ISSN 0022–9032

e-ISSN 1897–4279

February 2024, vol. 82, number 2

POLISH HEART JOURNAL

Kardiologia Polska

The Official Peer-reviewed Journal
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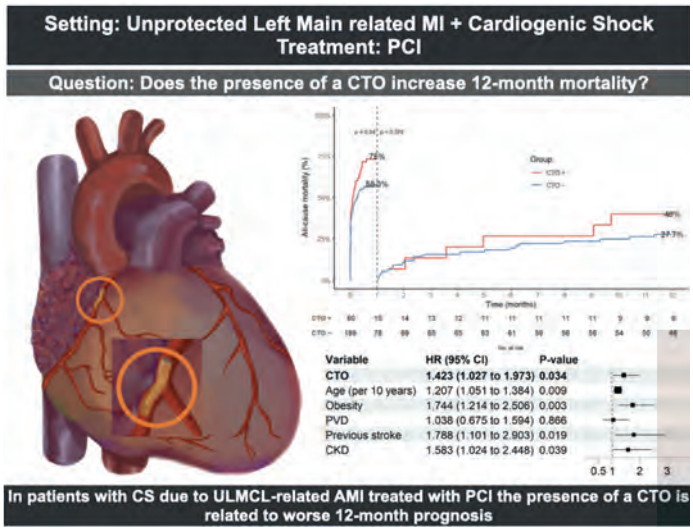

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Polskie Towarzystwo Kardiologiczne
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VM Media Group sp. z o.o.,
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ISSN 0022-9032
e-ISSN 1897-4279

Subscription rates: Paper subscription, 12 issues incl. package and postage individual 994 PLN
Paper subscription, 12 issues incl. package and postage institutional 1987 PLN
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Ministry of Science and Higher Education score: 100 pts.

The project on the development of the journal „Polish Heart Journal (Kardiologia Polska)" is co-financed from the state budget under the „Development of Scientific Journals" program as per the Regulation of the Minister of Education and Science of August 3, 2021 on the „Development of Scientific Journals" program (Journal of Laws of 2021, item Scientific Journals").

87 WIOSENNA KONFERENCJA PTK

XVI Konferencja Kardiologii Polskiej

Jubileusz 70-lecia PTK

Zapraszamy do wzięcia udziału w **87 Wiosennej Konferencji PTK oraz XVI Konferencji „Kardiologii Polskiej”** w dniach **13-14 kwietnia 2024 roku**, które odbędą się w gmachu Opery i Filharmonii Podlaskiej w Białymstoku. Podczas Konferencji odbędzie się również **Jubileusz 70-lecia Polskiego Towarzystwa Kardiologicznego**.

Program naukowy został przygotowany przez najwybitniejszych specjalistów polskiej kardiologii i kardiochirurgii. Omówione zostaną wytyczne ESC z 2023 roku.

Pozostałe sesje zostały przygotowane przez przedstawicieli wszystkich grup tematycznych Komitetu Naukowego Kongresu i obejmują całe spektrum podspecjalizacji nowoczesnej kardiologii. Kilka ważnych i ciekawych zagadnień praktycznych zostanie zaprezentowanych w atrakcyjnej konwencji warsztatowej.

Jesteśmy przekonani, że taki program zachęci Państwa do udziału w Konferencji, przyniesie istotne korzyści praktyce klinicznej, a także przyczyni się do rozwoju Polskiego Towarzystwa Kardiologicznego.

Zapraszamy nie tylko kardiologów i kardiochirurgów, ale również rezydentów, lekarzy rodzinnych, internistów i studentów medycyny. Dla studentów udział w Konferencji jest bezpłatny.

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Implantable-cardioverter defibrillators and COVID-19: A complicated relationship

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DOI: 10.33963/v.phj.99380

Received:
February 8, 2024

Accepted:
February 8, 2024

Early publication date:
February 13, 2024

The ongoing coronavirus pandemic has left a profound impact on humanity, unveiling the insidious nature of the virus whose influence extends beyond the upper respiratory tract. Cardiovascular disorders, including cardiac arrhythmias, are recognized as common extrapulmonary manifestations of coronavirus disease 2019 (COVID-19). Cardiac arrhythmias, such as atrial fibrillation and ventricular tachycardia, are prevalent among COVID-19 patients. Furthermore, the pandemic has also been linked to a sharp increase in out-of-hospital cardiac arrests, but the specifics of the cause of cardiac arrest and associated arrhythmias remain unclear.

