet
Department of Molecular Medicine and Surgery
Division of Clinical Physiology

It is not terrible to have VEA (Ventricular Ectopic Activity), but it is not a great honour either

(John B. Kostis)

It is wise to keep in mind that neither success nor failure is ever final

(Roger Babson)

Popular science summary of the thesis

Premature ventricular contractions (PVCs) are heart beats originating from any part of the cardiac ventricles, instead of being conducted from the atria through the atrioventricular node. The incidence of PVCs is not entirely established, but they are regarded as a common form of arrhythmia. There is evidence of PVCs' correlation to a poor prognosis in individuals with established heart disease. However, the prognostic significance among healthy individuals is unclear. This issue has been investigated during recent decades with conflicting and uncertain results. Although several studies have been published, few of them had rigorous inclusion criteria, allowing a reliable identification of structural heart disease; many have relied solely on patient history and physical examination. With this research project, we wanted to evaluate whether PVCs have a negative effect on life expectancy and cardiovascular illness among persons without structural heart diseases.

Beside this overarching aim, we wanted to study whether additional imaging-based heart examination can unveil signs of disease when standard examination is normal and whether PVCs originating from some part of the ventricles are linked to a worse outcome.

To evaluate prognosis we included and followed individuals with PVCs and compared their outcome with a sample from the general Swedish population. PVC individuals were identified through the database of three secondary care centres in the Stockholm area. After identification through ICD-code (International Classification of Diseases), the PVC diagnosis was confirmed by an experienced cardiologist viewing the patients' data. For inclusion we demanded that the patients did not have a history of cardiovascular disease and had completed a thorough examination, including echocardiography and exercise test, with normal results. A four times larger population sample matched for sex and age was created by Statistics Sweden, and the clinical outcome was compared to the one for the PVC-patients. In a majority of patients in the PVC-group, we had access to PVC recording on 12 lead-ECG, which allowed us to determine their morphology and duration. We used these data to conduct a sub-group analysis aimed to explore whether PVC morphology, as a proxy for the anatomical site of origin, and the QRS width of the PVCs had a prognostic impact.

In order to evaluate the role of advanced imaging techniques, patients with a PVC-burden exceeding 10,000 PVCs/day and normal findings at standard echocardiography (ultrasound imaging) were examined with cardiac magnetic resonance imaging (CMR) or advanced echocardiography.

Our overall results show that thoroughly examined PVC patients without heart disease do not have a worse prognosis than a registry sample from the general population when

followed up for five years. Signs of cardiac dysfunction were often found in patients with very high PVC burden when they were further investigated with CMR and advanced echocardiography, and PVCs from the left ventricle were linked to a worse outcome.

Abstract

Introduction

Premature ventricular contractions (PVCs) are a common form of arrhythmia associated with poor prognosis in patients with structural heart disease. However, their prognostic impact on healthy individuals is unclear. There is also a lack of evidence about risk stratification of this group through cardiac imaging and electrocardiographic features. With this project we wanted to study whether patients with PVCs in which structural heart disease had thoroughly been excluded, have a worse prognosis than a control population. Moreover, we wanted to investigate whether PVC morphology and/or PVC duration are associated with the clinical outcome. Finally, we explored whether cardiac magnetic resonance imaging (CMR) and advanced echocardiographic parameters could unmask signs of structural heart disease in patients with high PVC-burden and normal echocardiogram.

Methods

To study the prognostic impact of PVCs, we identified 807 patients with no history of structural heart disease, normal echocardiography and exercise test and verified PVCs. During a follow-up period of 5.2 years, we compared the clinical outcome—in terms of total mortality and cardiovascular morbidity—with a population matched by sex and age. To explore whether electrocardiographic features have a prognostic significance among healthy PVC-patients, we identified 541 patients to which we had access to PVC recording on 12-lead ECG and analysed PVC morphology and QRS width.

For the studies focusing on diagnostic evaluation through advanced cardiac imaging, we included patients with a PVC burden of at least 10,000 beats/day and with normal results at exercise test and echocardiography. They underwent additional investigation with CMR (study 2) or advanced echocardiographic parameters that are normally not included in clinical praxis (study 3).

Results

Healthy PVC-patients had a generally favourable prognosis, showing no worse clinical outcome than the sex- and age-matched control group that had not undergone investigation to rule out heart disease. However, patients with high PVC-burden showed signs of myocardial dysfunction when advanced imaging techniques were used, despite normal results at standard investigation that included echocardiogram.

Sub-group analysis based on PVC-morphology showed that PVC originating from the outflow tract and the right ventricle was associated with a more favourable prognosis than intra cavity- and left ventricular PVCs respectively. Analysis of PVC-duration– measured as QRS-width during PVC–showed no impact on clinical outcome.

Conclusions

PVC patients who had undergone a thorough medical examination with normal results did not have a worse outcome than matched controls during a median follow-up time of 5.2 years.

PVC duration did not seem to be associated with the clinical outcome in our study including 541 patients with different sites of origin. However, PVCs with a morphology originating from the outflow tract and the right ventricle were associated with a better outcome.

CMR and comprehensive advanced echocardiography could identify signs of myocardial dysfunction in patients with high PVC burden and normal findings at standard echocardiography. The clinical significance of these imaging findings needs to be assessed by larger longitudinal studies.

List of scientific papers

I. Scorza R.; Jonsson, M.; Friberg, L.; Rosenqvist, M.; Frykman, V. Prognostic implication of Premature Ventricular Contractions in patients without structural heart disease. *EP Europace*, 2022; *euac184, https://doi.org/10.1093/europace/euac184*

II. Scorza, R.; Jansson, A.; Sörensson, P.; Rosenqvist, M.; Frykman, V. Magnetic Resonance Detects Structural Heart Disease in Patients with Frequent Ventricular Ectopy and Normal Echocardiographic Findings. *Diagnostics 2021 Aug 20;11(8):1505, 11, 1505*.

III. Scorza, R.; Shahgaldi, K.; Rosenqvist, M.; Frykman, V. Evaluation of patients with high burden of premature ventricular contraction by comprehensive transthoracic echocardiography. *Int J Cardiol Heart Vasc. 2022 Sep 15;42:101124*

IV. Scorza, R.; Jonsson, M.; Corander, J.-M.; Rosenqvist, M.; Frykman, V. Prognostic impact of morphology and duration of Premature Ventricular Contractions in a population without structural heart disease. *Submitted*

TABLE OF CONTENTS

List of abbreviations

AF	Atrial Fibrillation
ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
cESS	Circumferential End-Systolic Wall Stress
CI	Confidence Interval
CMR	Cardiac Magnetic Resonance Imaging
CT	Computerized Tomography
ECG	Electrocardiogram
EF	Ejection Fraction
ESC	European Society of Cardiology
GLS	Global Longitudinal Strain
HR	Hazard Ratio
ICD	International Classification of Diseases
LV	Left Ventricle
OT	Outflow Tract
PICMP	Premature Ventricular Contraction-induced Cardiomyopathy
PVC	Premature Ventricular Contraction
RV	Right Ventricle
RWMA	Right Wall Motion Anomalies
SCD	Sudden Cardiac Death
VT	Ventricular Tachycardia

1 Introduction and literature review

1.1 Historic perspective and epidemiology

Already in 600 BC, the Chinese physician Pien Ts'lo described intermittent perturbations of the heart rhythm[1]. He studied the life span of subjects with irregular heartbeats and concluded that life-length was not affected by this disturbance, unless it presented with a high frequency which implied a poor prognosis. In the 19th century, French scientist Etienne-Jules Marey managed to record ECG in animals and was the first to describe premature ventricular complexes (PVCs); the British physiologist August Waller succeeded with the same enterprise on humans in the late 19th century[2]. The American biophysicist Norman Holter contributed to the further development of diagnostic techniques with telemetric cardiac rhythm monitoring[3]. One of the first ECG-based epidemiologic investigations of a large population was published in 1962. Roland Hiss and Lawrence Lamb recorded ECG on about 120,000 apparently healthy males and found that almost 5% of them had electrocardiographic anomalies and 7.8 per 1000 had PVCs[4]. In 1967 Lown and colleagues associated extra beats originating from the heart's ventricles with an increased risk of malignant arrhythmia[5], which sparked the quest for a pharmacological treatment of PVCs[6]. In 1971 the same author also tried to classify PVCs based on their electrophysiological qualities and "complexity"[7]. During the 1970s and '80s, PVCs were described to occur in patients with previous heart diseases (especially myocardial infarction), extra-cardiac conditions (pulmonary disease) and healthy subjects[8-10].

In 1985 Kennedy et al. published a paper about 73 asymptomatic healthy subjects with frequent and complex ventricular ectopy who had been followed for ten years and had similar prognoses to that of the general population[11]. These findings were confirmed in a later study by the same author[12] and highlighted the continued interest in determining the prognostic impact of PVCs on healthy subjects[1]. A multitude of studies were published on this topic in the 1980s and '90s, showing conflicting results. A common criticism of many of these publications was the lack of rigorous use of proper diagnostics in order to rule out underlying heart disease[6], and the resulting evidence was summarised in 1992 by Kostis[1] who concluded that PVCs' contribution to mortality is not independent and rather that PVCs are possibly a marker of underlying heart disease. The subsequent notion that PVCs are associated with a worsened prognosis in the presence of structural disease but are quite benign in its absence was widely accepted at the turn of the millennium.

New times, however, bring new findings, and a new entity was soon to make its appearance in scientific journals. It was already known that tachycardia could induce a

form of cardiomyopathy, that has a favourable prognosis when the underlying arrhythmia is effectively treated[13]. What Chugh and colleagues described in the year 2000 was a PVC-related cardiomyopathy[14], a possible cause of potentially reversible heart failure. During the following years, several papers were published about PVC-induced cardiomyopathy and how it could be effectively treated with PVC ablation. However, the hypothesis that PVCs *per se* could lead to heart failure, even in normal subjects, sparked a new wave of interest in the old PVC debate. This culminated in the publishing of the two first meta-analyses[15, 16] in the matter, which both concluded that PVCs could represent a risk factor (or a risk marker?) even in individuals without apparent heart disease. The evidence was blurred, however, by both the high heterogeneity of the included studies and the poor use of diagnostic methods to exclude individuals with silent heart disease. All in all, the evidence according to the authors was unclear; more studies were needed. More recent publications continue to show conflicting evidence, showing a benign course in some cases[17, 18] and a negative prognostic impact in others[19]. Two review articles suggest that patients with low burden of PVCs and normal findings at echocardiography can be offered reassurance, while those with potentially significant burden or deemed at risk for cardiomyopathy should undergo clinical follow up[20, 21].

This issue, though clinically quite relevant, therefore remains open and unanswered. Many questions within the topic still engage physicians and researchers, such as: an adequate way to evaluate patients with PVCs, the potential significance of PVC number and morphology, the definition of specific risk factors and, maybe most interesting of all, whether PVCs are a *primus motor* of disease or "merely" a risk marker.

The significance of these questions is easily understood when one looks at the reported prevalence of PVCs in the general population. Data from the ARIC study[22, 23] show a PVC prevalence of about 5%, which increases to 23% among subjects with hypertension[23]. A well-known study by Fisher reported an incidence of about 7%[24], Kennedy et al. estimated a prevalence of 1-4% in the general population[11], and Kostis et al. reported a prevalence of nearly 40%[10]. The MRFIT study[25] based on a large cohort stated a prevalence of 4%, and in another large cohort undergoing Holter-recording, Yang et al. could report that 1.3% of the patients had a very high burden of PVCs (at least 20% of the total heart beats)[26]. More recently patch ECG has allowed extended recording periods, and screening of an elderly population has shown that a very high percent (99.5%) have at least one isolated PVC per hour, with 34.6% having ventricular tachycardia (more than four ventricular beats in a row) on a 24-hour basis[27].

The large variation of these data likely depends on different ways of recording and storing ECG in the different studies. Hence, despite the attempt to study PVC prevalence, the actual status of individuals outside research settings remains unknown.

It is reasonable, however, to believe that PVCs are common in the general population and that determining their prognostic impact is very important.

1.2 Pathophysiology

Three mechanisms have been described as being associated with the origin of ectopic beats,: re-entry, increased automaticity and triggered activity. For a re-entry phenomenon to originate, it is required that two different electric pathways exist, with one pathway being blocked in one direction. The different pathways will form the substrate for the arrhythmia and can either consist of existing anatomical structures (i.e. bundle branches, fascicles) or areas with different conduction velocity that may be the result of a pathologic process in the cardiac tissue; a classic example of this is the scar left by myocardial infarction or myocarditis. A depolarisation wave that passes through a fibrotic area can be slowed down enough to reach a healthy area of the myocardium that is no longer refractory, resulting in one or several extra beats. This mechanism explains why PVCs are common in populations with a higher incidence of cardiovascular events, such as males, smokers, the elderly and individuals with hypertension or an impaired ventricular function[23, 28, 29].

During triggered activity an increased calcium entry leads to high intracellular concentration and spontaneous calcium release from the sarcoplasmic reticulum and delayed afterdepolarisation, albeit the exact mechanisms leading further to electric activity from a specific area remain unclear[30]. Prolonged repolarisation and delayed afterdepolarisation can occur in conditions such as bradycardia, digitalis intoxication, hypokalaemia or Long QT-syndrome[31-33]. An enhanced electrical automaticity (i.e. the capacity to depolarise spontaneously and start a new depolarisation wave) can also be multifactorial and include catecholaminergic effect, transient or permanent tissue alterations and inherent cellular characteristics[34, 35].

Although it may appear as mostly a question of an academic nature, it is clinically relevant to understand the biological mechanism behind PVCs, because it is one of the factors determining the success of therapeutic intervention[36]

1.3 Clinical outcome and prognostic impact

The negative effect of PVCs on prognosis in presence of structural heart disease is well established. The findings from the aforementioned studies from the 1960s and '70s were corroborated in the decades that followed by similar findings amongst patients with previous ischaemic events[37-40]. Even in non-ischaemic cardiomyopathy a link between PVCs and poor outcome has been established[41, 42]. In a review article from

1993[43], Myerburg et al. stressed the importance of PVCs in the pathophysiology of malignant arrhythmias, the PVCs being the link between ischaemia and ventricular tachycardia/fibrillation. In the meantime, the CAST study had shown that suppressing ventricular ectopy with class I anti arrhythmic drugs in myocardial infarction survivors did not lead to a better prognosis. On the contrary, the study participants who had received flecainide or encainide had a higher mortality than those who received placebo[44].

If the prognostic impact (or the risk marker role) of PVCs in structural heart disease seems unquestionable, the evidence about the same impact in healthy subjects is much more uncertain.

Many of the studies showing a negative prognostic impact use the patients' history to exclude structural heart disease and/or are based exclusively on male participants[19, 22, 25, 45-48] . Among large population studies, the one published by Agarwal[49] showed a higher incidence of heart failure (HF) when PVC patients were compared to a large control group (figure 1). Interestingly enough, the relation between PVC and incident HF was stronger in patients with fewer cardiovascular risk factors (6-fold risk increase for patients <65 years, without CHD, diabetes, hypertension or atrial fibrillation). In a large cohort of Japanese men and women followed for 12 years[50], Hirose reported an increased risk for cardiovascular mortality among men with PVC, while PVCs didn't seem to have a prognostic impact among women. More recently, studies on Asian populations again showed an association between PVCs and all-cause mortality, hospitalisation and heart failure on a population basis [19, 51].

A few studies have used echocardiographic evaluation at enrolment. Dukes et al.[52] studied 1,139 individuals who had their PVC frequency quantified by Holter monitoring. Associations were studied between number of Holter-detected PVCs and Left Ventricular Ejection Fraction (LVEF) measured at baseline and every fifth year during follow-up. Individuals in the quartile with the highest PVC frequency had a threefold risk for a five-year decrease in LVEF, a 48% increased risk of incident CHF and a 31% increase of death compared to those in the lowest quartile after adjustment for confounders and a median follow-up of 13 years. The results were similar when PVCs were analysed as a continuous variable. In contrast, the study by Lee and colleagues showed that only few PVC patients with normal LVEF developed left ventricular systolic dysfunction during follow-up of about five years[17].

PVC prevalence and clinical implication in a paediatric population has recently been investigated by Nomura and colleagues, who concluded that few patients developed VT, but some patients with "complex" PVCs needed careful observation[18].

Variable	VPC Diagnosis (n= 35,817)	No VPC Diagnosis (n= 16,722, 086)	p-value
Mean Age (years)	65.8 ± 17.1	50.2 ± 19.4	<0.001
Male	18,294 (51.1%)	7,073,296 (42.3%)	<0.001
			<0.001
White	22,584 (63.4%)	8,144,664 (54.2%)	
Black	2,508 (7.0%)	1,100,724 (7.3%)	
Hispanic	5,825 (16.3%)	3,818,663 (25.4%)	
Other	4,723 (13.3%)	1,962,942 (13.1%)	
Hypertension	26,672 (74.5%)	4,112,770 (24.6%)	<0.001
Diabetes mellitus	13,202 (36.9%)	2,018,290 (12.1%)	<0.001
CAD	14,928 (41.7%)	1,106,269 (6.7%)	<0.001
Atrial Fibrillation	7,737 (21.6%)	528, 252 (3.2%)	<0.001
Median Income * (quartile)			<0.001
1 st	6,411 (18.8%)	3,220,554 (21.4%)	
2 nd	7,562 (22.1%)	3,637,799 (24.2%)	
3 rd	9,418 (27.6%)	4,020,788 (26.7%)	
4 th	10,745 (31.5%)	4,179,027 (27.7%)	

Figure 1 Characteristics of PVC patients compared to individuals without PVC diagnosis. Reproduced with permission from Agarwal et al. Relation Between Ventricular Premature Complexes and Incident Heart Failure. *American Journal of Cardiology*. 2017;119:1238-1242. © 2017 Elsevier Inc

Extra-cardiac clinical outcomes have also been studied in relation to PVCs; studies from Ofoma[53] and Agarwal[54], in fact, have shown an increased risk for ischaemic stroke in subjects with PVCs. The possible link in this case could be atrial fibrillation (AF), given that the risk for developing AF has been demonstrated to be increased with increased incidence of PVCs[55]. A more recent study by Im[56] focused on patients with a high PVC burden (>10%) and concluded that high burden of PVCs was associated with central neurological symptoms without a prior diagnosis of stroke or transient ischaemic attack.