Patients with implantable cardioverter--defibrillators (ICD), who are inherently predisposed to ventricular tachyarrhythmias due to underlying structural or electrical heart disease, became a focal point of study during the pandemic. That research aimed to discover the arrhythmic mechanisms underlying cardiac arrests. However, despite the heightened vulnerability to severe SARS-CoV-2 infection in these patients, the frequency of ICD therapies has been surprisingly variable (Figure 1).

Exploring the data from various studies provides a kaleidoscopic view of ICD therapies during the pandemic. Adabag et al. [1] reported a significant increase in ICD therapies in New York City, Boston, and New Orleans, focusing on the zip codes with the highest prevalence of COVID-19 in the USA during the first phase of the pandemic. However, using

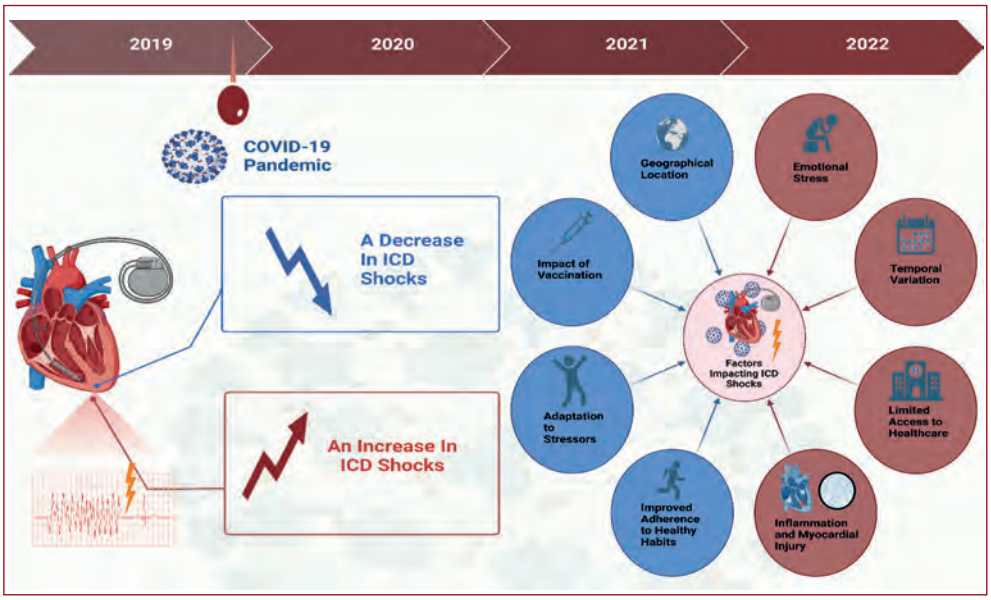

Figure 1. Central figure

state-level data from a wide region in the USA, O'Shea et al. [2] reported a 32% decrease in ICD shocks. In studies from 3 separate regions in Italy, Malanchini et al. [3], Sassone et al. [4], and Zorzi et al. [5] reported no change in ventricular arrhythmia burden and ICD therapies during the COVID-19 pandemic, disputing a higher incidence of cardiac arrests in the same period in Italy. However, Ducceschi et al. [6] reported an increase in both ventricular and atrial tachyarrhythmias during the pandemic in the Campania region of Italy. In Germany, Hauck et al. [7] reported no change in cardiac arrhythmias in ICD patients enrolled in a clinic, but Rath et al. [8] reported an increase in cardiac arrhythmias in ICD patients during the second wave of the COVID-19 pandemic. In a multi-center study from France, Galand et al. [9] noted a significant increase in ICD therapy with anti-tachycardia pacing during the initial weeks of the pandemic, coinciding with heightened emotional stress, but observed a subsequent significant decrease in ICD therapies after the lockdown. In Poland, Tajstra et al. [10] reported no change in appropriate ICD therapies during the pandemic but inappropriate therapies, delivered for atrial tachyarrhythmias, occurred less frequently.

These disparate results may arise from each study focusing on a different aspect of the pandemic's influence on people. While the patients infected with SARS-CoV-2 may have a greater likelihood of arrhythmias, others may have been protected due to lockdowns. While the patients who had to delay necessary medical care may have suffered adverse consequences, those who avoided the physical and emotional stressors of work may have had more favorable outcomes. Thus, these varied outcomes underscore the intricate relationship between COVID-19 and ICD interventions. Notably, prior studies lacked information on patients' COVID-19 status. A comprehensive analysis involving a large group of patients with and without ICD therapy is necessary to determine the true association of COVID-19 with ICD shocks.

In this issue of the journal, Biel et al. [11] report the outcomes of patients presenting to the hospital with ICD shocks in the COVID-19 era, providing data elucidating part of this puzzle. They note that the number of hospital admissions for ICD shocks during the pandemic was similar to the pre-pandemic era. However, only 11% of the patients hospitalized during the pandemic had COVID-19, which does not appear to be a sufficient proportion to alter the overall hospitalization rate. The authors acknowledge as a limitation that there may have been patients with ICD shocks who were not hospitalized due to reluctance to go to the emergency department. Biel et al. [11] also report a higher mortality rate among patients who had COVID-19. This is not a surprise, given that high-risk study population. Furthermore, the patients with COVID-19 had a higher likelihood of ICD discharges in the hospital compared to those without COVID-19. Although the sample size of this subgroup is small, this observation suggests a positive association between potentially lethal ventricular arrhythmias and COVID-19.

Indeed, the current body of evidence supports the hypothesis that COVID-19 may trigger cardiac arrhythmias. However, this potential is not exclusive to COVID-19. Existing data also highlight a higher incidence of sudden cardiac death, cardiac arrhythmias, and ICD shocks during the influenza season. The potential mechanism of cardiac arrhythmias triggered by upper respiratory tract viral infections includes cytokine activation, viral myocarditis, hypercoagulability, and adrenergic activation as well as secondary factors such as hypoxemia, dehydration, electrolyte abnormalities, drug toxicities, and inability to take cardiac medications.

Despite significant progress in the field, sudden cardiac death (SCD) remains a major cause of death in the general population [12]. While left ventricular structural abnormalities associated with SCD have been identified, we cannot predict most SCD cases, and ICDs may not be beneficial in certain patient groups [13–15]. In addition to the abnormal myocardial substrate, there also appears to be a seemingly random component in SCD prediction that has puzzled investigators for a long time. This "random" component might involve transient SCD triggers, which are so elusive that they are undetectable by the time the healthcare team arrives on the scene. Wearable and implantable devices as well as machine-learning algorithms may help investigators identify some of these transient triggers for cardiac arrhythmias and SCD. The pandemic has taught us those viral infections of the upper respiratory tract, including COVID-19, may just be one of them.

Article information

Conflict of interest: None declared.

Funding: None.

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Aortic valve and arterial calcification in patients with familial hypercholesterolemia

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DOI: 10.33963/v.phj.98945

Received: June 19, 2023

Accepted: January 15, 2024

Early publication date: February 6, 2024

ABSTRACT

Heterozygous familial hypercholesterolemia (heFH) is an autosomal dominant lipid metabolism disorder. Its prevalence is 1:250–1:300 people in the population. Patients with heFH have an up to 13-fold increased risk of premature coronary artery disease (CAD). If left untreated, men and women with heFH typically develop early CAD before the ages of 55 and 60, respectively.

There is evidence that coronary artery calcification (CAC) and aortic valve calcification (AoVC) are more prevalent in FH patients than in the general population. It is documented that CAC and AoVC are predictors of increased risk of cardiovascular morbidity and mortality in heFH patients, like in the general population. However, the etiology and pathogenesis of vascular calcification in FH patients is not well understood. Risk factors for vascular calcification include age, increased levels of atherogenic lipoproteins, Lp(a), increased blood pressure, and inflammation. There are convincing data from clinical studies and animal atherosclerotic mouse models using low-density lipoprotein receptor (LDL-R) knockout mice that the vascular calcification processes in FH are associated with LDL-R mutations, probably partly due to a higher total cholesterol burden of FH subjects. Data from animal models as well as clinical studies indicate that the Wnt/beta-catenin pathway components and LDL receptor-related proteins 5 and 6 (LRP-5/6) might be involved in calcification processes in FH patients.

The purpose of the review is to describe the prevalence of coronary and aortic calcification and its risk factors in FH patients. The review covers data about the role of the Wnt/beta-catenin pathway and factors modulating calcification processes.

Key words: aortic valve calcification, coronary calcification, familial hypercholesterolemia

GENETIC BACKGROUND AND CLINICAL CONSEQUENCES OF FAMILIAL HYPERCHOLESTEROLEMIA

Familial hypercholesterolemia is caused by mutations in the low-density lipoprotein receptor (*LDLR*) gene, apolipoprotein *B100* gene, or the proprotein convertase subtilisin-kexin type 9 (*PCSK9*) gene. Defects in these genes lead to impaired clearance of LDL cholesterol (LDL-C) from the plasma. Low-density lipoprotein receptors are responsible for uptake of LDL particles and thus removal of cholesterol from plasma. Apolipoprotein B100 is the LDL-bound protein that binds to the LDL receptor. PCSK9 is responsible for the degradation of LDL receptors [1]. A single copy of the defective gene (heterozygous) leads to an increase of plasma LDL-C (5 to 13 mmol/l), whereas 2 copies of the same defective gene (homozygous) or 2 coexisting mutations (compound heterozygous) lead to very high concentrations (above 13 mmol/l) of LDL-C due to minimal or no LDL-C clearance. FH is associated with high circulating LDL-C levels from birth, which leads to the development of atherosclerosis early in life, premature atherosclerotic cardiovascular disease (ASCVD), and tendon xanthomas [1–3].