Along with the aforementioned studies showing a negative prognostic impact of PVCs in the general population or in cohorts without apparent heart disease, there are others that do not show such a link. The first of these studies by Fisher in 1973[24] found that the risk for coronary artery disease was not increased by the presence of PVCs on routine ECG in a population of factory workers, ages 35-69. A decade later Kennedy et al.[11] published results based on an average 6.5 years long follow-up of 73 asymptomatic healthy subjects with frequent ventricular ectopy and reported one case of sudden death, which compared to the standardised mortality ratio suggested that the long-term prognosis was not affected by the presence of PVCs. This study particularly

contributed to the emphasis that PVCs are harmless in absence of structural heart disease, and some subsequent studies seem to confirm these results[17, 57-60].

In a study that was more specifically focused on the potential development of Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), Gaita et al. followed sixty-one patients with frequent right-ventricular PVCs[61]. After an average follow-up of 15 years, no patient had died of SCD nor developed ARVC, and half of the patients no longer had PVCs. In a more selected population of 5,000 athletes, Verdile et al. observed that exercise-induced PVCs tended to either subside spontaneously over time or could be successfully treated, and did not affect the clinical outcome[62].

As shown, although the papers showing a prognostic impact of PVCs on subjects without apparent heart disease outnumber those not showing this association, the total picture is divided, and the resulting evidence unclear. The issue is complicated by the fact that very few studies consistently used imaging diagnostics to rule out heart disease; instead most studies relied basically on patient history. Meta analyses of the prognostic impact of PVCs in individuals without pre-existing heart disease were missing until 2012 when Lee et al. published the first one[15], which was rapidly followed by Ataklte and colleagues[16]. The meta-analysis by Lee included studies that used a control population and were based on adults without apparent heart disease and excluded studies on unselected populations that had not been evaluated for structural heart disease, studies on exercise-induced PVCs and subgroup-studies within a PVC-population. When multiple studies were based on the same cohort, only the most recent was included in the meta-analysis. Out of the >3,000 studies published about PVCs between 1966 and 2011, only eight met this inclusion criteria. All of them were prospective observational cohort studies. Sensitivity analysis showed that only studies based exclusively on men showed a negative prognostic impact from PVCs; the only study that used echocardiography and exercise test at inclusion did not show worsened prognosis. According to the authors heterogeneity among the studies was large and bias publication was not apparent. The pooled OR of the meta-analysis for developing death, cardiovascular death, SCD or ischaemic heart disease compared to those without PVCs was 1.72 (95% CI 1.28-2.31). Classic cardiovascular risk factors such as male gender, mean age, proportion of patients with diabetes and hypertension increased the odds for cardiovascular events, suggesting that patients with underlying undetected heart disease were included, affecting the results. According to the authors the result of the meta-analysis "suggests that if the studies had used more advanced techniques to rule out structural heart disease, they should have observed benign outcomes with PVCs". Consistent with this, assessment of the studies according to study quality suggested that the increase in OR for PVC patients was less pronounced in studies with higher quality (figure 2). Thus, the conclusions of this meta-analysis were that while current evidence supported the hypothesis of PVCs as a risk factor (or a risk marker) even in

healthy individuals, it suffered from many flaws as most of the viewed studies didn't properly rule-out structural heart disease.

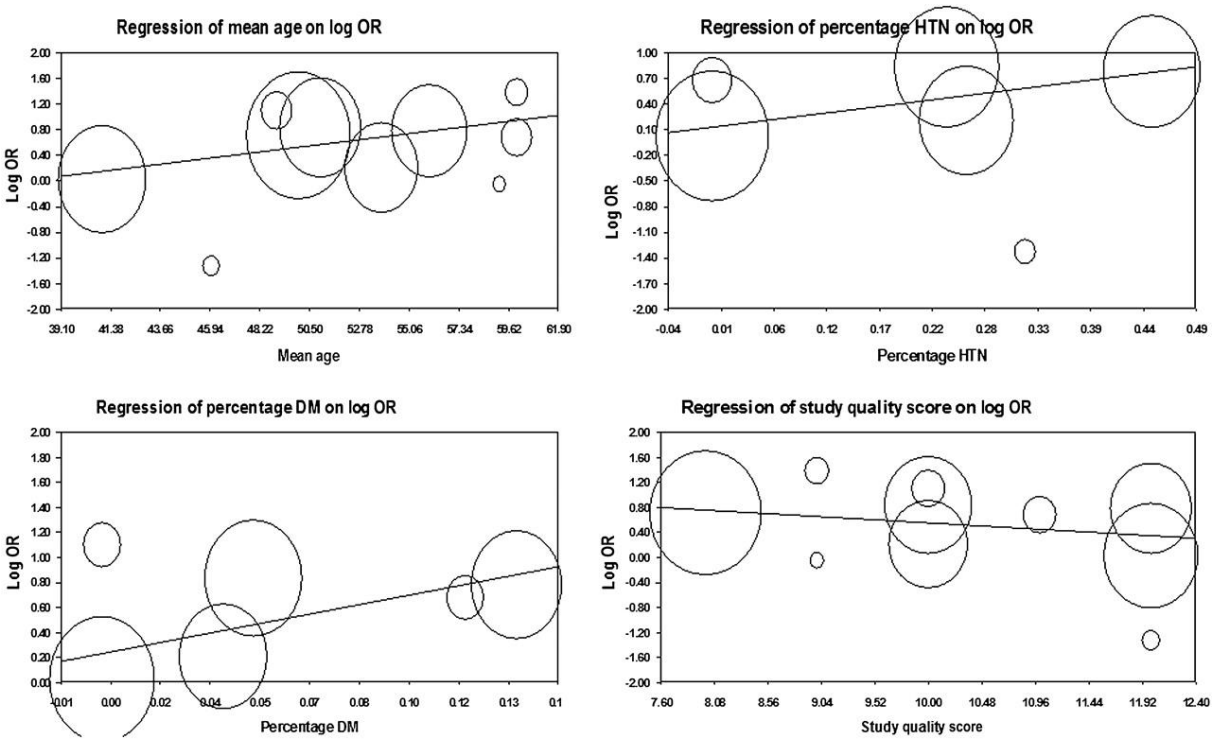

Figure 2 Correlation between Odds Ratio and characteristics, suggesting that presence classic risk factors for cardiovascular disease in the studied PVC populaiton were associated with higher risk for negative outcome. Reproduced with permission from Lee et al. The prognostic significance of premature ventricular complexes in adults without clinically apparent heart disease: a meta-analysis and systematic review. *Heart*. 2012;98:1290–1298. Copyright © 2012, BMJ Publishing Group Ltd. & British Cardiovascular Society

The meta-analysis by Ataklte included prospective cohort, nested case-control and retrospective cohort studies. Search and viewing processes left the authors with 11 relevant studies, many of them shared with the meta-analysis by Lee, involving a total of 106,000 patients. The prevalence of PVCs in the studies ranged from 1.2% to 10.7% and the mean follow-up time from five to 30 years. The six prospective studies included in this meta-analysis did not show significant heterogeneity. The total effect of PVCs on prognosis was assessed as "substantial" with a pooled RR for total cardiac death of 2.1 (figure 3), and two hypotheses in pathophysiology were proposed by the authors: PVCs trigger fatal ventricular arrhythmias or observations are a result of reverse causation, that is PVCs are a marker of underlying disease. The authors also suggested an insufficient adjustment for possible confounders in some of the studies, however, they didn't stress the lack of proper cardiac diagnostics at inclusion as much as Lee and colleagues did.

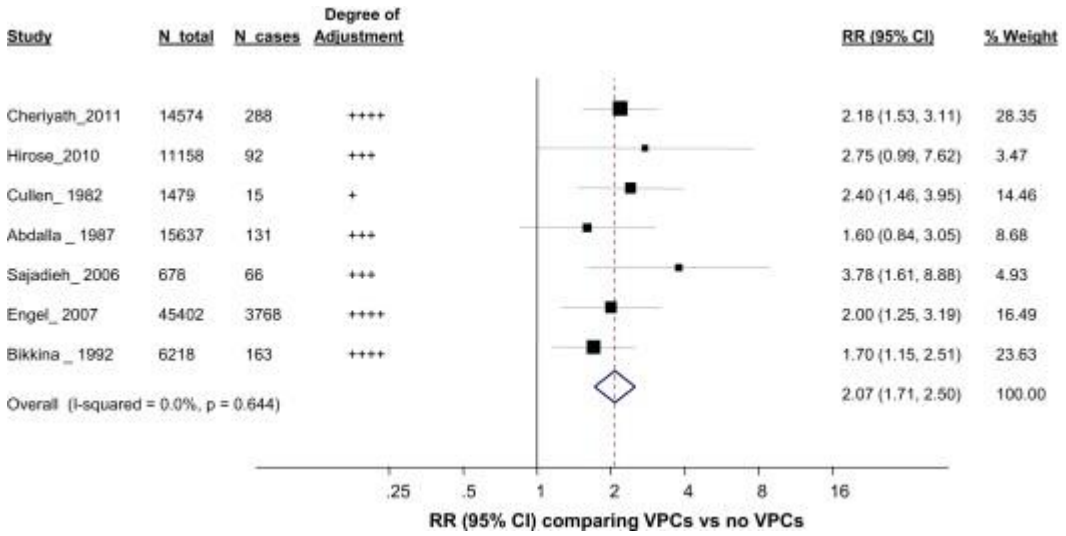

Figure 3 Association between presence of PVCs and risk for total cardiac death. Reproduced with permission from Ataklte et al. Meta-Analysis of Ventricular Premature Complexes and Their Relation to Cardiac Mortality in General Populations. *Am J Cardiol*. 2013;112:1263-1270. Copyright © 2013 Elsevier Inc.

Two meta-analyses have also been published in the matter of exercise-induced PVCs and their potential prognostic impact. The first, by Kim et al.[63], contained nine studies including 62,000 participants. PVCs during recovery were associated with an increased risk of death (RR 1.55, 95% CI 1.22-1.96), while the effect of PVCs during exercise did not reach statistical significance (RR 1.14, 95% CI 0.96-1.34), and the authors called for further studies. However, the overall effect for PVCs during exercise test corresponded to a RR of 1.41 (95% CI 1.23-1.61) for all-cause mortality and 1.86 (95% CI 1.51-2.30) for cardiovascular mortality. Similar conclusions were reached by the meta-analysis from Lee et al.[64], published in 2017, in which only PVCs during recovery, and not during exercise, were associated to poor prognosis. The authors suggested previously described autonomic dysregulation[65, 66], with increased sympathetic drive creating a pro-arrhythmic substrate, as a possible path leading to fatal disease.

1.4 PVC-induced cardiomyopathy

When summarising the evidence about the prognostic impact of PVCs on subjects without heart disease, PVC-induced cardiomyopathy (PICMP) must be treated separately. This entity, that was described about 25 years ago, has in fact a pathophysiology of its own. That pathophysiology Is likely distinguished from the multiple pathogenic ways that can be observed in the general PVC impact which we have summarised thus far. A proof of this is that PICMP is a reversible condition, associated with a good prognosis when underlying PVCs are effectively treated. However, it is possible that PICMP has historically contributed to the general prognostic impact from PVCs, especially before the condition was described and effective ablation

techniques were developed as successful therapeutic tool for PVCs[67]. The mechanisms leading to PICMP are currently unknown, though several theories have been formulated. Among those theories are: electromechanical dyssynchrony, extrasystolic potentiation, interpolation, R-R variability and myocardial remodelling by short-coupled PVCs[68]. On a cellular level the suggested pathophysiology involves alteration of myocardial perfusion and oxygen consumption, altered expression of ion channel and intracellular proteins and changes in autonomic tone[69]. Especially dyssynchrony has been discussed as a possible pathophysiologic mechanism[70]. The prevalence of PICMP varies between 6-7% in studies based on populations with frequent PVCs to 38% in populations referred for ablation[71].

Even if the amount of evidence around PICMP is increasing, the majority of studies supporting a link between PVCs and cardiomyopathy are based on retrospective or cross-sectional data[72]. As mentioned before, the first papers to describe PICMP were the ones published in 1997 by Vijgen[13] and in 2000 by Chugh[14]. Some studies showed that patients with idiopathic dilated cardiomyopathy improved in EF after pharmacological suppression of PVCs[73,74]. Vijgen and colleagues described a patient who presented with repetitive runs of non-sustained ventricular tachycardia and dilated cardiomyopathy, in which ablation of the arrhythmia focus lead to improvement of the ventricular systolic function. The paper by Chugh was the first to describe cardiomyopathy directly associated with isolated, although frequent, PVCs. Even in this case, the authors could describe recovery from heart failure after successful radiofrequency ablation. A couple of years later Shiraishi published a similar case report[75] and recommended ablation as choice of therapy in such patients.

Bogun et al. studied 60 consecutive patients with frequent PVCs treated with ablation, concluding that idiopathic PVCs may cause a form of cardiomyopathy that can be reversed by ablation[76]. Similar results where shown by Sekiguchi[77], who also showed that patients in which ablation was unsuccessful failed to restore their LVEF. The 22 patients of this cohort who had a reduced EF had significantly more PVCs than the rest, and 18 of them had a normalised EF after ablation. In 2005 Takemoto et al.[78] described how ablation of RVOT PVCs lead to an improvement in LVEF, left ventricular end-diastolic diameter and functional NYHA class in patients with a very high (>20%) PVC burden.

Since then several papers have been published concerning PICMP and its resolution by successful ablation. In 2013 Hasdemir et al.[79] evaluated 348 patients with frequent PVCs or short runs of ventricular tachycardia. Definition criteria for PICMP were impaired left ventricular function with ejection fraction (LVEF) lower than 55% without detectable underlying heart disease and 15% improvement of LVEF after arrhythmia treatment. During the five years of follow-up, 24 patients developed PICMP. Greatest improvement in EF was observed the first week after PVC ablation, and subjects who improved their EF early had a better total recovery after one year. Baman[80] constructed receiver-

operator curves to identify a cut-off PVC burden associated with left ventricular dysfunction and concluded that a burden of 24% served best as separator between subjects with preserved and impaired left ventricular function.

In the last five years, the evidence around PICMP and ablation results has grown larger, and additional knowledge about subgroup predisposition and response to treatment is now available. Yokokawa et al. showed that epicardial origin of PVCs predicts late recovery in LVEF after ablation[81]. Fang compared ablation effects to those from anti-arrhythmic drugs (although groups were not randomly assigned therapy) concluding that the clinical results were comparable in the two groups, and both performed better than a control group of PVC patients[82]. Baser was the first to study long-term results of PVC ablation[83] in a study of 60 patients who underwent successful ablation for PICMP and were followed up for a mean of two years. Ten patients relapsed in recurrent PVCs, and their EF significantly decreased since post ablation, while EF was preserved in the remaining patients in which ablation effects lasted longer. The authors concluded that patients with a history of PICMP must be controlled after ablation, especially if originally asymptomatic and with multifocal PVCs. Wojdyla-Hordynska et al. compared ablation effects in patients with and without underlying structural heart disease and concluded that patients with LVEF<50% at baseline presented greatest recovery in ejection fraction as both groups were benefitted by ablation[84].

A meta-analysis focusing on characteristics linked to risk for developing PICMP has recently been published[85]. A total of 26 studies and 11 risk factors were included and analysed, concluding that eight characteristics (age, presence of symptoms, non-sustained VT, LV origin, epicardial origin, presence of interpolation, PVC duration, and PVC burden) were associated with risk for PICMP.

Two meta-analyses have also been published on PICMP and ablation results, both in 2014. Zang et al.[86] included results from fifteen studies with a total of 712 patients and reported a mean PVC burden before ablation of 24% as well as an overall mean increase in LVEF post ablation of 7.7% (12.4% in patients with LV-dysfunction at baseline), leading to the conclusion that ablation of frequent PVCs improves cardiac function, especially in parents with impaired LVEF. The other meta-analysis by Lamba and colleagues[87] focused on PVCs with RVOT origin and analysed results from six articles. Ablation significantly reduced PVC burden and improved LVEF by a mean of 10.36.

Although there is strong evidence today to support catheter-ablation's efficiency at improving EF in PICMP, there is some evidence that the same effect can be obtained by pharmacological treatment, as long as it is equally successful in quenching PVC burden.

1.5 PVC burden, PVC morphology and other electrophysiological features

In addition to studies evaluating the effects on heart function and clinical outcome, there has been some focusing on risk stratification of PVC patients based on electrophysiological features. Some authors have even used a series of electrophysiological features to build risk scores for PVC patients[88].

The issue of whether there is a tipping point in the number of PVCs has been explored in several studies, yielding different results. However, a lower-than-expected PVC burden has sometimes been linked to a worsened prognosis[52, 80, 89-91]. Through receiver operator characteristics curves, Lin et al. could obtain the value of 12 PVCs/day as the (surprisingly low) optimal cut-off value for increased risk of heart failure and sudden death[51], yielding both sensitivity and specificity values of around 60%. However, in other studies there was no clear correlation between PVC burden and outcome[17].

A broad PVC, measured as width of the QRS complex during the ectopic contraction, has been associated to an adverse prognosis, and an approximate cut-off value of about 150 milliseconds has been identified[92-96]. A wide QRS during PVC can act both as a risk marker and a risk factor because a low myocardial conduction can be due to the presence of fibrotic tissue and a slow depolarisation can per se lead to dyssynchrony. Moreover, wider PVCs can be a sign of an epicardial origin. PVC morphology–as a surrogate for site of origin–has also been investigated as a means of risk stratification. Even in this field the evidence seems to be clearer for individuals with established heart disease, among whom multifocal PVCs are associated to a worse prognosis than unifocal[58, 97, 98]. For structurally healthy individuals with PVCs, it is unclear whether QRS morphology has a prognostic significance. A clear limitation is that most relevant studies are carried out in ablation settings and therefore on selected material[78, 80, 93, 99-101].