The goal of FH treatment is to reduce mortality and premature coronary artery disease (CAD) events by reducing plasma LDL

levels. Heterozygous familial hypercholesterolemia (heFH) patients are categorized as being at high risk of atherosclerotic cardiovascular disease, or as very-high-risk patients due to the presence of ASCVD or the presence of one of the major risk factors [3]. Pharmacotherapeutic management of heFH patients consists of high-dose statins usually in combination with ezetimibe as first-line therapy followed by a PCSK9 inhibitor to further lower LDL-C levels to achieve the recommended targets. Despite intensive drug therapy, most heFH patients are still at high cardiovascular risk, and, interestingly, patients with a monogenic form of hypercholesterolemia are at higher risk than those with a polygenic form [4]. This might be due to inadequate treatment, too late onset of treatment, or possibly due to not addressing all risk factors, such as calcification processes [5].

PREVALENCE OF CALCIFICATION IN FAMILIAL HYPERCHOLESTEROLEMIA PATIENTS

Vascular calcification is the pathological deposition of calcium phosphate mineral, usually hydroxyapatite, in vascular structures. Vascular calcification can be located in the intima (atherosclerotic intimal calcification), media — medial artery calcification (Monckeberg's sclerosis), and in cardiac valves. Calcification forms within the intimal and medial layers of the vessel wall and heart valves through active mechanisms similar to bone development. Coronary artery calcification can be characterized by early changes, such as microcalcification to well-developed calcified fibroatheromas [5, 6].

Calcification of aortic valves is a slowly progressive fibro-calcific remodeling of the valve leaflets leading to aortic valve stenosis. This process can be divided into two phases: the initiation phase, which shows similarities with atherosclerosis including endothelial damage due to increased mechanical stress and reduced shear stress, lipid deposition, inflammation, and oxidative stress, and the propagation phase, which is mainly characterized by fibrosis and calcification. Valve calcification is highly dependent on biomechanical and hemodynamic factors and has the characteristics of atherosclerotic and medial calcification, with a strong inflammatory component [7, 8]. Valvular interstitial cells (VICs), the most abundant valvular cells, play a major role in valve calcification and are responsible for differences between the pathobiology of aortic stenosis and atherosclerosis [9]. Mineralization of the heart valve includes nodule formation and stenosis, which causes the narrowing of the valve opening [10]. Increased oxidation of valvular lipids and subsequent chronic valvular inflammation lead to VIC differentiation into osteogenic phenotype. VICs can release osteopontin and osteocalcin, which are responsible for valvular calcification and pro-inflammatory cytokines, clotting factors, and proteins involved in the propagation of calcification [9]. Experimental data, comparing molecular profiles of calcification in aortic vascular smooth muscle cells and aortic VICs suggest that the pathogenesis of cardiovascular calcification is significantly more diverse than previously appreciated [11].

High LDL is associated with increased atherosclerosis and vascular calcification due to oxidative modification of LDL-C, lipid deposition, and inflammation [3–5].

Calcification commonly affects patients with diabetes mellitus, dyslipidemia, heart valve disease, and end-stage renal disease [12].

There is strong evidence that calcification processes are more prevalent in patients with FH than in the general population [13, 14]. Interestingly, some data indicate that vascular calcification processes in FH patients are associated with *LDLR* mutations [13–18].

In the study measuring the degree of aortic calcification in heFH patients compared to both homozygous familial hypercholesterolemia (hoFH) and controls, aortic calcification was observed in patients with heFH at a later time and was less extensive than in hoFH (34 vs. 14 years, respectively). In this study, the age at which the abdominal aorta calcium score reaches 1000 was 22, 28, and 62 years in hoFH, heFH, and controls, respectively. The authors suggested that aortic calcification may be partly independent of serum cholesterol levels in FH patients [16] (Table 1).

AoVC is associated with an elevated cardiovascular risk. The degree of AoVC is correlated with the severity of aortic stenosis, disease progression, heart failure, and the development of cardiovascular events [17–19].

In FH patients prevalence of AoVC is higher than in healthy controls. In the study by Ten Kate et al. [13], the prevalence of aortic valve calcification (%) and the AoVC-score (median, IQR) were markedly higher in 145 heFH patients than in controls: 41%, 51 (9–117) vs. 21%, 21 (3––49), respectively. In this study, patients' age, untreated maximal LDL-C equal to 7.1 ± 2.2 mmol/l, coronary artery calcification (CAC), and diastolic blood pressure were independently associated with AoVC. However, the strongest predictor of the AoVC-score was *LDLR*-negative mutational heFH [13]. Awan et al. examined 25 hoFH patients, at a mean age of 32 years and a mean baseline cholesterol level before treatment of 19.5 mmol/l. An elevated mean calcium score in aortic valves was found in patients under the age of 20 and correlated significantly with age [14]. In the study by Gałązka et al. [15] assessment of computed tomography (CT) calcium scores showed that patients with *LDLR* gene mutations have significantly increased AoVC scores in comparison to those without mutations: 13.8 ± 37.9 vs. 0.94 ± 3.1, respectively. Also, other authors showed that patients with FH due to mutations in the *LDLR* gene exhibited severe, premature aortic calcification in a gene-dosage, age-dependent fashion [20–22]. In the LDLR-deficient mouse model for aortic calcification, elevated cholesterol alone was not sufficient to produce severe aortic calcification. This observation suggests that the absence of the LDLR might be the major contributor to aortic calcification [23].

In heFH patients accelerated aortic calcification increases exponentially with age. According to Kindi M. et al. [20],

Table 1. Studies on coronary artery calcification (CAC) and aortic valve calcification in FH patients

Vascular calcification	Patients	Results	Ref No
Aortic valve calcification (AVC)	145 heFH patients and 131 non-FH controls, mean age 52 ± 8 years	Prevalence (%) of AVC was higher in heFH than in controls: 41% vs. 21% LDLR-negative mutational heFH was a strong predictor of AVCS (OR: 4.81; 95% CI, 2.22–10.4; *P* <0.001)	[8]
Aortic calcification (AoCa)	25 hoFH patients, mean age 32 years, mean baseline cholesterol 19 ± 5 mmol/l	Elevated calcium score was found by age 20 and correlated with age; 24% of patients underwent aortic valve surgery	[9]
Aortic valve calcification score (AVCS)	72 FH patients with LDLR mutation vs. 50 patients without mutation	AVCS was higher in patients with vs. without mutation: 13.8 ± 37.9 vs. 0.94 ± 3.1; *P* = 0.03 The *LDLR* mutation was a strong predictor of AVCS (OR, 7.83; 95% CI, 2.08–29.50; *P* = 0.002)	[10]
AoCa	heFH due to the French Canadian mutation (Delta15 kb del. null allele), Mean age 50 ± 15 years Initial cholesterol 10.45 ± 1.73 mmol/l Comparison to both hoFH and controls	A strong correlation between age and calcium score was found (r = 0.72; *P* =0.0016) Aortic calcification in heFH patients occurred later than in hoFH patients (34 vs. 14 years, respectively), and were less extensive, but much earlier than in controls, suggesting a gene-dosage effect of LDL-R mutations and aortic calcium deposition. Conclusion: aortic calcification may be partly independent of serum cholesterol levels in FH patients.	[11]
AoCa	16 heFH patients with the null LDLR DEL15Kb mutation Rescanned after 8.2 ± 0.8 years 38 controls	An abdominal AoCa score in heFH was 7916 ± 7060 Agatston U; and in controls: 1472 ± 2489; *P* <0.001 The rate of progression was 159 vs. 312 Agatston U/y in controls vs. those with heFH; heFH patients exhibited accelerated AoCa that increased exponentially with age	[15]
AoCa	LDLR-deficient mouse model	Aortic calcification was an age- and diet-dependent process. Data suggest that the absence of the LDLR is a major contributor to aortic calcification LDLR deficiency increases aortic calcification independently of cholesterol level	[18]
CAC	112 heFH patients (50% males), median age 45 years	The prevalence of CAC was 58% Patients without CAC showed lower total cholesterol burden (TCB) than patients with CAC (298 ± 110 vs. 417.9 ± 89 mmol-years/l, *P* <0.001) Multivariate analysis indicated that TCB was independently associated with CAC Conclusion: Asymptomatic heFH subjects exhibit early coronary atherosclerosis directly associated with TCB burden. CAC score may be useful to identify higher-risk heFH patients who can benefit from earlier and more aggressive treatment	[20]
CAC	Patients with genetically defined heFH (68 women and 78 men) 95 patients had prevalent CAC	In heFH patients age, family history of premature cardiovascular disease, sex, statin use, diet quality, smoking status, the LDLR genotype, and lipoprotein(a) levels were independently associated with CAC prevalence and severity	[21]
Coronary calcification Agatston score	50 heFH patients, diagnosed according to DLCN criteria and 70 controls	Significantly greater Agatston calcium score in heFH patients than in the controls (260 vs. 46; *P* = 0.002)	[22]