Other electrophysiological evaluations have included PVC interpolation, coupling interval and Peak Deflection Index[92, 96, 102, 103] . Regarding the coupling interval, both long- and short-coupled PVCs have been reported as being capable of triggering malignant ventricular arrhythmias[92, 104, 105]. This discrepancy could be explained by two different mechanisms: While short coupling intervals are more likely to start malignant arrhythmias, long ones can increase the risk for LV dysfunction. Another hypothesis is that a pronounced irregularity of the rhythm per se, with both long and short intervals (high “interval dispersion”), is a predictor of cardiomyopathy[106].

1.6 Diagnostics and significance of imaging findings

Current guidelines recommend a thorough examination of patients with ventricular arrhythmia, including individual and family history, physical examination, 12-lead ECG, ambulatory electrocardiography, exercise testing and echocardiography[107, 108]. However, not all PVC patients in clinical practice undergo all relevant examinations to exclude structural disease.

Another open question is whether traditional imaging methods are accurate enough to identify subtle findings such as limited damaged areas of myocardium, which could act as site of origin for PVCs, or if more advanced imaging should be performed. Cardiac magnetic resonance imaging (CMR) has particularly gained evidence during recent years as a method able to identify subtle heart disease in PVC patients. A forerunner in this area, Proclemer published findings in 1997 from CMR examinations of 19 patients with frequent monomorphic PVCs, and 10 controls[109]. Results showed that RVOT dimensions were wider in PVC patients, and wall motion anomalies were present in 16/19 PVC patients, while all controls had normal MRI findings. These results were corroborated thereafter by a series of following studies[61, 110-113]. Some of these studies could even show a link between CMR findings and prognostic outcome [114, 115]. An interesting study is the one by Nucifora[116], in which 46 patients with monomorphic ventricular arrhythmia of LV origin and 74 patients with idiopathic monomorphic arrhythmia of RV origin were included in two different groups. The LV group in this study had significantly more CMR anomalies that were also associated with cardiac events. CMR has also been used for etiological diagnosis in a population with and without previously assessed mixed ventricular arrhythmias[117, 118] or to reveal different contribution of PVCs to hemodynamics[119, 120]. However, the majority of these studies have narrow inclusion criteria regarding PVC morphology or patient characteristics, so there are still open questions about a wider use of CMR in evaluation of PVC patients.

The study published in 2020 by Muser and colleagues is particularly interesting; 518 patients with >1,000 PVCs/day and normal findings at echocardiography were included on a multicentre basis and underwent CMR. During a median follow-up of 67 months, patients with myocardial anomalies on CMR had a higher risk for negative outcome (defined as a composite of sudden cardiac death, resuscitated cardiac arrests and appropriate therapy from implantable cardioverter defibrillator) compared to individuals without CMR findings[121]. Recently, Edward Gerstenfeld published a paper with the thought-provoking title "Should CMR be performed for every patient with frequent premature ventricular contractions?", in which he suggests an algorithm including PVC burden and morphology to determine CMR indication[122] (figure 4).

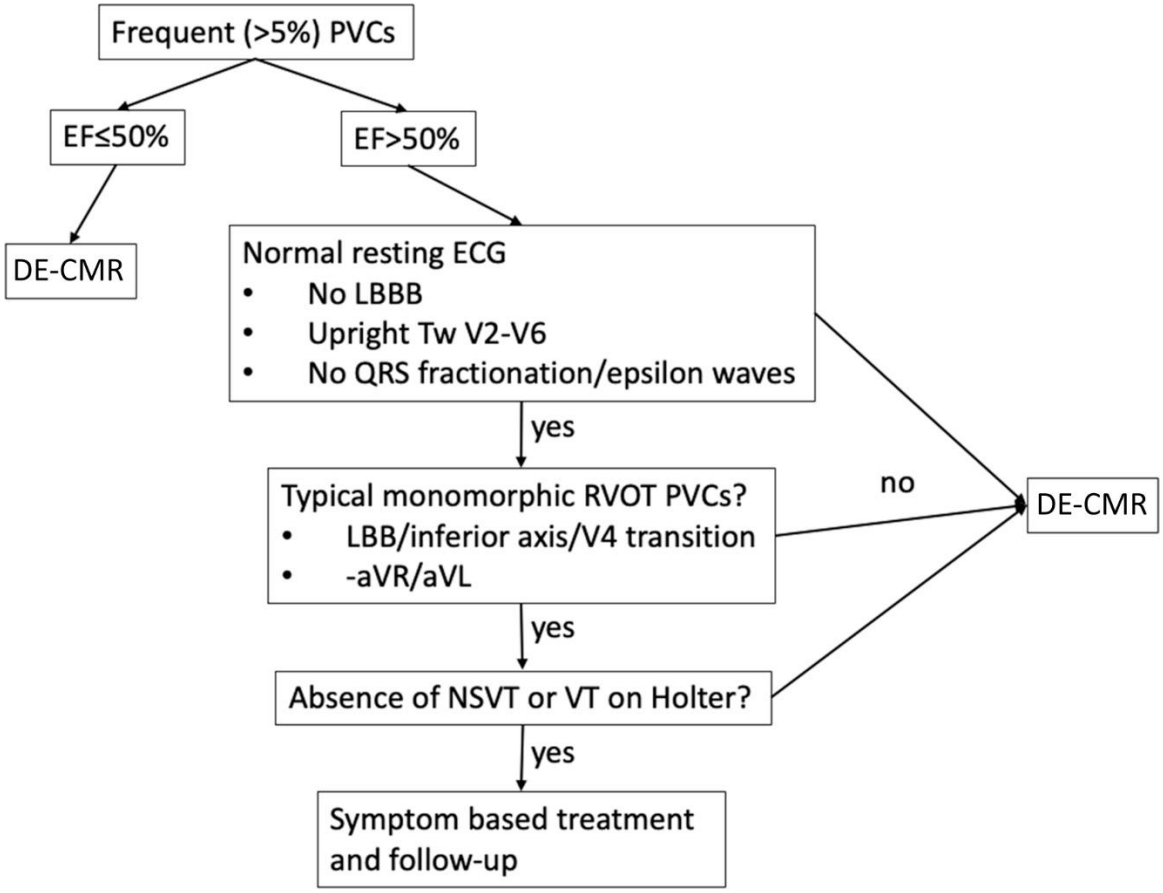

Figure 4 Suggested algorithm for PVC patients, DE-CMR= delayed-enhancement cardiac magnetic resonance. Reproduced with permission from Gerstenfeld EP. Should CMR Be Performed for Every Patient With Frequent Premature Ventricular Contractions? *JACC Clin Electrophysiol.* 2022;8:1133-1135. © 2022 by the American College of Cardiology Foundation. Published by Elsevier.

Although CMR is recommended in both European and American guidelines, and its role is generally more clearly highlighted in a recently published ESC paper[108], the method is not broadly used in clinical praxis. This is partially due to its cost and limited accessibility. Echocardiography, on the other hand, is a more common evaluation method, and it has been studied whether additional echocardiographic parameters can add clinically relevant information. However, the body of literature in this field is not as large as for CMR. We have already mentioned the study by Lie about the burden of PVCs leading to PICMP[89]. This study used speckle tracking echocardiography to assess left ventricular global longitudinal strain (GLS) and mechanical dispersion and stated that PVC burden correlated with GLS and mechanical dispersion but not with ejection fraction. Other studies have used speckle-tracking echocardiography to identify subtle myocardial dysfunction in PVC patients. In the study from Wijnmaalen[123], 49 subjects with PVCs and 26 healthy controls had normal LVEF, however speckle tracking showed reduced ventricular strain significantly more often in PVC cases than in controls. Radial, circumferential and longitudinal strain improved significantly after ablation but remained unchanged in untreated patients. Ling studied 40 subjects with monomorphic frequent PVCs and 40 controls[124] and detected no significant differences in standard 2D-echocardiographical findings (including EF) between the two groups; however,

parameters evaluated with 3D-speckle tracking echocardiography were significantly worse in the PVC group.

Most studies (and evaluations in clinical praxis) focus on systolic LV function. A study by Topaloglu[125], however, examined the effect of frequent PVCs on diastolic LV function. This study included 33 symptomatic patients with normal systolic function and 30 healthy controls. Among the cases, 13 subjects showed impaired relaxation and both PVC burden and age were found to be independent predictors in these individuals. Circumferential end-systolic wall stress (cESS) measured by echocardiography was associated with symptoms in PVC patients with normal systolic function according to a study by von Taxis et al.[126] and authors reported that cESS decreased after successful ablation and remained unchanged after non-successful procedure.

1.7 Evidence in brief

To summarise the current evidence about PVCs with focus on prognosis in absence of structural heart disease, it would be appropriate to start with the most solid piece of evidence: PVCs are related to a poor prognosis in subjects with structural heart disease, whereas PVCs may induce cardiomyopathy (PICMP) in healthy subjects. We know that the risk of developing cardiomyopathy increases with a higher PVC burden and with "broad" PVCs. We also know that multiform PVCs herald a worse prognosis than uniform PVCs**,** but it is not sure whether that is true among patients without structural disease. Some of the more recent studies in the field are summarised in table 1.

In general the prognostic significance of PVCs in healthy individuals is uncertain, and it is not stated which level of PVC burden is associated with a higher risk for cardiomyopathy. Although CMR seems to be able to identify subtle signs of pathology in PVC-patients with normal echocardiogram, more evidence is needed for supporting a broader use of the method. The evidence about the role of advanced, non-conventional echocardiographic parameters is limited.

First Author	Publ. year	Design/Population	Main findings
Lee	2012	Meta-analysis of eight studies with a total of 37,387 patient years followed	PVC patients had an increased risk for all cause-mortality when compared to PVC-free individuals. Most included studies did not have sufficient methods to exclude concomitant heart disease.
Ataklte	2013	Meta-analysis of eleven studies comprising a total of 106,195 participants	Increased risk for mortality was shown for PVC patients. The included studied had no significant heterogeneity and were population based, implying a high external validity.
Dukes	2015	Follow up of 1,139 individuals over 65 years of age examined with 24-hour ambulatory ECG and echocardiography	Correlation between number of PVCs and risk for developing LV dysfunction.
Agarwal	2017	California healthcare-data-based comparison of 35,817 subjects with PVC diagnosis to 16 million without PVC diagnosis	Increased risk for incident systolic heart failure after appropriate adjustment.
Lee	2019	Follow up of 100 individuals with >5% PVC burden and normal echocardiography	A few patients developed LV dysfunction.
Nomura	2020	Student screening of 82,000 first graders and 87,000 seventh graders	Individuals with PVC showed a generally favourable course.

Table 1 Summary of some of the studies published in the last decade exploring prognostic significance of PVCs in healthy patients

2 Research aims

With this project we tried to fill in some of the aforementioned knowledge gaps. The overarching aim of the project was to assess whether PVCs are associated with a negative prognostic outcome in healthy individuals and whether cardiac imaging and ECG-features can be valuable tools to identify risk patients. More specifically, the following aims were set:

Study 1

To compare prognosis for individuals with PVCs and normal findings at exercise test and echocardiography with a sex- and age-matched sample of the general population

Study 2

To assess whether CMR reveal signs of pathology in subjects with high PVC burden and normal echocardiogram, regardless of PVC morphology

Study 3

To investigate whether advanced echocardiography with non-conventional parameters add clinically relevant information in subjects with high PVC burden

Study 4

To study the importance of PVC morphology and QRS width during PVC as a prognostic tool among subjects without underlying heart disease

3 Methods

3.1 Study 1

3.1.1 Inclusion process and study base

To identify patients with PVCs we conducted a search in the database of three major hospitals in the Stockholm area within time interval January 2010 to December 2016. After identification of patients through ICD codes, the correctness of the PVC diagnosis was verified by an experienced cardiologist through scrutiny of their medical records. We then excluded patients with previous cardiovascular disease (myocardial infarction, heart failure, sustained ventricular tachycardia, survived cardiac arrest, moderate or severe valvular dysfunction, and previous cardiac surgery). Among remaining patients only those who had been evaluated with ECG recording, echocardiography and exercise test, with echocardiography and exercise test (or completing exams to rule out coronary artery disease) showing normal findings, were included. We defined normal findings at echocardiography as Left Ventricular Ejection Fraction (LVEF) equal or higher than 55%, absence of class II-IV valvular heart disease, normal ventricular dimensions and normal ventricular wall thickness. Normal exercise test was defined as absence of electrocardiographic finding indicating possible coronary artery disease, such as exercise-induced depression of the ST interval, or exercise-induced ventricular arrhythmia. In presence of such findings, we included patients only if an additional exam (myocardial scintigraphy, magnetic resonance tomography, or coronary angiography, according to clinical practice) ruled out coronary artery disease.

After these steps we included 863 individuals with PVCs. We linked each PVC patient to four controls matched for age and sex, obtained from Statistics Sweden. Data for both PVC cohort and controls were obtained from the National Patient Registry (NPR) and the Swedish Prescribed Drugs Registry, which are both run by the National Board of health and Warfare. These data covered all in-patient hospital care and hospital associated out-patient care in Sweden for the years 1997 to 2018. However, after linkage with NPR, we could state that 40 of them had previously received a cardiovascular diagnosis, which led to their exclusion, leaving us with 823 PVC patients. Amongst the controls 64 individuals had a previous PVC diagnosis and were therefore excluded, along with their matched cases.

As a result of this process, we had a study base of 807 PVC patients and 3,228 controls on which we performed our survival analysis. To analyse cardiovascular morbidity we chose to exclude controls with previous cardiovascular diagnosis and their corresponding PVC cases, meaning that 639 PVC patients and 2,556 controls remained for the morbidity analysis (figure 5). Cardiovascular morbidity was defined as diagnosis of ischaemic heart disease (ICD-10 codes I20-I25), cardiomyopathy (I42, I43), cardiac

arrest (I46), ventricular tachycardia (I47.2), ventricular fibrillation (I49.0) and heart failure (I50).

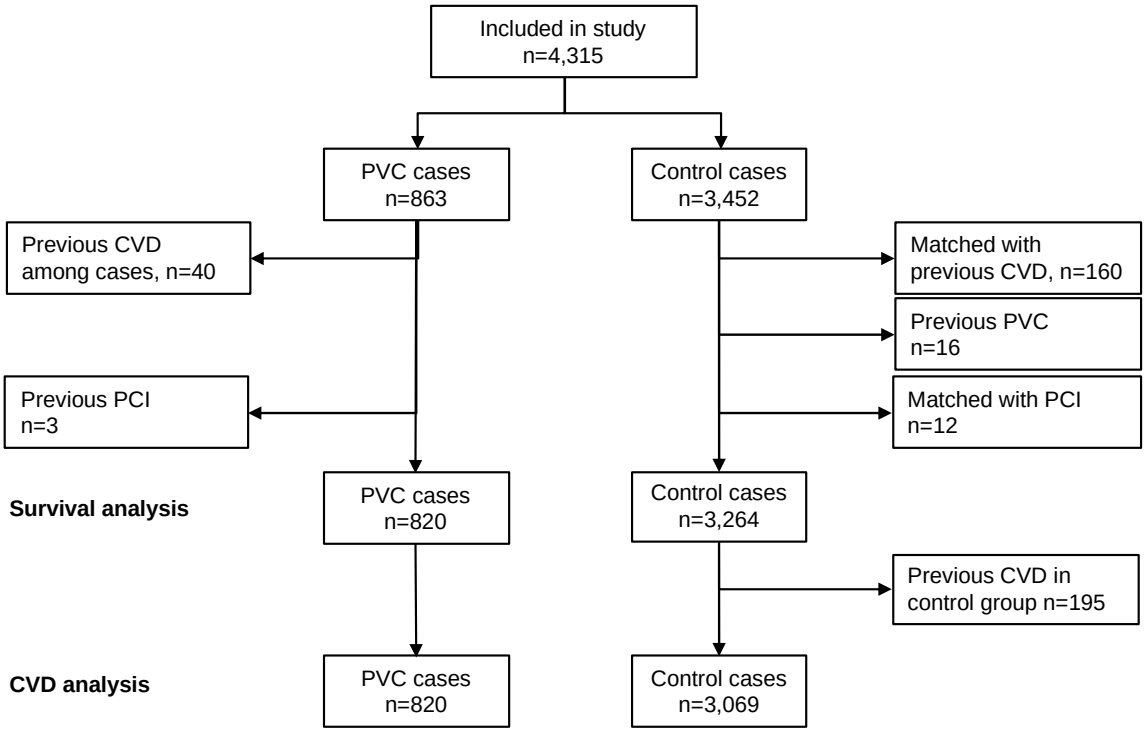

Figure 5 Inclusion process in study 1. Copyright © 2022, Oxford University Press

3.1.2 Power calculation and statistics

Prior to the study we ran a power calculation based on the hypothesis of non-inferiority, given that our hypothesis was that "truly" healthy individuals did not have a worse prognosis than controls. According to the calculation, by including 700 persons and following them up during an average time of five years we would have a high statistical power to identify a two-times higher mortality risk among the PVC cases (figure 6). The assumption of two-times higher risk was based on published meta-analysis[15, 16].