LDL-C at baseline or during treatment seems to have little effect on the rate of progression of the AoCa score. However, Rajamannan et al. [22] pointed out in their publication that progression of calcification in treated FH patients was slower than in controls, which suggests the inhibiting effect of lipid-lowering therapy on calcification processes.

Interestingly, patients with FH caused by PCSK9 gain-of-function mutation exhibit an age- and gene-dosage-dependent increase in the incidence of AoVC [20]. Also, PCSK9 gain-of-function mutations in experimental animal models induced cardiovascular calcification [22–24].

Patients with heFH are characterized also by increased CAC, which is related to the total cholesterol burden and *LDLR* gene mutational status [25–27]. In a group of 112 heFH patients (50% males, median age 45 years), coronary artery calcification prevalence was 58% and, in multivariate analysis, was independently associated with the total cholesterol burden. Patients with CAC showed a significantly higher total cholesterol burden (TCB) than patients without CAC. Among patients aged <45 years, 39% exhibited CAC and a higher TCB compared with patients without CAC (352 ± 71 vs. 255 ± 88 mmol-years/l) due to higher total cholesterol levels at diagnosis (10.2 ± 2 vs. 8.7 ± 2 mmol/l) [25]. In a group of 146 heFH patients, aged 47.8 ± 14.1 years, included in the study by Drouin-Chartier et al. [26], 95 had prevalent CAC. CAC prevalence and severity in this study correlated independently with age, family history of premature cardiovascular disease, male sex, statin use and diet quality, smoking, receptor-negative phenotype, and lipoprotein(a) (Lp[a]) [26]. In the study by Medel et al. [27], a significantly higher Agatston calcium score, which is a measure of arterial calcification, was observed in comparison with the control group (260 vs. 46) and was associated, apart from age and HDL-C, with null allele *LDLR* gene mutations. Also, in the study by Ten Kate et al. [17], the CAC score was associated with *LDLR* mutational status (Table 1).

To conclude, data from clinical studies and animal atherosclerotic mouse models with the *LDLR* knockout mice suggest that vascular calcification processes in FH are associated, apart from the TCB, also with *LDLR* mutational status; however, the mechanisms of these processes remain to be elucidated.

ROLE OF CALCIFICATION IN PREDICTING CARDIOVASCULAR RISK

The CAC score has been widely used to predict the future risk of acute coronary events. The accuracy of coronary artery calcification score has been demonstrated in cardiovascular risk assessment in the general population,

Table 2. Trials on coronary artery calcification (CAC) and aortic valve calcification confirming their role as predictors of cardiovascular risk in FH patients

Vascular calcification	Patients	Result	Ref No
CAC	206 patients with molecularly proven FH mean age: 45 ± 14 years; 36.4% men; treated LDL-C: (150 ± 34 mg/dl) follow-up 3.7 years (IQR, 2.7–6.8 years)	CAC was the only marker independently associated with future cardiovascular events	[24]
CAC	SAFEHEART and REFERCHOL national registries on heFH 1624 patients (mean age: 48.5 ± 12.8 years; men: 45.7%), median follow-up of 2.7 years (IQR, 0.4–5.0) Atherosclerosis was present in 81 subjects	The presence of a CAC score of >100 was associated with a hazard ratio of 32.05 (95% CI, 10.08–101.94) of developing cardiovascular events as compared to a CAC score of 0. CAC score confirmed its use in improving cardiovascular risk stratification and cardiovascular events prediction in statin-treated heFH	[25]
Aortic root calcification	113 FH patients, age 52.1 ± 15.6 years, mean LDL-C 299 ± 94.6 mg/dl Follow-up period 1635 days	Independent predictor of major adverse cardiovascular events OR, 1.48; 95 CI, 1.11–1.87	[16]

and recent data in heFH patients confirm this observation [27–30]. In the study including 206 FH subjects receiving standard lipid-lowering therapy, CAC was independently associated with ASCVD events [28].