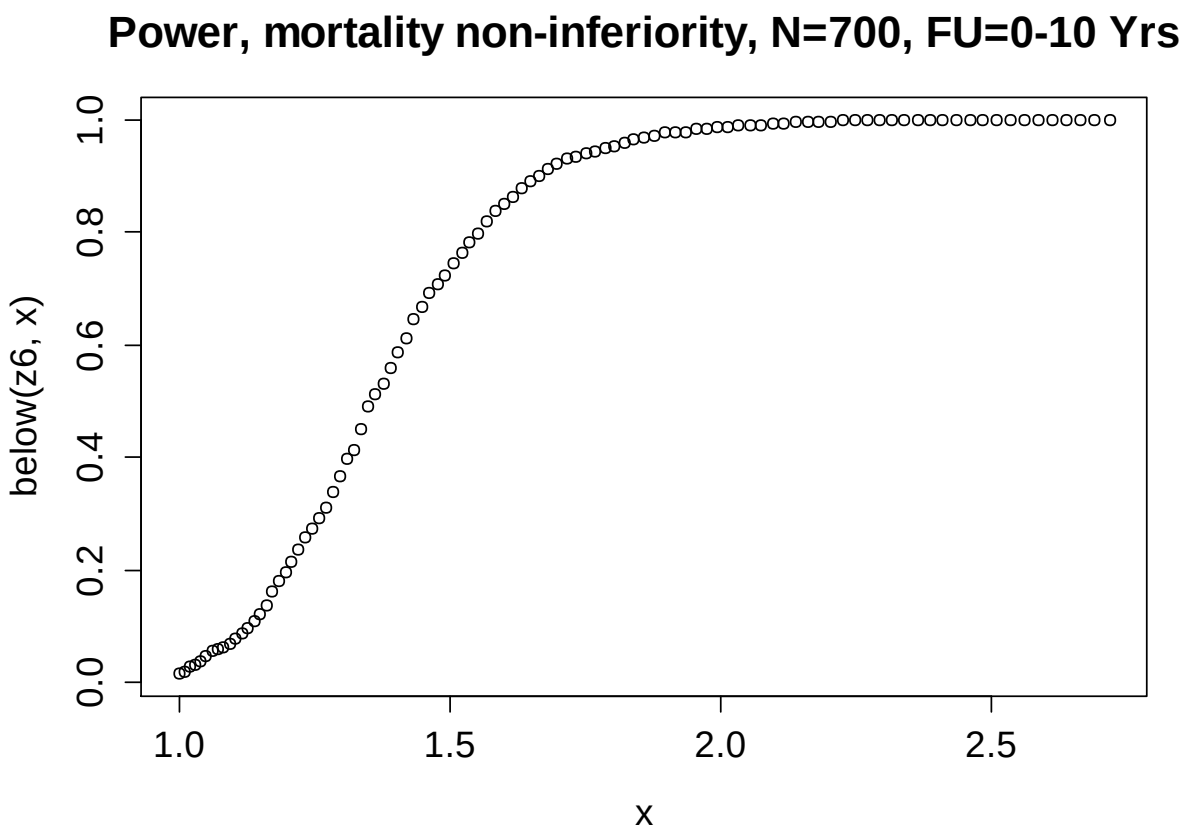

Figure 6 Power calculation based on 700 included study persons and mean follow-up of 5 years (0-10 years) for a x2 risk for mortality

The primary outcomes for the study were total mortality and cardiovascular morbidity. Cardiovascular morbidity was defined as diagnosis of ischaemic heart disease (ICD-10 codes I20-I25), cardiomyopathy (I42, I43), cardiac arrest (I46), ventricular tachycardia (I47.2), ventricular fibrillation (I49.0) and heart failure (I50).

We used a Cox proportional hazard model to analyse the outcomes. For each of them, three regressions models were used. Model 1 was only adjusted for the matching variables (age and sex); model 2 added adjustment for hypertension, cerebrovascular disease, diabetes, malignancy, hyperlipidaemia, and atrial fibrillation; model 3 further adjusted for previous medication use (beta blockers, diuretics and calcium channels blockers). The proportional hazard assumption was tested by proportional hazard test and visual inspection. When a covariate violated the proportional hazard assumption, we stratified the analysis on that variable. Moreover, we performed a sensitivity analysis with a nearest neighbour propensity score matching (1:1, calliper width=0.2) including all variables in model 3.

3.2 Study 2

3.2.1 Inclusion process

Between 2016 and 2018 we included prospectively 51 consecutive patients with a burden of at least 10,000 PVCs per day according to Holter recording. None of the participants had a history of structural heart disease or sustained ventricular tachycardia participants and all included had undergone exercise test and echocardiography with normal results. Contraindications to CMR or inability to perform the exam (e.g., claustrophobia) lead to exclusion.

An experienced physician analysed Holter data to ensure accuracy, and the minimum ECG-recording time was 24 hours.

Normal finding at exercise test was defined as physiological reaction without exercise-induced ST-depression and/or exercise-induced arrhythmia (if eventual prior-to-test ventricular arrhythmia was not aggravated during exercise, the result was not considered pathologic).

Normal finding at echocardiogram was defined as left ventricular ejection fraction (LVEF) equal to or higher than 55%, visually normal right ventricular ejection fraction (RVEF), normal ventricular dimensions including wall thickness, absence of local dyskinesia and absence of moderate to severe valvular dysfunction. Two additional independent and blinded examiners reviewed the echocardiograms and in case of conflict, the exam was considered normal or pathologic if two of three examiners had assessed the exam as such. This process resulted in the exclusion of one of the 52 original patients.

3.2.2 Examination with Cardiac Magnetic Resonance

CMR examinations were performed using a 1.5 T Signa HDxt scanner (GE, Milwaukee, Wisconsin) using 16 channels out of a cardiac phased array 32 channel coil.

Black blood T2w images (STIR) were performed in long axes views and short axis stack (12-mm slice thickness, 8 mm gap) for evaluation of oedema.

Regional wall motion anomalies (RWMA) and left ventricular (LV) and right ventricular (RV) volumes were assessed by cine images with a steady-state free precession (FIESTA) with sequence in long axis views and short-axis stack (from the right ventricular outflow tract to the apex, 8-mm slice thickness, 2 mm gap). Transaxial cine stack (from diaphragm to the pulmonary bifurcation, 8-mm slice thickness, no gap), sagittal RVOT and RV in/outflow views were added if the PVC morphology was unknown or suggestive

of RV origin. The following acquisition parameters were typically applied: 30 phases, 24 views per segment adjusted for heart rate, NEX 1, FOV 35 cm, a matrix of 256 × 224, a 40–45 °C flip angle, TR/TE approximately equal to 3.5/1.5, and a bandwidth of 125 kHz. Segmental LV and RV WM abnormalities were investigated from all available cine images and reported as hypokinetic, akinetic or aneurysmal.

For late gadolinium enhancement (LGE) a standard 2D–IR GRE sequence was performed in long and short axis views. The same slice thickness and gap as for SSFP cines was used. A gadolinium dose of 0.2 mmol/kg bodyweight (decreased to 0.1 mmol/kg in patients with GFR 30–60 mL/min) was administered. If oedema or LGE was present the segmental, and for LGE transmural (subendocardial, mid-wall, transmural), extent was reported.

We used dedicated software (Segment CMR, Medviso, Lund, Sweden) for post-processing, and functional parameters were obtained from the short-axis images. End-diastolic and end-systolic volume indexes and ejection fraction were reported for both LV and RV and compared to the respective reference values for class age and sex [25]. Two experienced investigators (one with EACVI level III expertise) who were blinded from one another's opinion evaluated each examination; consensus was sought in case of inconsistency. Ultimately, pathology at CMR was defined as one or more of the following: abnormal LV or RV volume, abnormal wall thickness, regional dyskinesia, myocardial oedema, fibrosis and ejection fraction (EF) lower than 55%.

3.2.3 Statistics

The study is to be considered as a pilot and no power calculation was carried out. Statistical calculations were performed in Excel (Microsoft, Redmond, WA, USA).

3.3 Study 3

3.3.1 Inclusion and echocardiographic examination

We included 40 consecutive patients with at least 10,000 PVCs/day and 22 controls. Both PVC patients and controls had no history of structural heart disease and had normal findings at standard echocardiography. PVC patients had also been investigated with exercise test and Holter recording at home. A normal echocardiogram was defined as LVEF >55% and right ventricular systolic function assessed by tricuspid annular plane systolic excursion (TAPSE) >17mm, absence of moderate to severe valve dysfunction, absence of regional wall motion abnormality, normal ventricular dimension, and normal

wall thickness. The echocardiographic exams were reviewed by two additional independent and blinded examiners. In case of conflicting evaluations of the echocardiographic findings, the exam was considered normal if two of three examiners assessed the exam as such, and pathologic if two of the three examiners found signs of pathology.

All included individuals were further examined with comprehensive echocardiography, including functional parameters which are not routinely assessed in clinical praxis. All the standard echocardiography parameters and Doppler measurements were performed according to the current recommendations[127, 128] . The examinations and analysis were performed by European Association of Cardiovascular Imaging (EACVI) certified sonographers.

LV Global longitudinal strain (GLS) by speckle tracking is calculated from four-, two-and three-chamber apical views. Tracing the LV endocardium is performed manually, and the thickness of the region of interest (ROI) is adjusted to exclude the papillary muscles and the pericardium. The ROI is also adjusted to exclude the LV outflow tract and the left atrium. Reliable tracking of all myocardial segments throughout the cardiac cycle must be confirmed visually. Views were excluded from analysis if insufficient tracking as indicated by the software.

Mechanical dispersion was defined as the standard deviation of time to peak negative strain in 17 LV segments. RV GLS of the free wall and LA strain assessment if performed in concordance to the "How to perform right ventricular strain" paper[129] and "How to do LA strain" document[130]. LA stiffness, an added parameter of the LA performance, representing the change in pressure required to increase the volume of the atrium in a given measure[131, 132], was calculated as ratio of E/é to LA reservoir strain. LV elastance as an index of myocardial contractility was calculated by modified single-beat method[133], employing systolic (SBP, mmHg) arm-cuff pressure to end-systolic LV volume.

Ventricular-arterial (VA) coupling was measured as ratio of end-systolic LV volume to Doppler-derived stroke volume[134]. Integrated backscatter (IBS) curves were acquired in the parasternal long-axis view in grey-scale 2D image, with framerates between 50-70 frames/s by locating a 5 x 5 mm sample volume in the basal-mid septum and inferolateral wall. A smaller fixed ROI (2 x 3 mm) was positioned in the pericardium in end-diastole as reference. Calibrated IB was calculated by subtracting average pericardial IB intensity from average myocardial IB intensity of the septum and inferolateral wall and were expressed in decibels[135, 136] . The sample volume was tracked manually to maintain the same region throughout the cardiac cycle.

LA activation time was assessed by color-coded tissue Doppler in apical four-chamber view. A fixed ROI of 12 x 5mm was placed on the lateral LA wall, just above the mitral annulus to acquire the tracing of mechanical activation in this area. The activation time

was obtained by measuring the duration of the time delay between the onset of the P-wave on ECG and the peak of the Á -wave on the tissue Doppler tracing.

3.3.2. Statistics

This was a pilot study and no power calculation was carried out. Statistical calculations were performed in Excel (Microsoft, Redmond, WA, USA). Continuous data were presented as mean ± standard deviation or median and interquartile range (IQR) when appropriate. Categorical variables were compared using Chi-squared with Yates' correction. A two-sided p-value of ≤0.05 was considered statistically significant.

The results from two independent investigators on six PVC patients and ten control subjects were compared, and interclass correlation coefficient for absolute agreement and coefficient of variation were calculated in order to determine interobserver variability of the parameters.

3.4 Study 4

3.4.1 Inclusion and design

Out of the study base for study 1, consisting of healthy PVC patients, we identified 541 individuals in which we had access to PVCs on 12-lead ECG, allowing us to analyse their morphology and duration. We aimed to separately study the effect of the PVC morphology and QRS width on the clinical outcome in different sub-group analyses. As in study 1, we had access to their clinical data through the National Patient Registry.

The considered clinical outcome was a composite outcome of mortality and cardiovascular morbidity during follow-up. Cardiovascular morbidity was defined as diagnosis of ischaemic heart disease (ICD-10 codes I20-I25), cardiomyopathy (I42, I43), cardiac arrest (I46), ventricular tachycardia (I47.2), ventricular fibrillation (I49.0) and heart failure (I50).

3.4.2 Evaluation of PVC duration and morphology

ECG analyses were performed on the CardioSoft Diagnostic System (GE Healthcare, Chicago, Illinois, USA) which allows high resolution viewing of the stored electrocardiographic registration. Scrutiny was carried out by two independent examiners, the mean of two measurements was used to minimise measurement error, and consensus was sought in case of different conclusions. The ECG-viewing process was based on relevant publications[21, 137-139]. Depending on the PVC-vector on the

horizontal and frontal plane we classified morphologies into six groups according to the suggested site of origin: right ventricular outflow tract, left ventricular outflow tract, outflow tract (when a left or right origin within the outflow tract could not be determined), right Ventricular other than RVOT, Left Ventricular other than LVOT and multifocal.

QRS width was measured in milliseconds, and the measurement was done from the earliest onset to the latest offset of the waveform in all leads.

3.4.3 Statistics

We included participants from study 1 in which PVC analyses were possible on 12-lead ECG. There was no previous power calculation. Data management and statistical analyses were performed in R version 4.0.3 (R Foundation, Vienna, Austria).

3.5 Ethical considerations

This research project ensues from a poignant clinical question that is common for physicians with interest in arrhythmia. It is not unusual that the patient, who has undergone structural examinations with normal results, is more interested in the condition's prognosis than its treatment. In fact, if we could reassure the patients about the prognostic impact of PVCs, many of them wouldn't be interested in any treatment at all. So, what should we tell them? Are PVCs dangerous for healthy individuals? And how can we identify those with potentially dangerous PVCs?

Like all projects involving prognostic data, and its communication, this presents ethical challenges. The issue gets even more intricate here as this condition is very common in the population, its prevalence varying from 2% to 40% according to different studies. If we show that PVCs have a negative prognostic impact, then we are going to say that a considerable percent of the population has an increased risk of having a heart disease and even of dying of it. This can obviously be a challenging message to handle, leading to anxiety for the affected individuals and, on a population level, to a demand for cardiological care that the Healthcare System could be unable to handle. As today, we do not always have access to therapeutic tools that would safely and effectively curb the potential negative effect of PVCs. This implies that we could end up in a position of delivering a negative message about the prognosis in PVCs without being able to offer an adequate treatment to it. On the other hand, such a result would put a bigger pressure on the medical research system to focus on this issue. Today's most common

routine is to evaluate PVC patients at a secondary care centre and follow the high-risk patients on that level of care, whereas the majority of patients will be referred to a primary care centre for follow-up or planned for no follow-up at all. If our research shows that PVC patients have increased health risks, that would lead to a need for stricter follow-up programs, a goal not easy to achieve with limited public resources. In such a case, there is also the risk that other patient groups would get a lower priority in their access to the healthcare system. If we, in the opposite scenario, could show that PVCs do not increase the risk for cardiovascular disease and death, that would lead to a reassuring message to patients and a decreased need for healthcare. In fact, many PVC patients have repeated contacts with the Healthcare System mostly because of the anxiety that ensues PVCs.

It is necessary to give the diagnostic pathway some special consideration. When using CMR or advanced echocardiography as an additional tool to evaluate PVC patients with normal findings at standard echocardiography, we find that some patients have subtle signs of myocardial pathology that standard exams had overlooked. However, we don't currently know it these findings have any current clinical implication or if they are early signs of an eventual cardiomyopathy. Therefore, we deliver to the participants the information that they have subtly pathological findings without being able to tell whether they are clinically relevant, and whether we should follow them or not. On the other hand, this could form the ground for future research investigating whether persons with PVCs and pathological findings at advanced imaging (MR or advanced echocardiography) run a higher risk of cardiovascular disease and should be followed more strictly, thus paving the way for a more accurate risk evaluation.

When investigating the participants with cardiac MR, in some cases we get secondary findings, leading to additional examinations in one case. Because of the size of the camera it is not uncommon that the examiner notices anomalies in extra-cardiac organs such as the lungs, the liver, or the spleen. We discussed this possibility at the start of the project and considered whether it was our responsibility as researchers to further investigate these accidental findings or if we should refer the patient to the general practitioner for that task, since it lays outside the research question. Our choice was to take care of the needed completing investigation ourselves, to minimize waiting time for the patient and the following anxiety. While CMR is a non-ionising radiological exam, when we need to further investigate accidental extra-cardiac findings, we often refer the participant to Computerized Tomography (CT), which is an ionising exam. Ionising exams implicate a certain risk of inducing cancer, which is well-known but can be hard to accept when investigating findings that were accidently shown (that is not linked to any clinical symptoms or signs and seen on an exam that wasn't meant to investigate that organ). None of the completing CT-exams lead to a diagnosis of malignancy.

When it comes to principles of biomedical ethics, we think that our research project fulfils the requirements for an ethically good study. The principle of "doing good" is the guiding light of this project, because the study has its origin in a relevant clinical question that needs to be answered in order to better comprehend how we can take care of this patient group. The principle of avoiding harm is also respected; in our study we do not expose participants to any harmful evaluation or treatment. In study 2 we opted not to include healthy controls based on the recommendations from the International Society for Magnetic Resonance in Medicine, urging caution in the use of gadolinium as it has been shown that it tends to deposit in brain tissue. In study 3 we included healthy controls because echocardiography is not associated to any risk for the examined.

In study 2 and 3, the recruited patients were given oral and written information. For observational studies 1 and 4, the Ethics Committee found that written consent was not required. In study 2 a few patients turned down the offer of participation because of claustrophobia; however, a large majority of the eligible patients wanted to be enrolled. Even the principle of treating equally was considered during the recruitment process, because all eligible patients were asked about participation, regardless of age (as long as adult), gender, race or other personal qualities. The patients who did not want to participate in the study were offered the same state of the art care as the participants.

Finally, we obviously intended to publish our research results in a scientific paper regardless of the results, and the project is filed in the ClinicalTrials-database with identifier NCT03370679.

4 Results

4.1 Study 1

Mortality analyses was based on 820 PVC patients and 3,264 controls. Their characteristics are summarised in table 2.

	PVC cohort (n= 820)	Controls (n=3,264)	p	SMD
Age (median [IQR])	59.0 [45.0, 70.0]	59.0 [45.0, 70.0]	0.983	<0.001
Men, N (percent)	347 (42.3)	1376 (42.2)	0.965	0.003
Ischaemic heart disease, N (%)	0 (0.0)	155 (4.7)	<0.001	0.316
Heart Failure, N (%)	0 (0.0)	60 (1.8)	<0.001	0.194
Cancer, N (%)	112 (13.7)	317 (9.7)	0.001	0.123
Hypertension, N (%)	173 (21.1)	535 (16.4)	0.002	0.121
Diabetes, N (%)	39 (4.8)	212 (6.5)	0.076	0.076
Cerebrovascular disease, N (%)	23 (2.8)	128 (3.9)	0.158	0.062
Hyperlipidaemia, N (%)	66 (8.0)	161 (4.9)	0.001	0.127
Atrial Fibrillation, N (%)	50 (6.1)	137 (4.2)	0.025	0.086
Beta Blockers, N (%)	410 (50.0)	760 (23.3)	<0.001	0.577
Anticoagulants and platelet-inhibitors N (%)	238 (29.0)	752 (23.0)	<0.001	0.137
Antiarrhythmic drug, class 1, N (%)	14 (1.7)	9 (0.3)	<0.001	0.145
Antiarrhythmic drug, class 3, N (%)	11 (1.3)	3 (0.1)	<0.001	0.149
Calcium channel blockers, N (%)	216 (26.3)	611 (18.7)	<0.001	0.183
Diuretics, N(%)	311 (37.9)	983 (30.1)	<0.001	0.165
Digitalis	6 (0.7)	27 (0.8)	0.956	0.011
ACE-Inhibitors	159 (19.4)	602 (18.4)	0.567	0.024
Angiotensin receptor blockers	108 (13.2)	401 (12.3)	0.531	0.027

Table 2 Baseline characteristics of the primary analytic sample. SMD= Standardized mean difference

During a median follow-up time of 5.2 years (IQR 3.9-6.4 years), 24 deaths occurred in the PVC group and 194 among controls, yielding a mortality rate of 5.7/1,000 person-years and 11.9/1,000 person years respectively. Tumours were the most common cause of death in the PVC group while controls died most often from cardiovascular disease. The conditional Hazard Ratio for overall mortality in the PVC group was 0.44 (CI 0.27-0.71). Adjustment for potential confounders did not affect the association between PVC and survival with similar HR in all models (figure 7).

When looking at cardiovascular morbidity we found a morbidity rate of 12.1/1,000 person-years among PVC patients (median follow-up time of 5.1 years, IQR 3.8-6.4) and

7.4/1,000 person-years among controls (follow-up time 5.1 years, IQR 3.8-6.3). The conditional HR for PVC patients was 1.53 (CI 1.06-2.21). Addition of comorbidity data modified the HR to 1.31 (CI 0.72-2.37). In a third model, where previous medications were added, the HR was 1.34 (CI 0.71-2.53).

A sensitivity analysis after propensity score matching showed similar results as in the main analysis regarding all-cause mortality (HR 0.32, CI 0.20-0.50). For cardiovascular morbidity, the propensity-score-matched analysis did not show a significant difference between cases and controls (HR 1.37, CI 0.90-2.09).

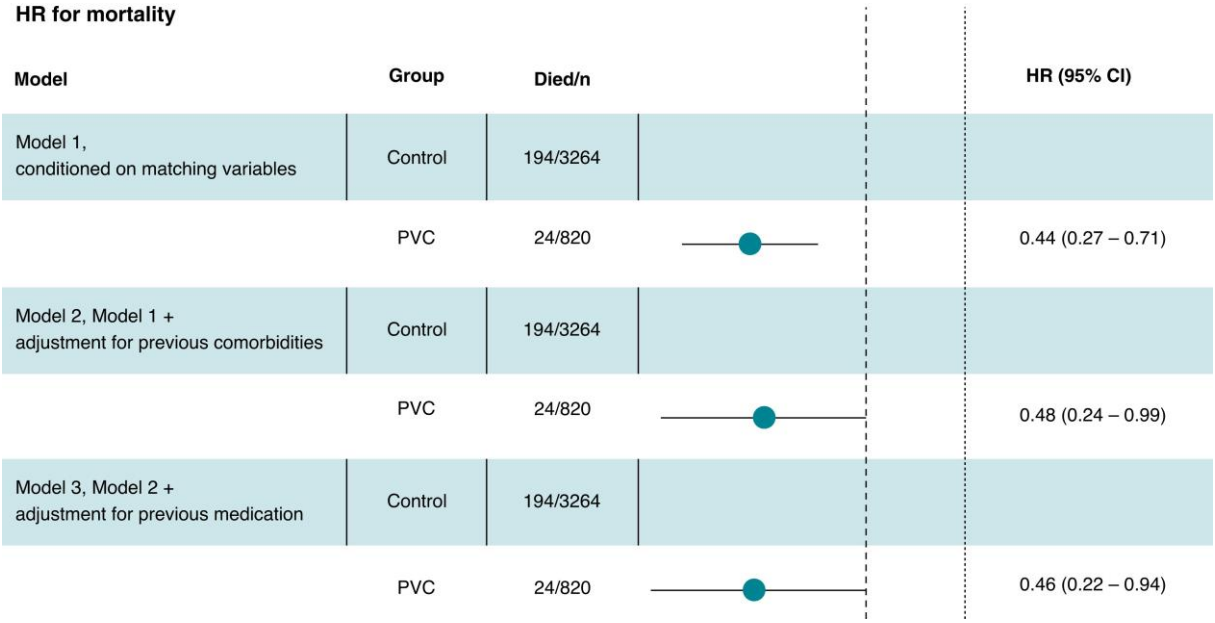

Figure 7 Hazard Ratio for total mortality in PVC group compared to controls with different conditioning models. The dotted line represents the non-inferiority limit of HR=2. Copyright © 2022, Oxford University Press

4.2 Study 2

No CMR-related complications were observed. Among the 51 included patients (45% women, median age 62 years), 16 (31%) had at least one pathologic CMR finding, with three patients (6%) presenting several findings. Regional wall motion anomalies (RMWA), dilated left ventricle and fibrosis were the most recurrent findings. All cases with RMWA and dyskinetic areas were found in the right ventricle, while fibrosis was only seen in the left ventricle. A correlation between topographic localisation of the finding and the PVC morphology was seen in the two cases of fibrosis in which we had access to 12-lead ECG. No patient showed signs of myocardial oedema. The findings are summarised in figure 8.

We could not state a correlation between number of PVCs and presence of CMR findings according to a logistic regression. Even analysis of PVC morphology as a predictor variable failed to show correlation to incidence of findings.

In five patients we identified extra-ventricular pathology: enlarged atria in three cases (one of which with history of atrial fibrillation), enlarged thoracic aorta and pericardial exudate in one case each.

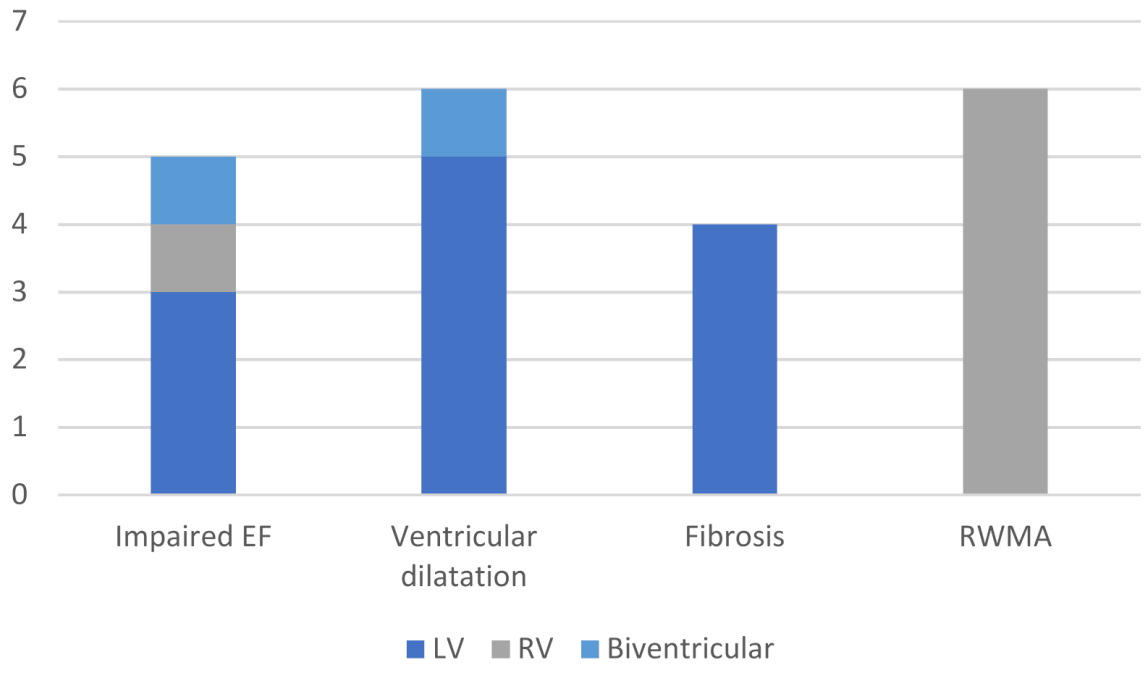

Figure 8 Summary of CMR findings in study 2.

4.3 Study 3

The 40 PVC patients (45% women, median age 65 years) differed from controls in several parameters when comprehensive advanced echocardiography was used. The PVC group showed reduced LV elastance (2.9 vs 3.33 mmHg/mL, $p< 0.01$) and altered VA coupling compared to the controls (0.62 ± 0.15 vs. 0.52 ± 0.11, $p<0.01$). Integrated Backscatter and LA activation time were also statistically different between the groups. LA mechanical dispersion, LA strain and LA stiffness did not reach the level of significant between the groups.

Left ventricular GLS and mechanical dispersion had a high reproducibility while left atrial strain, left atrial activation time and integrated backscatter scored lower. Jittered scatter plots summarise results in figure 9.

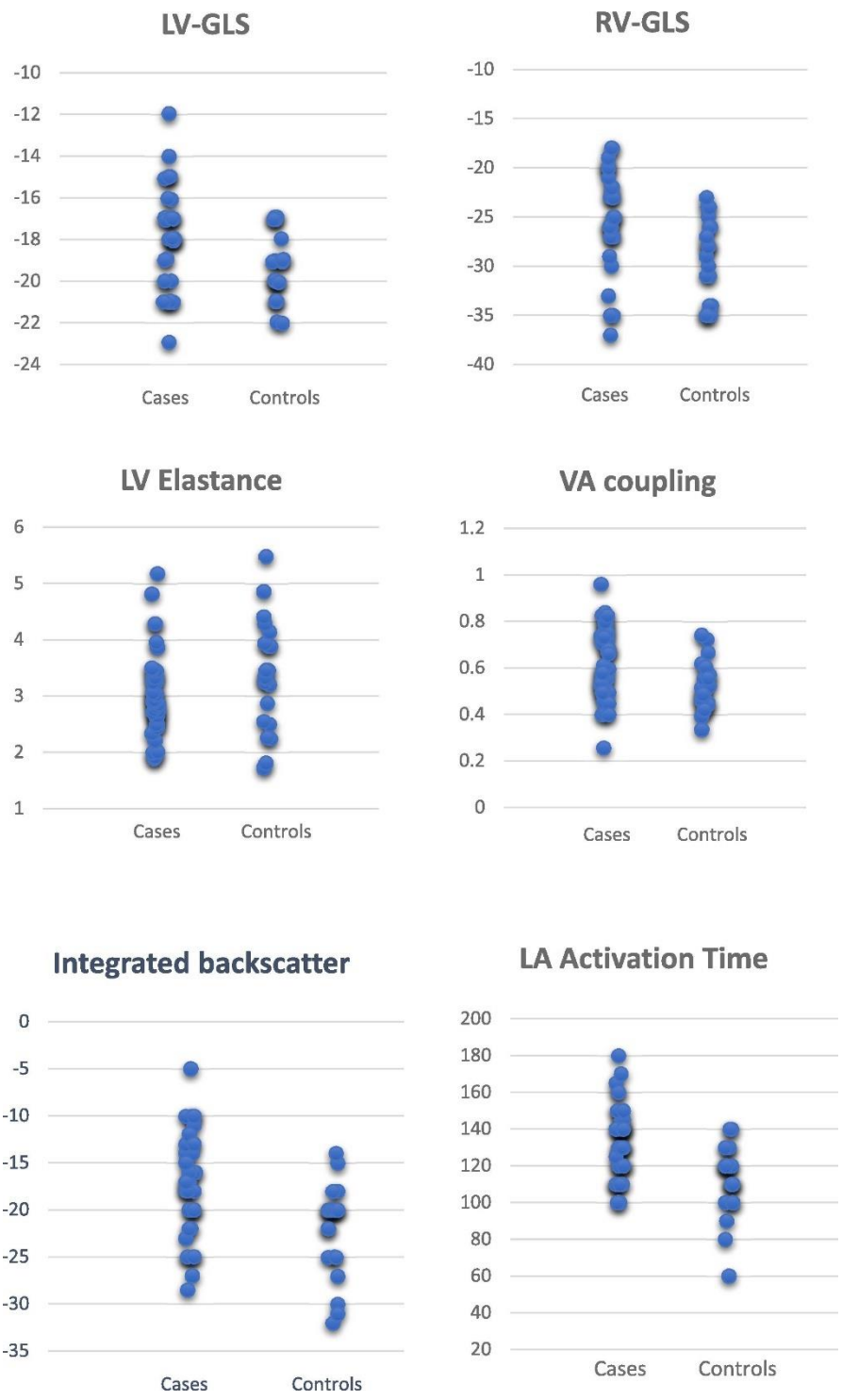

Figure 9 Outcome for cases and controls in six echocardiographic parameters.

4.4 Study 4

Categorisation of 541 structurally healthy PVC patients based on QRS morphology during PVC showed that 81% of patients had unifocal PVCs while 19% had multifocal. RVOT was the most common site of origin (30%) followed by intracavitary left ventricular (25%) and right ventricular (22%) PVCs. Patients with multifocal PVCs did not significantly differ in clinical outcome after relevant adjustment compared to individuals with unifocal PVCs. However, there was a significant difference in outcome in favour of PVCs from outflow tract when compared to intra-cavitary and right ventricular PVCs when compared to left ventricular. PVC duration, measured as QRS width during PVC, did not seem to yield significant impact on prognosis.

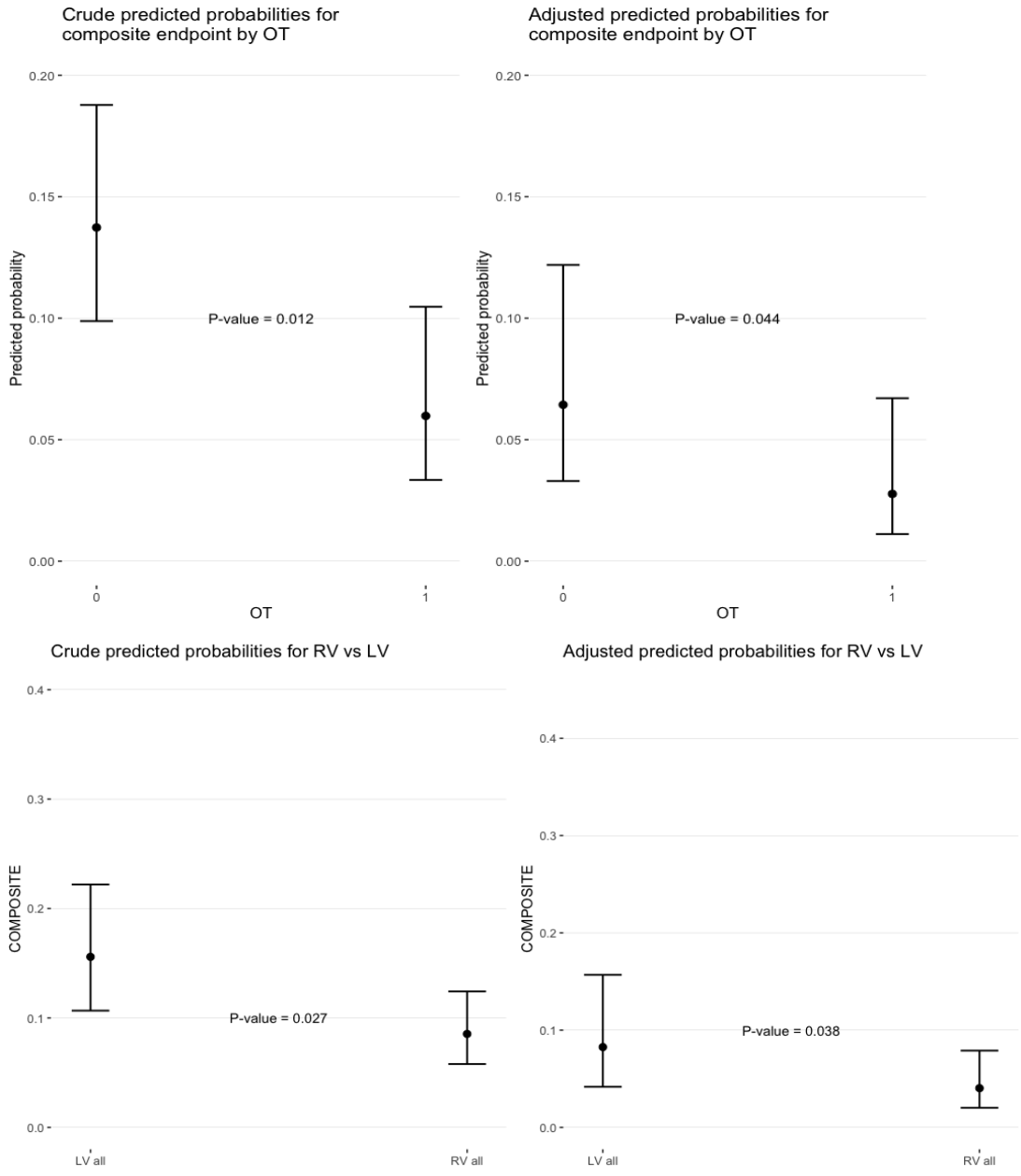

Figure 10 Risk for outcome when comparing OT-PVC to non-OT-PVC and RV-PVC to LV-PVC.