Interestingly, Mszar et al. [31, 32] noticed, using data from coronary CT performed on more than 1000 heFH patients, that coronary atherosclerotic disease burden in middle-aged heFH patients is heterogeneous. The authors found that nearly half of the heFH patients were free of clinical ASCVD and demonstrated no detectable CAC despite significantly elevated LDL-C levels. These data indicate that determining calcification scores in heFH patients would be helpful as prognostic factors to identify those with higher risk who can benefit from earlier and more aggressive treatment [31]. The severity of CAC was recently identified as the most discriminant risk factor associated with the incidence of cardiovascular events in patients with heFH [29–33]. Also, the aortic root calcification score was an independent risk factor for cardiac events in FH [21]. A large study on the heFH population conducted by Gallo et al. [30] included 1624 patients with molecular diagnosis of heFH, at the mean age of 45 years. They were followed for a median of 2.7 years (interquartile range [IQR], 0.4–5.0 years). In this study, CAC scores of 0.1–100, and >100 were observed in 38.7%, 32.2%, and 29% of study participants, respectively. Patients with clinical events exhibited higher CAC scores (387 [IQR, 146–879] vs. 8 [IQR, 0–109]) and a higher frequency of CAC of >100 (82.72% vs. 26.18%). Cardiovascular endpoints in this study were acute coronary syndromes, stroke, aortic valve replacement (which is also an important endpoint in heFH patients), peripheral artery disease, cardiovascular death, and elective myocardial revascularization (Table 2).

SUGGESTED MECHANISMS OF ARTERIAL CALCIFICATION AND THE WNT/ /BETA-CATENIN PATHWAY

The mechanisms of vascular calcification are not fully elucidated. In the available literature, the data on mechanism of CAC and AoVC in FH are sparse and derived mainly from experimental models. Coronary artery calcification and aortic valve calcification was thought to be a passive and degenerative disorder; however, it has been shown to be an active process, very similar to bone mineralization, and many of the key regulators of bone mineralization are active in cardiovascular calcification [5].

Studies have found that vascular calcification is thought to be mediated by osteoblast-like cells. Calcifying vascular cells originate from local smooth muscle cells and circulating hematopoietic stem cells, especially in intimal calcification. There is evidence, that also endothelial cells can function as an additional source of osteogenic progenitors in vascular calcification [34, 35]. The process of transition of endothelial-to-mesenchymal cells possessing osteogenic potential and leading to vascular calcification requires cooperation between distinct stimuli, including inflammatory cytokines and transforming growth factor beta family members.

During calcification vascular smooth muscle cells (VSMC) switch into cells similar to bone-forming osteoblasts with upregulation of osteogenic markers and extracellular matrix remodeling. In the calcifying condition, e. g. with a high level of serum phosphate, VSMCs begin to express osteogenic markers including RUNX2 (Runt-related Transcription Factor 2), SP7 (Osterix), osteopontin (OPN, SPP1), osteocalcin (OCN, BGLAB1), alkaline phosphatase (ALPL), SOX9 (SRY-box transcription factor 9), collagen types I and X. Calcifying VSMCs form small discrete regions of calcification. A similarity was found between bone formation and artery calcification. However, as Patel et al. [36] showed by comparing mouse osteoblast with controls and calcifying VSMCs, early osteoblast markers in calcifying VSMCs (Runx2, Sp7) were 6-fold upregulated but still 3-fold lower in comparison to the osteoblast. Because the *RUNX2* gene is directly targeted by the canonical WNT signaling pathway, it was postulated that mineral deposition, like bone formation, is regulated by the WNT signaling pathway. The WNT pathway activates the genes connected with bone formation during development. The WNT signaling pathway regulates many cellular functions during development and in adults (e.g., cell fate determination, differentiation, proliferation, and morphogenesis). The WNT signaling pathway is stimulated by binding of extracellular WNT ligands to Frizzled receptors. WNT ligands