5 Discussion

5.1 Prognostic significance of PVCs in healthy patients

The prognostic impact of PVCs and their role in risk assessment have been discussed for decades. While the evidence (though based mostly on old studies) for individuals with previous heart disease is relatively strong, the question remains unanswered for healthy patients. In the latter group, PVCs have historically been treated as benign, while in fact the results from the two existing meta-analyses point to a negative prognostic effect. However, the major underlying methodological problem is that few of the published studies have rigorous inclusion criteria capable of excluding persons with silent or unknown heart disease. We coherently used echocardiogram, exercise test and, when needed, other completing diagnostic tools to identify and exclude cardiovascular disease. After reaching the number of patients and the length of follow-up required by a previous power calculation, we created through Statistics Sweden a four-times larger control group of sex- and age-matched individuals. We had broad access to the clinical outcome for both groups through diagnostic data in the National Patient Registry.

Analyses for overall mortality with Cox regression, corroborated by propensity score, showed that the PVC group had no worse mid-term prognosis than controls. The study was designed on the concept of non-inferiority, so it would be technically incorrect to state that PVC patients had a better clinical outcome than controls. However, the data suggested this kind of scenario in our study. Although counter-intuitive there may be an explanation to such a picture. PVC patients were in fact recruited at secondary care centres, possibly reflecting a selection in the patient material. Moreover, these three centres were located within large hospitals in the Stockholm area, while controls were recruited from the whole country, possibly with different access to both primary and secondary care centres. The Stockholm area has, in fact, a higher density of cardiologists and a more accessible health care than other parts of Sweden. This difference could also explain why our data for cardiovascular morbidity point in the opposite direction, with the PVC group showing higher hazard for cardiovascular morbidity. Here we find a possible explanation in the fact that PVC patients had an established contact with a cardiologist, possibly creating a higher possibility for receiving a cardiovascular diagnosis during follow-up. However, the difference in cardiovascular morbidity was no longer significant after adjustment for previous comorbidities and medications; moreover, sensitivity analysis with propensity score matching did not confirm the difference in morbidity. Another important difference between PVC patients and controls is that all individuals in the first group were examined with at least exercise test and echocardiogram, leading to a much higher

chance to exclude structural heart disease than within controls, for whom we had to rely on register data.

With all these limitations in mind, we still find it reasonable to claim that PVC should be examined thoroughly, and PVCs should be considered benign–at least in the mid-term–when structural examinations show normal results. However, it may be relevant to define which diagnostic method should be included in the examination. While it is broadly accepted that echocardiography and exercise test are important tools and probably sufficient in most cases, there is evidence about CMR being able to identify subtle signs of structural disease in PVC patients with normal standard echocardiography. The results from our study seem to corroborate this notion. Less previous evidence is available about the role of advanced echocardiography, which we also find to be useful in demasking myocardial dysfunction as an additional tool to standard echocardiogram. The prognostic significance of these diagnostic findings, both regarding CMR and advanced echo-parameters, needs to be assessed by larger longitudinal studies.

When it comes to PVC morphology and PVC duration, the evidence has been controversial. Most studies in this subject are based on patients referred for ablation, often with a limited number of participants. Studies on broader population and with consecutive inclusion have been missing. We consecutively included 541 PVC patients with normal findings at echocardiography and exercise test and in which PVCs were recorded on 12-lead ECG. We classified them according to QRS morphology and width during PVC, based on high resolution ECG data. After relevant adjustment we found that right-sided PVCs were linked to a better prognosis than left-sided PVCs. The same was true for PVCs originating from the outflow tract compared to intra-cavity PVCs. Comparisons between unifocal and multifocal PVCs did not yield a significant difference. This may not be in line with the common knowledge that multifocal PVCs are more dangerous than unifocal ones. However, this has been proved to be true in a more heterogeneous group of patients, our study being the first to our knowledge exploring this issue in a cohort of structurally healthy patients. Similarly, we could not show a prognostic effect of the duration of the PVC, measured as QRS width. It has previously been hypothesised that broad PVCs can either be risk factors, as they are more likely to induce interventricular and intraventricular dyssynchrony, or risk markers, as they can be caused by slow-conduction tissue such as myocardial scars and other fibrotic conversion.

5.2 The role of advanced imaging

Two of the studies focused on the role of advanced imaging in evaluation of patients with a high PVC burden. Both CMR and extended echocardiographic examination were able to uncover signs of structural or functional pathology despite a normal standard echocardiography. European Society of Cardiology recently published new guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death[108]. In these guidelines CMR receives a IIa-recommendation in patients with PVCs/VT and a presentation atypical for an idiopathic origin, despite a normal echocardiogram. CMR receives the same degree of recommendation in patients with PVC induced cardiomyopathy. Advanced echocardiography is not considered in these or previously published guidelines. During the last decade some evidence has been gathering about CMR in PVC patients. However, most studies are based on selected populations such as ablation patients. Moreover, CMR remains an expansive method that is not broadly available. Echocardiography is, on the other hand, accessible and relatively inexpensive, and the addition of more comprehensive functional parameters has the potential to be an important tool in PVC-evaluation when standard exams are normal. The evidence about advanced echocardiography in this patient group, which is summarised in the introduction, is thin, and ours is to our knowledge the first study to evaluate consecutive patients.

In the CMR study we found that 31% of patients had signs of pathology despite normal echocardiography, which is in line with previous similar studies. There was even some correlation between findings' localisation and PVC morphology. The prognostic significance of these results has to be further investigated with larger longitudinal studies. Perhaps even more interesting were the findings from our study focusing on advanced echocardiography that showed worsened outcomes for PVC patients in six of nine included parameters when compared to healthy controls. The aggregated picture resulting from the difference in these parameters was that PVC patients showed signs of cardiac dysfunction, not only in the ventricles but even in the atria, with myocardial fibrosis as a possible common denominator. Among the affected parameters GLS showed a high reproducibility, which is interesting considering the growing evidence supporting its use. However, even these echocardiographic findings must be further assessed, and their prognostic value has to be determined by larger longitudinal studies.

6 Conclusions

The aggregated conclusions from this research project are that:

- PVC patients who have undergone echocardiography and exercise test with normal results did not show a worse prognosis than a matched sample from the general population after a median follow-up of 5 years

- CMR is able to detect signs of pathology in a population with high PVC burden and normal echocardiogram

- Comprehensive echocardiography with additional parameters shows signs of cardiac dysfunction in a population with high PVC burden and normal echocardiogram

- In PVC patients who have undergone echocardiography and exercise test with normal results, PVCs originating from the ventricular outflow tracts and from the right ventricle were associated with a better prognosis than non-OT respectively left ventricular PVCs. In this population PVCs' duration did not seem to be associated with the clinical outcome

7 Clinical implications and future perspectives

Evaluating and understating the prognostic impact of PVCs on healthy patients has been a challenge within cardiologic research for several decades. More and larger studies are needed to fully understand epidemiological implications and to identify especially vulnerable groups. Moreover, it is relevant to understand whether PVCs are to be regarded as a risk factor or as a risk marker.

The core issue can be summarised as follows: How should a physician respond to a patient undergoing evaluation for PVCs and seeking reassurance about the prognosis after a thorough examination has shown normal results? According to our results it is reasonable to give this patient a reassuring answer, at least regarding the mid-term prognosis. However, it is even recommended to include an analysis of PVC morphology and, if the patient has a high PVC burden, advanced imaging methods in the total evaluation. The ultimate aim of the clinical evaluation should be to identify patients who are eligible for more intensive and prolonged follow-up.

To address current evidence gaps and further investigate areas with limited evidence, we suggest that future projects focus on the following:

-the long-term prognosis of PVC patients

-the role of comprehensive echocardiography in the diagnostic work-up

-the prognostic significance of CMR-findings

-the role of PVC morphology in the prognostic evaluation

-the definition of PVC patients who are at low risk and can be followed unfrequently

8 Svensk sammanfattning

Bakgrund

Ventrikulära extraslag (VES) är en vanlig typ av arytmi, men deras exakta prevalens och incidens är inte känd. Redan på 60- och 70-talet började man intressera sig för deras eventuella påverkan på prognosen. Det har historiskt funnits metodologiska svårigheter inbyggda i frågeställningen, men evidensen som började samlas med de första publicerade studierna visade att förekomst av VES var kopplad till en försämrad prognos i närvaro av strukturell hjärtsjukdom. Ännu svårare har varit att avgöra huruvida även patienter utan etablerad hjärtsjukdom har en försämrad prognos vid förekomst av VES. Två meta-analyser, publicerade 2012 och 2013, hade som slutsats att VES-förekomsten var associerad till en försämrad prognos även hos strukturellt hjärtfriska patienter, men att evidensunderlaget inte var starkt då inklusionskriterierna och metoderna för att utesluta strukturell hjärtsjukdom varierade mellan studierna och var ibland bristfälliga. Slutsatserna var att prognosen bland strukturellt friska VES-patienter var okänd. Vidare saknas i denna patientgrupp evidens kring betydelsen av VES:ens morfologi och duration samt huruvida mer avancerade imaging metoder än standard ekokardiografi kan tillföra information och värde i bedömningen av patienterna.

Med detta forskningsprojekt hade vi följande syften:

- Att jämföra prognosen för patienter med VES utan andra hjärtsjukdomar med kön- och åldersmatchade kontroller från den allmänna befolkningen.

- Att undersöka huruvida magnetkamera-undersökning av hjärtat (CMR) kan avslöja tecken på hjärtsjukdom hos individer med hög VES-börda och normal ekokardiografi, oberoende av VES-morfologi.

- Att undersöka huruvida ekokardiografi med avancerade parametrar, som inte ingår i rutinundersökning, kan avslöja tecken på hjärtsjukdom hos individer med hög VES-börda och normal ekokardiografi.

-Att jämföra prognosen för VES-patienter utan andra hjärtsjukdomar beroende på VES:ens morfologi och duration.

Metoder

VI identifierade 807 VES-patienter utan anamnes för strukturell hjärtsjukdom, med normalt fynd på ekokardiografi och arbetsprov. Vi jämförde det kliniska utfallet, i form av total mortalitet och kardiovaskulär sjuklighet, med en kontrollpopulation matchad på kön

och ålder, efter en medianuppföljningstid på 5,2 år. För att ytterligare undersöka huruvida elektrokardiografiska fynd har en prognostisk betydelse bland friska patienter identifierade vi individer från den ovan nämnda kohorten där vi hade tillgång till VES-inspelning på 12-avlednings EKG. Vi hade tillgång till data avseende PVC-morfologi och QRS-bredd under VES hos 541 patienter och analyserade denna population under samma uppföljningstid. Till studierna med fokus på imaging inkluderade vi patienter med en VES-börda på minst 10.000 slag/dag och med normala resultat på arbetsprov och standard-ekokardiografi. De genomgick ytterligare undersökning med CMR eller avancerade ekokardiografiska parametrar som normalt inte ingår i klinisk praxis.

Resultat

VES-patienter utan hjärtsjukdomar hade en generellt gynnsam prognos med ett kliniskt utfall som inte var sämre än det för den köns- och åldersmatchade kontrollgruppen, efter justering för relevanta faktorer. Patienter med hög VES-börda visade dock tecken på myokardiell dysfunktion när avancerade avbildningstekniker användes, trots normala resultat vid standardundersökning som inkluderar standardekokardiogram. Subgruppsanalys baserad på VES-morfologi visade att VES med ursprung i de ventrikulära utflödestrakterna och i höger kammare var associerade med en mer gynnsam prognos än VES med intrakavitärt respektive vänsterkammar-ursprung. Analys av VES-durationen, mätt som QRS-bredd under VES, visade ingen inverkan på kliniskt utfall.

Slutsatser

VES-patienter utan anamnes för strukturella hjärtsjukdomar och som hade genomgått en grundlig undersökning med normala resultat hade inte ett sämre utfall än matchade kontroller under en medianuppföljningstid på 5,2 år. I två studier utvärderade vi rollen av avancerad imaging hos patienter med hög VES-börda och normala fynd vid standardekokardiogram. Vi kunde visa att CMR och omfattande avancerad ekokardiografi kunde identifiera tecken på myokardiell dysfunktion. Den kliniska betydelsen av dessa fynd måste utvärderas vidare genom större longitudinella studier. VES-durationen var inte associerad med kliniskt utfall i vår studie. VES-morfologi verkade ha betydelse där VES med ursprung i utflödeskanalen och höger kammare var associerade till en bättre prognos.

9 Acknowledgements

Viveka Frykman, my main supervisor. Thank you for being a mentor and a guiding light, both in research and clinics. Thank you for gently pushing me to and through this project. But most of all thank you for all the talks and the fine moments together, they have affected and shaped me in many ways.

Mårten Rosenqvist, professor and co-supervisor. My interest in clinical research became serious when I had the opportunity of working with you. Thank you for all the discussions, the story telling and the support. I'll probably be the last of your PhD-students; I hope you can see this project as the grand finale.

Leif Friberg, co-supervisor. Thank you for your broad competence and for your accessibility. You often ask the right questions and see pitfalls we otherwise would have missed. This project would have not been as good without your inputs.

Mikael Runsiö, my boss and CEO at *Södersjukhuset*. Thank you for reminding me about my research project amongst the daily work with staffing challenges, economy and production goals (and an occasional pandemic). You were among Mårten's first PhD-students, so one could say this is like closing a circle.

Karin Malmqvist, my former boss and Head of Cardiology at Danderyd Hospital. Thank you for believing in me and showing me the way of medical leadership. You are a legend.

Petter Ljungman, my mentor. Thank you for being there when I needed an external look at the project, for being a friend and a person to whom it is always nice to talk.

Martin Jonsson, co-author and code breaker. Thank you for your impressive skills in statistics. Papers 1 and 4 would have never been possible without you.

Kambiz Shahgaldi, Peder Sörensson, Anders Jansson and John-Martin Corander, co-authors. Thank you for your valuable contributions.

Håkan Wallén, Nina Ringart, Tomas Jernberg and the staff at KI Danderyd Hospital. Thank you for all help and support.

Elif Günyeli, Pia Oblack, Josephine Muhrbeck and Johanna Sjöblom. Thank you for valuable help with papers 2 and 3.

Per Tornvall, professor and Head at KI Södersjukhuset. Thank you for your amazing achievements in developing research and instruction within the Cardiology Department I lead, and for your much appreciated clinical work.

The Management Team (*Ledningsgruppen*) at Department of Cardiology, *Södersjukhuset*. Thank you for being inspiring, capable and engaged leaders, team players and problem solvers.

All colleagues at Department of Cardiology and at the Hospital's Board, *Södersjukhuset*.

All former colleagues at Department of Cardiology, Danderyd Hospital.

My parents, Elisabetta and Lino. Thank you for highlighting the importance of education and self-improvement.

My siblings, Ada and Matteo, with their families. Thank you for being a part of the journey.

My wife Johanna. Thank you for more than twenty years together, and for being the most important person in my life.

My children, Emilia and Sebastian. Thank you for being who you are and for giving this all a meaning.

10 References

1. Kostis JB. THE PROGNOSTIC-SIGNIFICANCE OF VENTRICULAR ECTOPIC ACTIVITY. *American Journal of Cardiology*. 1992;70:807-808.
2. Luderitz B. Historical Perspectives of Cardiac Electrophysiology. *Hellenic Journal of Cardiology*. 2009;50:3-16.
3. Latchamsetty R and Bogun F. Premature Ventricular Complexes and Premature Ventricular Complex Induced Cardiomyopathy. *Current Problems in Cardiology*. 2015;40:379-422.
4. Hiss RG and Lamb LE. Electrocardiographic findings in 122,043 individuals. *Circulation*. 1962;25:947-61.
5. Lown B, Vassaux C, Hood WB, Fakhro AM, Kaplinsk.E and Roberge G. UNRESOLVED PROBLEMS IN CORONARY CARE. *American Journal of Cardiology*. 1967;20:494-&.
6. Ng GA. Treating patients with ventricular ectopic beats. *Heart*. 2006;92:1707-1712.
7. Lown B and Wolf M. APPROACHES TO SUDDEN DEATH FROM CORONARY HEART DISEASE. *Circulation*. 1971;44:130-&.
8. Hinkle LE, Carver ST and Argyros DC. PROGNOSTIC SIGNIFICANCE OF VENTRICULAR PREMATURE CONTRACTIONS IN HEALTHY PEOPLE AND IN PEOPLE WITH CORONARY HEART DISEASE. *Acta Cardiologica*. 1974:5-32.
9. Harrison DC, Fitzgerald JW and Winkle RA. AMBULATORY ELECTROCARDIOGRAPHY FOR DIAGNOSIS AND TREATMENT OF CARDIAC-ARRHYTHMIAS. *New England Journal of Medicine*. 1976;294:373-380.
10. Kostis JB, Mccrone K, Moreyra AE, Gotzoyannis S, Aglitz NM, Natarajan N and Kuo PT. Premature Ventricular Complexes in the Absence of Identifiable Heart-Disease. *Circulation*. 1981;63:1351-1356.
11. Kennedy HL, Whitlock JA, Sprague MK, Kennedy LJ, Buckingham TA and Goldberg RJ. LONG-TERM FOLLOW-UP OF ASYMPTOMATIC HEALTHY-SUBJECTS WITH FREQUENT AND COMPLEX VENTRICULAR ECTOPY. *New England Journal of Medicine*. 1985;312:193-197.
12. Fleg JL and Kennedy HL. LONG-TERM PROGNOSTIC-SIGNIFICANCE OF AMBULATORY ELECTROCARDIOGRAPHIC FINDINGS IN APPARENTLY HEALTHY SUBJECTS-GREATER-THAN-OR-EQUAL-TO-60 YEARS OF AGE. *American Journal of Cardiology*. 1992;70:748-751.
13. Vijgen J, Hill P, Biblo LA and Carlson MD. Tachycardia-induced cardiomyopathy secondary to right ventricular outflow tract ventricular tachycardia: Improvement of left ventricular systolic function after radiofrequency catheter ablation of the arrhythmia. *Journal of Cardiovascular Electrophysiology*. 1997;8:445-450.
14. Chugh SS, Shen WK, Luria DM and Smith HC. First evidence of premature ventricular complex-induced cardiomyopathy: A potentially reversible cause of heart failure. *Journal of Cardiovascular Electrophysiology*. 2000;11:328-329.
15. Lee V, Hemingway H, Harb R, Crake T and Lambiase P. The prognostic significance of premature ventricular complexes in adults without clinically apparent heart disease: a meta-analysis and systematic review. *Heart*. 2012;98:1290-1298.
16. Ataklte F, Erqou S, Laukkanen J and Kaptoge S. Meta-Analysis of Ventricular Premature Complexes and Their Relation to Cardiac Mortality in General Populations. *Am J Cardiol*. 2013;112:1263-1270.
17. Lee AKY, Andrade J, Hawkins NM, Alexander G, Bennett MT, Chakrabarti S, Laksman ZW, Krahn A, Yeung-Lai-Wah JA and Deyell MW. Outcomes of untreated frequent premature ventricular complexes with normal left ventricular function. *Heart*. 2019;105:1408-1413.
18. Nomura Y, Seki S, Hazeki D, Ueno K, Tanaka Y, Masuda K, Nishibatake M and Yoshinaga M. Risk factors for development of ventricular tachycardia in patients with ventricular premature contraction with a structurally normal heart. *J Arrhythm*. 2020;36:127-133.

19. Kim YG, Choi YY, Han KD, Min KJ, Choi HY, Shim J, Choi JI and Kim YH. Premature ventricular contraction increases the risk of heart failure and ventricular tachyarrhythmia. *Scientific Reports*. 2021;11.
20. Lee A, Walters TE, Gerstenfeld EP and Haqqani HM. Frequent Ventricular Ectopy: Implications and Outcomes. *Heart Lung Circ*. 2019;28:178-190.
21. Marcus GM. Evaluation and Management of Premature Ventricular Complexes. *Circulation*. 2020;141:1404-1418.
22. Cheriyath P, He F, Peters I, Li XA, Alagona P, Wu CT, Pu M, Cascio WE and Liao DP. Relation of Atrial and/or Ventricular Premature Complexes on a Two-Minute Rhythm Strip to the Risk of Sudden Cardiac Death (the Atherosclerosis Risk in Communities ARIC Study). *American Journal of Cardiology*. 2011;107:151-155.
23. Simpson RJ, Cascio WE, Schreiner PJ, Crow RS, Rautaharju PM and Heiss G. Prevalence of premature ventricular contractions in a population of African American and white men and women: The Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J*. 2002;143:535-540.
24. Fisher FD and Tyroler HA. Relationship between ventricular premature contractions on routine electrocardiography and subsequent sudden death from coronary heart disease. *Circulation*. 1973;47:712-9.
25. Abdalla ISH, Prineas RJ, Neaton JD, Jacobs DR and Crow RS. Relation between Ventricular Premature Complexes and Sudden Cardiac Death in Apparently Healthy-Men. *Am J Cardiol*. 1987;60:1036-1042.
26. Yang JK, Dudum R, Mandyam MC and Marcus GM. Characteristics of Unselected High-Burden Premature Ventricular Contraction Patients. *Pace-Pacing and Clinical Electrophysiology*. 2014;37:1671-1680.
27. Heckbert SR, Austin TR, Jensen PN, Floyd JS, Psaty BM, Soliman EZ and Kronmal RA. Yield and consistency of arrhythmia detection with patch electrocardiographic monitoring: The Multi-Ethnic Study of Atherosclerosis. *J Electrocardiol*. 2018;51:997-1002.
28. Kerola T, Dewland TA, Vittinghoff E, Heckbert SR, Stein PK and Marcus GM. Modifiable Predictors of Ventricular Ectopy in the Community. *J Am Heart Assoc*. 2018;7:e010078.
29. von Rotz M, Aeschbacher S, Bossard M, Schoen T, Blum S, Schneider S, Estis J, Todd J, Risch M, Risch L and Conen D. Risk factors for premature ventricular contractions in young and healthy adults. *Heart*. 2017;103:702-707.
30. Katra RP and Laurita KR. Cellular mechanism of calcium-mediated triggered activity in the heart. *Circ Res*. 2005;96:535-42.
31. Brachmann J, Scherlag BJ, Rosenshtraukh LV and Lazzara R. Bradycardia-dependent triggered activity: relevance to drug-induced multiform ventricular tachycardia. *Circulation*. 1983;68:846-56.
32. Rosen MR. Cellular electrophysiology of digitalis toxicity. *J Am Coll Cardiol*. 1985;5:22A-34A.
33. Priori SG and Chen SR. Inherited dysfunction of sarcoplasmic reticulum Ca2+ handling and arrhythmogenesis. *Circ Res*. 2011;108:871-83.
34. Tisdale JE, Patel R, Webb CR, Borzak S and Zarowitz BJ. Electrophysiologic and proarrhythmic effects of intravenous inotropic agents. *Prog Cardiovasc Dis*. 1995;38:167-80.
35. Antzelevitch C, Bernstein MJ, Feldman HN and Moe GK. Parasystole, reentry, and tachycardia: a canine preparation of cardiac arrhythmias occurring across inexcitable segments of tissue. *Circulation*. 1983;68:1101-15.
36. Lerman BB. Mechanism, diagnosis, and treatment of outflow tract tachycardia. *Nat Rev Cardiol*. 2015;12:597-608.
37. Kostis JB, Byington R, Friedman LM, Goldstein S and Furberg C. PROGNOSTIC-SIGNIFICANCE OF VENTRICULAR ECTOPIC ACTIVITY IN SURVIVORS OF ACUTE MYOCARDIAL-INFARCTION. *Journal of the American College of Cardiology*. 1987;10:231-242.
38. Maggioni AP, Zuanetti G, Franzosi MG, Rovelli F, Santoro E, Staszewsky L, Tavazzi L and Tognoni G. PREVALENCE AND PROGNOSTIC-SIGNIFICANCE OF VENTRICULAR ARRHYTHMIAS

AFTER ACUTE MYOCARDIAL-INFARCTION IN THE FIBRINOLYTIC ERA - GISSI-2 RESULTS. *Circulation*. 1993;87:312-322.
39. Bigger JT and Weld FM. ANALYSIS OF PROGNOSTIC-SIGNIFICANCE OF VENTRICULAR ARRHYTHMIAS AFTER MYOCARDIAL-INFARCTION - SHORTCOMINGS OF LOWN GRADING SYSTEM. *British Heart Journal*. 1981;45:717-724.
40. Carrim ZI and Khan AA. Mean frequency of premature ventricular complexes as predictor of malignant ventricular arrhythmias. *Mount Sinai Journal of Medicine*. 2005;72:374-380.
41. Bikkina M, Larson MG and Levy D. ASYMPTOMATIC VENTRICULAR ARRHYTHMIAS AND MORTALITY RISK IN SUBJECTS WITH LEFT-VENTRICULAR HYPERTROPHY. *Journal of the American College of Cardiology*. 1993;22:1111-1116.
42. O'Neill JO, Young JB, Pothier CE and Lauer MS. Severe-frequent ventricular ectopy after exercise as a predictor of death in patients with heart failure. *Journal of the American College of Cardiology*. 2004;44:820-826.
43. Myerburg RJ, Kessler KM and Castellanos A. SUDDEN CARDIAC DEATH - EPIDEMIOLOGY, TRANSIENT RISK, AND INTERVENTION ASSESSMENT. *Annals of Internal Medicine*. 1993;119:1187-1197.
44. Echt DS, Liebson PR, Mitchell LB, Peters RW, Obiasmanno D, Barker AH, Arensberg D, Baker A, Friedman L, Greene HL, Huther ML and Richardson DW. MORTALITY AND MORBIDITY IN PATIENTS RECEIVING ENCAINIDE, FLECAINIDE, OR PLACEBO - THE CARDIAC-ARRHYTHMIA SUPPRESSION TRIAL. *New England Journal of Medicine*. 1991;324:781-788.
45. Massing MW, Simpson RJ, Rautaharju PM, Schreiner PJ, Crow R and Heiss G. Usefulness of ventricular premature complexes to predict coronary heart disease events and mortality (from the atherosclerosis risk in communities cohort). *American Journal of Cardiology*. 2006;98:1609-1612.
46. Rabkin SW, Mathewson FAL and Tate RB. RELATIONSHIP OF VENTRICULAR ECTOPY IN MEN WITHOUT APPARENT HEART-DISEASE TO OCCURRENCE OF ISCHEMIC-HEART-DISEASE AND SUDDEN-DEATH. *American Heart Journal*. 1981;101:135-142.
47. Engel G, Cho S, Ghayoumi A, Yamazaki T, Chun S, Fearon WF and Froelicher VF. Prognostic significance of PVCs and resting heart rate. *Annals of Noninvasive Electrocardiology*. 2007;12:121-129.
48. Sajadieh A, Nielsen OW, Rasmussen V, Hein HO, Frederiksen BS, Davanlou M and Hansen JF. Ventricular arrhythmias and risk of death and acute myocardial infarction in apparently healthy subjects of age >= 55 years. *American Journal of Cardiology*. 2006;97:1351-1357.
49. Agarwal V, Vittinghoff E, Whitman IR, Dewland TA, Dukes JW and Marcus GM. Relation Between Ventricular Premature Complexes and Incident Heart Failure. *American Journal of Cardiology*. 2017;119:1238-1242.
50. Hirose H, Ishikawa S, Gotoh T, Kabutoya T, Kayaba K and Kajii E. Cardiac mortality of premature ventricular complexes in healthy people in Japan. *J Cardiol*. 2010;56:23-6.
51. Lin CY, Chang SL and Lin YJ. An observational study on the effect of premature ventricular complex burden on long-term outcome (vol 96, e5476, 2017). *Medicine*. 2017;96.
52. Dukes JW, Dewland TA, Vittinghoff E, Mandyam MC, Heckbert SR, Siscovick DS, Stein PK, Psaty BM, Sotoodehnia N, Gottdiener JS and Marcus GM. Ventricular Ectopy as a Predictor of Heart Failure and Death. *J Am Coll Cardiol*. 2015;66:101-109.
53. Ofoma U, He F, Shaffer ML, Naccarelli GV and Liao DP. Premature Cardiac Contractions and Risk of Incident Ischemic Stroke. *Journal of the American Heart Association*. 2012;1.
54. Agarwal SK, Chao J, Peace F, Judd SE, Kissela B, Kleindorfer D, Howard VJ, Howard G and Soliman EZ. Premature Ventricular Complexes on Screening Electrocardiogram and Risk of Ischemic Stroke. *Stroke*. 2015;46:1365-1367.
55. Watanabe H, Tanabe N, Makiyama Y, Chopra SS, Okura Y, Suzuki H, Matsui K, Watanabe T, Kurashina Y and Aizawa Y. ST-segment abnormalities and premature complexes are predictors of new-onset atrial fibrillation: The Niigata Preventive Medicine Study. *American Heart Journal*. 2006;152:731-735.

56. Im SI, Kim SH, Kim BJ, Cho KI, Kim HS and Heo JH. Association of frequent premature ventricular complex >10% and stroke-like symptoms without a prior diagnosis of stroke or transient ischemic attack. *Ijc Heart & Vasculature*. 2018;19:58-62.
57. Engstrom G, Hedblad B, Janzon L and Juul-Moller S. Ventricular arrhythmias during 24-h ambulatory ECG recording: incidence, risk factors and prognosis in men with and without a history of cardiovascular disease. *Journal of Internal Medicine*. 1999;246:363-372.
58. Haruta D, Akahoshi M, Hida A, Sera N, Imaizumi M, Ichimaru S, Nakashima E, Takahashi I, Ohishi W, Fukae S and Maemura K. Prognostic Significance of Premature Ventricular Contractions without Obvious Heart Diseases Determined by Standard 12-Lead Electrocardiography Considering their Morphology. *Annals of Noninvasive Electrocardiology*. 2016;21:142-151.
59. Niwano S, Wakisaka Y, Niwano H, Fukaya H, Kurokawa S, Kiryu M, Hatakeyama Y and Izumi T. Prognostic significance of frequent premature ventricular contractions originating from the ventricular outflow tract in patients with normal left ventricular function. *Heart*. 2009;95:1230-1237.
60. Nomura Y, Seki S, Hazeki D, Ueno K, Tanaka Y, Masuda K, Nishibatake M and Yoshinaga M. Risk factors for development of ventricular tachycardia in patients with ventricular premature contraction with a structurally normal heart. *J Arrythm*. 2020;36:127-133.
61. Gaita F, Giustetto C, Di Donna P, Richiardi E, Libero L, Brusin MCR, Molinari G and Trevi G. Long-term follow-up of right ventricular monomorphic extrasystoles. *Journal of the American College of Cardiology*. 2001;38:364-370.
62. Verdile L, Maron BJ, Pelliccia A, Spataro A, Santini M and Biffi A. Clinical significance of exercise-induced ventricular tachyarrhythmias in trained athletes without cardiovascular abnormalities. *Heart Rhythm*. 2015;12:78-85.
63. Kim J, Kwon M, Chang J, Harris D, Gerson MC, Hwang SS and Oh SW. Meta-Analysis of Prognostic Implications of Exercise-Induced Ventricular Premature Complexes in the General Population. *American Journal of Cardiology*. 2016;118:725-732.
64. Lee V, Perera D and Lambiase P. Prognostic significance of exercise-induced premature ventricular complexes: a systematic review and meta-analysis of observational studies. *Heart Asia*. 2017;9:14-24.
65. Ducceschi V, Sarubbi B, Lucca P, Pierro C, Briglia N, Russo B, Mayer MS, Santangelo L and Iacono A. QTc and not QTc dispersion behavior affects the occurrence of ventricular extrasystole during exercise in infarcted patients. *Heart and Vessels*. 1997;12:27-33.
66. Cole CR, Blockstone EH, Pashkow FJ, Snader CE and Lauer MS. Heart rate recovery immediately after exercise as a predictor of mortality. *Herz Kreislauf*. 2000;32:156-156.
67. Zhu DWX, Maloney JD, Simmons TW, Nitta J, Fitzgerald DM, Trohman RG, Khoury DS, Saliba W, Belco KM, Rizopatron C and Pinski SL. RADIOFREQUENCY CATHETER ABLATION FOR MANAGEMENT OF SYMPTOMATIC VENTRICULAR ECTOPIC ACTIVITY. *Journal of the American College of Cardiology*. 1995;26:843-849.
68. Saurav A, Smer A, Abuzaid A, Bansal O and Abuissa H. Premature Ventricular Contraction-Induced Cardiomyopathy. *Clinical Cardiology*. 2015;38:251-258.
69. Cha YM, Lee GK, Klarich KW and Grogan M. Premature Ventricular Contraction-Induced Cardiomyopathy A Treatable Condition. *Circulation-Arrhythmia and Electrophysiology*. 2012;5:229-236.
70. Laplante L and Benzaquen BS. A Review of the Potential Pathogenicity and Management of Frequent Premature Ventricular Contractions. *Pace-Pacing and Clinical Electrophysiology*. 2016;39:723-730.
71. Luebbert J, Auberson D and Marchlinski F. Premature Ventricular Complexes in Apparently Normal Hearts. *Card Electrophysiol Clin*. 2016;8:503-14.
72. Tran CT and Calkins H. Premature ventricular contraction-induced cardiomyopathy: an emerging entity. *Expert Review of Cardiovascular Therapy*. 2016;14:1227-1234.
73. Duffee DF, Shen WK and Smith HC. Suppression of frequent premature ventricular contractions and improvement of left ventricular function in patients with presumed idiopathic dilated cardiomyopathy. *Mayo Clinic Proceedings*. 1998;73:430-433.

74. Hohnloser SH, Zabel M, Krause T and Just H. SHORT-TERM AND LONG-TERM ANTIARRHYTHMIC AND HEMODYNAMIC-EFFECTS OF D,L-SOTALOL IN PATIENTS WITH SYMPTOMATIC VENTRICULAR ARRHYTHMIAS. *American Heart Journal*. 1992;123:1220-1224.
75. Shiraishi H, Ishibashi K, Urao N, Tsukamoto M, Hyogo M, Keira N, Hirasaki S, Shirayama T and Nakagawa M. A case of cardiomyopathy induced by premature ventricular complexes. *Circulation Journal*. 2002;66:1065-1067.
76. Bogun F, Crawford T, Reich S, Koelling TM, Armstrong W, Good E, Jongnarangsin K, Marine JE, Chugh A, Pelosi F, Oral H and Morady F. Radiofrequency ablation of frequent, idiopathic premature ventricular complexes: Comparison with a control group without intervention. *Heart Rhythm*. 2007;4:863-867.
77. Sekiguchi Y, Aonuma K, Yamauchi Y, Obayashi T, Niwa A, Hachiya H, Takahashi A, Nitta J, Iesaka Y and Isobe M. Chronic hemodynamic effects after radiofrequency catheter ablation of frequent monomorphic ventricular premature beats. *Journal of Cardiovascular Electrophysiology*. 2005;16:1057-1063.
78. Takemoto M, Yoshimura H, Ohba Y, Matsumoto Y, Yamamoto U, Mohri M, Yamamoto H and Origuchi H. Radiofrequency catheter ablation of premature ventricular complexes from right ventricular outflow tract improves left ventricular dilation and clinical status in patients without structural heart disease. *J Am Coll Cardiol*. 2005;45:1259-1265.
79. Hasdemir C, Kartal Y, Simsek E, Yavuzgil O, Aydin M and Can LH. Time Course of Recovery of Left Ventricular Systolic Dysfunction in Patients with Premature Ventricular Contraction-Induced Cardiomyopathy. *Pace-Pacing and Clinical Electrophysiology*. 2013;36:612-617.
80. Baman TS, Lange DC, Ilg KJ, Gupta SK, Liu TY, Alguire C, Armstrong W, Good E, Chugh A, Jongnarangsin K, Pelosi F, Crawford T, Ebinger M, Oral H, Morady F and Bogun F. Relationship between burden of premature ventricular complexes and left ventricular function. *Heart Rhythm*. 2010;7:865-869.
81. Yokokawa M, Good E, Crawford T, Chugh A, Pelosi F, Latchamsetty R, Jongnarangsin K, Armstrong W, Ghanbari H, Oral H, Morady F and Bogun F. Recovery from left ventricular dysfunction after ablation of frequent premature ventricular complexes. *Heart Rhythm*. 2013;10:172-175.
82. Fang YQ, Wen CL, Yang L, Zhang XQ, Chu W and Zeng CY. Radiofrequency ablation can reverse the structural remodeling caused by frequent premature ventricular contractions originating from the right ventricular outflow tract even in a "normal heart". *Clinics*. 2013;68:1312-1317.
83. Baser K, Bas HD, LaBounty T, Yokokawa M, Good E, Latchamsetty R, Morady F and Bogun F. Recurrence of PVCs in patients with PVC-induced cardiomyopathy. *Heart Rhythm*. 2015;12:1519-1523.
84. Wojdyla-Hordynska A, Kowalski O, Hordynski GJ, Dinov B, Sommer P, Hindricks G, Feusette P and Arya A. The effect of radiofrequency catheter ablation of frequent premature ventricular complexes and arrhythmia burden on left ventricular function. *Kardiologia Polska*. 2017;75:697-703.
85. de Lavallaz JDF, Mezier J, Mertz L, Mannhart D, Serban T, Knecht S, Abid QU, Nguyen TT, Kuhne M, Sticherling C, Huang H, Gold MR and Badertscher P. Risk factors for the development of premature ventricular complex-induced cardiomyopathy: a systematic review and meta-analysis. *J Interv Card Electrophysiol*. 2022.
86. Zang MH, Zhang T, Mao JL, Zhou SH and He B. Beneficial effects of catheter ablation of frequent premature ventricular complexes on left ventricular function. *Heart*. 2014;100:787-793.
87. Lamba J, Redfearn DP, Michael KA, Simpson CS, Abdollah H and Baranchuk A. Radiofrequency Catheter Ablation for the Treatment of Idiopathic Premature Ventricular Contractions Originating from the Right Ventricular Outflow Tract: A Systematic Review and Meta-Analysis. *Pace-Pacing and Clinical Electrophysiology*. 2014;37:73-78.
88. Voskoboinik A, Hadjis A, Alhede C, Im SI, Park H, Moss J, Marcus GM, Hsia H, Lee B, Tseng Z, Lee R, Scheinman M, Vedantham V, Vittinghoff E, Park KM and Gerstenfeld EP. Predictors

of adverse outcome in patients with frequent premature ventricular complexes: The ABC-VT risk score. *Heart Rhythm*. 2020;17:1066-1074.
89. Lie OH, Saberniak J, Dejgaard LA, Stokke MK, Hegbom F, Anfinsen OG, Edvardsen T and Haugaa KH. Lower than expected burden of premature ventricular contractions impairs myocardial function. *Esc Heart Failure*. 2017;4:585-594.
90. Shanmugam N, Chua TP and Ward D. 'Frequent' ventricular bigeminy - A reversible cause of dilated cardiomyopathy. How frequent is 'frequent"? *European Journal of Heart Failure*. 2006;8:869-873.
91. Ban JE, Park HC, Park JS, Nagamoto Y, Choi JI, Lim HE, Park SW and Kim YH. Electrocardiographic and electrophysiological characteristics of premature ventricular complexes associated with left ventricular dysfunction in patients without structural heart disease. *Europace*. 2013;15:735-741.
92. Lee YH, Zhong L, Roger VL, Asirvatham SJ, Shen WK, Slusser JP, Hodge DO and Cha YM. Frequency, Origin, and Outcome of Ventricular Premature Complexes in Patients With or Without Heart Diseases. *American Journal of Cardiology*. 2014;114:1373-1378.
93. Pol LC, Deyell MW, Frankel DS, Benhayon D, Squara F, Chik W, Kohari M, Deo R and Marchlinski FE. Ventricular premature depolarization QRS duration as a new marker of risk for the development of ventricular premature depolarization-induced cardiomyopathy. *Heart Rhythm*. 2014;11:299-306.
94. Deyell MW, Park KM, Han Y, Frankel DS, Dixit S, Cooper JM, Hutchinson MD, Lin D, Garcia F, Bala R, Riley MP, Gerstenfeld E, Callans DJ and Marchlinski FE. Predictors of recovery of left ventricular dysfunction after ablation of frequent ventricular premature depolarizations. *Heart Rhythm*. 2012;9:1465-1472.
95. Eugenio PL. Frequent Premature Ventricular Contractions An Electrical Link to Cardiomyopathy. *Cardiology in Review*. 2015;23:168-172.
96. Yamada S, Chung FP, Lin YJ, Chang SL, Lo LW, Hu YF, Chao TF, Liao JN, Lin CH, Lin CY, Chang YT, Te ALD, Liao YC, Chi PC and Chen SA. Electrocardiographic characteristics for predicting idiopathic right ventricular outflow tract premature ventricular complex-induced cardiomyopathy. *Journal of Interventional Cardiac Electrophysiology*. 2018;53:175-185.
97. Ephrem G, Levine M, Friedmann P and Schweitzer P. The Prognostic Significance of Frequency and Morphology of Premature Ventricular Complexes during Ambulatory Holter Monitoring. *Annals of Noninvasive Electrocardiology*. 2013;18:118-125.
98. Lin CY, Chang SL, Lin YJ, Lo LW, Chung FP, Chen YY, Chao TF, Hu YF, Tuan TC, Liao JN, Huang YC, Chang YT, Chiou CW and Chen SA. Long-term outcome of multiform premature ventricular complexes in structurally normal heart. *International Journal of Cardiology*. 2015;180:80-85.
99. Yarlagadda RK, Iwai S, Stein KM, Markowitz SM, Shah BK, Cheung JW, Tan V, Lerman BB and Mittal S. Reversal of cardiomyopathy in patients with repetitive monomorphic ventricular ectopy originating from the right ventricular outflow tract. *Circulation*. 2005;112:1092-1097.
100. Hasdemir C, Ulucan C, Yavuzgil O, Yuksel A, Kartal Y, Simsek E, Musayev O, Kayikcioglu M, Payzin S, Kultursay H, Aydin M and Can LH. Tachycardia-Induced Cardiomyopathy in Patients With Idiopathic Ventricular Arrhythmias: The Incidence, Clinical and Electrophysiologic Characteristics, and the Predictors. *J Cardiovasc Electr*. 2011;22:663-668.
101. Munoz FD, Syed FF, Noheria A, Cha YM, Friedman PA, Hammill SC, Munger TM, Venkatachalam KL, Shen WK, Packer DL and Asirvatham SJ. Characteristics of Premature Ventricular Complexes as Correlates of Reduced Left Ventricular Systolic Function: Study of the Burden, Duration, Coupling Interval, Morphology, and Site of Origin of PVCs. *Journal of Cardiovascular Electrophysiology*. 2011;22:791-798.
102. Olgun H, Yokokawa M, Baman T, Kim HM, Armstrong W, Good E, Chugh A, Pelosi F, Crawford T, Oral H, Morady F and Bogun F. The role of interpolation in PVC-induced cardiomyopathy. *Heart Rhythm*. 2011;8:1046-1049.
103. Park KM, Im SI, Park SJ, Kim JS and On YK. Risk factor algorithm used to predict frequent premature ventricular contraction-induced cardiomyopathy. *International Journal of Cardiology*. 2017;233:37-42.

104. Haissaguerre M, Shoda M, Jais P, Nogami A, Shah DC, Kautzner J, Arentz T, Kalushe D, Lamaison D, Griffith M, Cruz F, de Paola A, Gaita F, Hocini M, Garrigue S, Macle L, Weerasooriya R and Clementy J. Mapping and ablation of idiopathic ventricular fibrillation. *Circulation*. 2002;106:962-967.
105. Shimizu W. Arrhythmias originating from the right ventricular outflow tract: How to distinguish "malignant" from "benign"? *Heart Rhythm*. 2009;6:1507-1511.
106. Kawamura M, Badhwar N, Vedantham V, Tseng ZH, Lee BK, Lee RJ, Marcus GM, Olgin JE, Gerstenfeld EP and Scheinman MM. Coupling Interval Dispersion and Body Mass Index Are Independent Predictors of Idiopathic Premature Ventricular Complex-Induced Cardiomyopathy. *Journal of Cardiovascular Electrophysiology*. 2014;25:756-762.
107. Al-Khatib. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death : A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society (vol 15, pg e73, 2018). *Heart Rhythm*. 2018;15:E276-E277.
108. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, Charron P, Corrado D, Dagres N, de Chillou C, Eckardt L, Friede T, Haugaa KH, Hocini M, Lambiase PD, Marijon E, Merino JL, Peichl P, Priori SG, Reichlin T, Schulz-Menger J, Sticherling C, Tzeis S, Verstrael A, Volterrani M and Group ESCSD. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2022.
109. Proclemer A, Basadonna PT, Slavich GA, Miani D, Fresco C and Fioretti PM. Cardiac magnetic resonance imaging findings in patients with right ventricular outflow tract premature contractions. *European Heart Journal*. 1997;18:2002-2010.
110. Sestito A, Pardeo M, Sgueglia GA, Natale L, Delogu A, Infusino F, De Rosa G, Bellocci F, Crea F and Lanza GA. Cardiac magnetic resonance of healthy children and young adults with frequent premature ventricular complexes. *Journal of Cardiovascular Medicine*. 2007;8:692-698.
111. Bogun FM, Desjardins B, Good E, Gupta S, Crawford T, Oral H, Ebinger M, Pelosi F, Chugh A, Jongnarangsin K and Morady F. Delayed-Enhanced Magnetic Resonance Imaging in Nonischemic Cardiomyopathy Utility for Identifying the Ventricular Arrhythmia Substrate. *Journal of the American College of Cardiology*. 2009;53:1138-1145.
112. Jeserich M, Merkely B, Olschewski M, Kimmel S, Pavlik G and Bode C. Patients with exercise-associated ventricular ectopy present evidence of myocarditis. *Journal of Cardiovascular Magnetic Resonance*. 2015;17.
113. Oebel S, Dinov B, Arya A, Hilbert S, Sommer P, Bollmann A, Hindricks G, Paetsch I and Jahnke C. ECG morphology of premature ventricular contractions predicts the presence of myocardial fibrotic substrate on cardiac magnetic resonance imaging in patients undergoing ablation. *Journal of Cardiovascular Electrophysiology*. 2017;28:1316-1323.
114. Aquaro GD, Pingitore A, Strata E, Di Bella G, Molinaro S and Lombardi M. Cardiac Magnetic Resonance Predicts Outcome in Patients With Premature Ventricular Complexes of Left Bundle Branch Block Morphology. *Journal of the American College of Cardiology*. 2010;56:1235-1243.
115. Yokokawa M, Siontis KC, Kim HM, Stojanovska J, Latchamsetty R, Crawford T, Jongnarangsin K, Ghanbari H, Cunnane R, Chugh A, Pelosi F, Oral H, Morady F and Bogun F. Value of cardiac magnetic resonance imaging and programmed ventricular stimulation in patients with frequent premature ventricular complexes undergoing radiofrequency ablation. *Heart Rhythm*. 2017;14:1695-1701.
116. Nucifora G, Muser D, Masci PG, Barison A, Rebellato L, Piccoli G, Daleffe E, Toniolo M, Zanuttini D, Facchin D, Lombardi M and Proclemer A. Prevalence and Prognostic Value of Concealed Structural Abnormalities in Patients With Apparently Idiopathic Ventricular Arrhythmias of Left Versus Right Ventricular Origin A Magnetic Resonance Imaging Study. *Circulation-Arrhythmia and Electrophysiology*. 2014;7:456-462.
117. Cabanelas N, Ferreira MJV, Donato P, Gaspar A, Pinto J, Caseiro-Alves F and Providencia LA. Added value of cardiac magnetic resonance in etiological diagnosis of ventricular arrhythmias. *Revista Portuguesa De Cardiologia*. 2013;32:785-791.

118. Markowitz SM, Weinsaft JW, Waldman L, Petashnick M, Liu CF, Cheung JW, Thomas G, Ip JE and Lerman BB. Reappraisal of Cardiac Magnetic Resonance Imaging in Idiopathic Outflow Tract Arrhythmias. *Journal of Cardiovascular Electrophysiology*. 2014;25:1328-1335.
119. Contijoch F, Rogers K, Rears H, Shahid M, Kellman P, Gorman J, Gorman RC, Yushkevich P, Zado ES, Supple GE, Marchlinski FE, Witschey WRT and Han Y. Quantification of Left Ventricular Function With Premature Ventricular Complexes Reveals Variable Hemodynamics. *Circulation-Arrhythmia and Electrophysiology*. 2016;9.
120. Contijoch F, Iyer SK, Pilla JJ, Yushkevich P, Gorman JH, Gorman RC, Litt H, Han YC and Witschey WRT. Self-gated MRI of multiple beat morphologies in the presence of arrhythmias. *Magnetic Resonance in Medicine*. 2017;78:678-688.
121. Muser D, Santangeli P, Castro SA, Casado Arroyo R, Maeda S, Benhayon DA, Liuba I, Liang JJ, Sadek MM, Chahal A, Magnani S, Pieroni M, Santarossa E, Desjardins B, Dixit S, Garcia FC, Callans DJ, Frankel DS, Alavi A, Marchlinski FE, Selvanayagam JB and Nucifora G. Risk Stratification of Patients With Apparently Idiopathic Premature Ventricular Contractions: A Multicenter International CMR Registry. *JACC Clin Electrophysiol*. 2020;6:722-735.
122. Gerstenfeld EP. Should CMR Be Performed for Every Patient With Frequent Premature Ventricular Contractions? *JACC Clin Electrophysiol*. 2022;8:1133-1135.
123. Wijnmaalen AP, Delgado V, Schalij MJ, van Taxis C, Holman ER, Bax JJ and Zeppenfeld K. Beneficial effects of catheter ablation on left ventricular and right ventricular function in patients with frequent premature ventricular contractions and preserved ejection fraction. *Heart*. 2010;96:1275-1280.
124. Ling YL, Wan Q, Chen QX and Zhu WQ. Assessment of subtle cardiac dysfunction in patients with frequent premature ventricular complexes by real-time three-dimensional speckle tracking echocardiography. *Clinical Cardiology*. 2017;40:554-558.
125. Topaloglu S, Aras D, Cagli K, Yildiz A, Cagirci G, Cay S, Gunel EN, Baser K, Baysal E, Boyaci A and Korkmaz S. Evaluation of left ventricular diastolic functions in patients with frequent premature ventricular contractions from right ventricular outflow tract. *Heart and Vessels*. 2007;22:328-334.
126. van Taxis C, Piers SRD, Silva MD, Dekkers OM, Pijnappels DA, Schalij MJ, Wijnmaalen AP and Zeppenfeld K. Fatigue as Presenting Symptom and a High Burden of Premature Ventricular Contractions Are Independently Associated With Increased Ventricular Wall Stress in Patients With Normal Left Ventricular Function. *Circulation-Arrhythmia and Electrophysiology*. 2015;8:1452-1459.
127. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W and Voigt JU. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiog*. 2015;28:1-U170.
128. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA and Waggoner AD. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiog*. 2016;29:277-314.
129. Badano LP, Muraru D, Parati G, Haugaa K and Voigt JU. How to do right ventricular strain. *European Heart Journal-Cardiovascular Imaging*. 2020;21:825-827.
130. Voigt JU, Malaescu GG, Haugaa K and Badano L. How to do LA strain. *European Heart Journal-Cardiovascular Imaging*. 2020;21:715-717.
131. Cameli M, Mandoli GE, Loiacono F, Dini FL, Henein M and Mondillo S. Left atrial strain: a new parameter for assessment of left ventricular filling pressure. *Heart Failure Reviews*. 2016;21:65-76.
132. Kurt M, Wang JW, Torre-Amione G and Nagueh SF. Left Atrial Function in Diastolic Heart Failure. *Circulation-Cardiovascular Imaging*. 2009;2:10-15.

133. Chen CH, Fetics B, Nevo E, Rochitte CE, Chiou KR, Ding PYA, Kawaguchi A and Kass DA. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. *Journal of the American College of Cardiology*. 2001;38:2028-2034.
134. Antonini-Canterin F, Poli S, Vriz O, Pavan D, Bello VD and Nicolosi GL. The Ventricular-Arterial Coupling: From Basic Pathophysiology to Clinical Application in the Echocardiography Laboratory. *J Cardiovasc Echogr*. 2013;23:91-95.
135. Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G, Galderisi M, Marwick T, Nagueh SF, Sengupta PP, Sicari R, Smiseth OA, Smulevitz B, Takeuchi M, Thomas JD, Vannan M, Voigt JU and Zamorano JL. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. *Eur J Echocardiogr*. 2011;12:167-205.
136. Picano E, Pelosi G, Marzilli M, Lattanzi F, Benassi A, Landini L and L'Abbate A. In vivo quantitative ultrasonic evaluation of myocardial fibrosis in humans. *Circulation*. 1990;81:58-64.
137. Surawicz B, Childers R, Deal BJ and Gettes LS. AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram Part III: Intraventricular Conduction Disturbances A Scientific Statement From the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society Endorsed by the International Society for Computerized Electrocardiology. *J Am Coll Cardiol*. 2009;53:976-981.
138. Yamada T. Idiopathic ventricular arrhythmias Relevance to the anatomy, diagnosis and treatment. *Journal of Cardiology*. 2016;68:463-471.
139. Yamada T. Twelve-lead electrocardiographic localization of idiopathic premature ventricular contraction origins. *Journal of Cardiovascular Electrophysiology*. 2019;30:2603-2617.