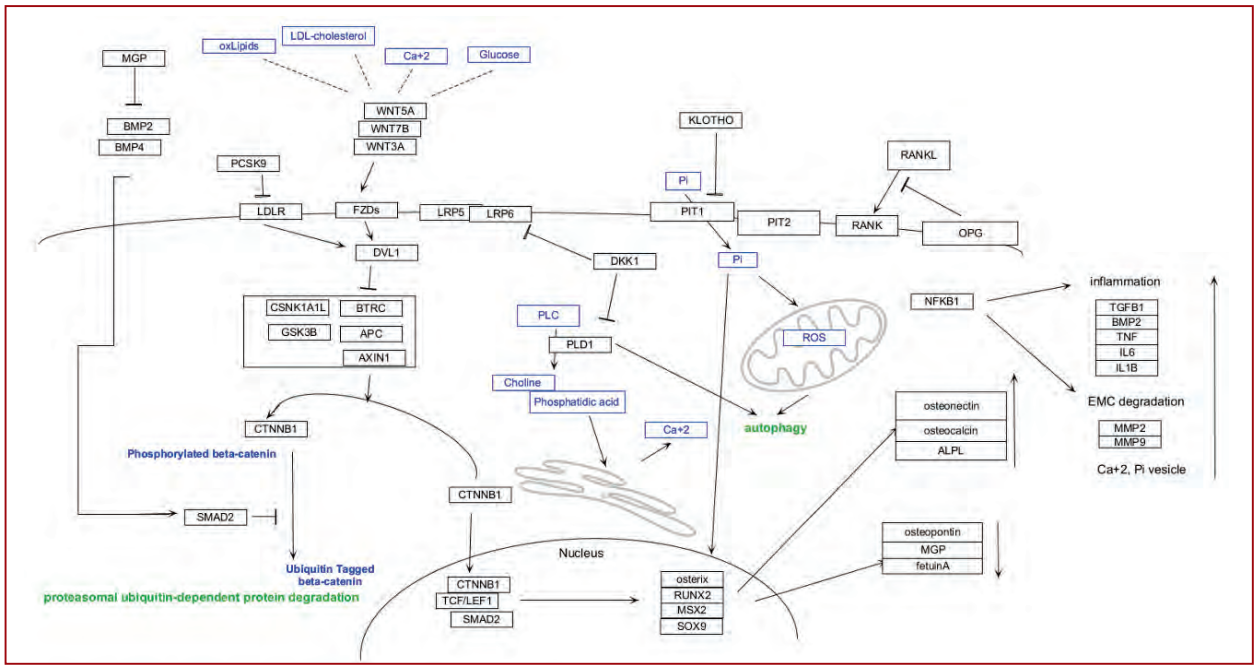

Figure 1. Proteins involved in vascular calcification processes in vascular smooth muscle cells (VSCM). Prepared using Pathvisio 3.2.1

Abbreviations: APC, APC regulator of the WNT signaling pathway; AXIN1, axin 1; BMP2, bone morphogenetic protein 2; BMP4, bone morphogenetic protein 4; BTRC, beta-transducin repeat containing E3 ubiquitin protein ligase; CSNK1A1L, casein kinase 1 alpha 1 like; CTNNB1, catenin beta 1; DKK1, dickkopf WNT signaling pathway inhibitor 1; DVL1, dishevelled segment polarity protein 1; FZDs, frizzled class receptors; GSK3B, glycogen synthase kinase 3 beta; IL1B, interleukin 1b; IL6, interleukin 6; LEF1, lymphoid enhancer binding factor 1; LRP5, LDL receptor related protein 5; LRP6, LDL receptor related protein 6; LDLR, low density lipoprotein receptor; MMP2, matrix metallopeptidase 2; MMP9, matrix metallopeptidase 9; MSX2, msh homeobox 2; NFKB1, nuclear factor kappa B subunit 1; OPG, (TNFRSF11B) TNF receptor superfamily member 11b; OSTERIX (Sp7), Sp7 transcription factor; PCSK9, proprotein convertase subtilisin/kexin type 9; PLD1, phospholipase D1; PIT1, (SLC20A1) solute carrier family 20 member 1; PIT2, (SLC20A2) solute carrier family 20 member 2; RANK, (TNFRSF11A) TNF receptor superfamily member 11a; RANKL, (TNFSF11) TNF superfamily member 11; RUNX2, RUNX family transcription factor 2; SMAD2, SMAD family member 2; SOX9, SRY-box transcription factor 9; TCF, (HNF4A) hepatocyte nuclear factor 4 alpha; TGFB1, transforming growth factor beta 1; TNF, tumor necrosis factor; WNT3A, Wnt family member 3A; WNT5A, Wnt family member 5A; WNT7B, Wnt family member 7B

(family of 19 proteins) activate intracellular signaling by binding to Frizzled receptors associated with co-receptors LRP5/LRP6 (low-density lipoprotein receptor family) and recruit cytoplasmic phosphoprotein Disheveled (DVL). DVL serves as a branch point for the canonical and non-canonical WNT signaling pathways. Propagation of canonical WNT signaling through receptor activation inhibits proteasomal beta-catenin utilization. Release of beta-catenin from the inhibitory complex (Axin, Glycogen Synthase Kinase 3 [GSK-3], Casein Kinase 1 [CK1], adenomatous polyposis coli protein [APC], and the E3-ubiquitin ligase β-TrCP [BTRC]) leads to beta-catenin translocation to nucleus and induces expression of WNT target genes. Some studies have begun testing specific WNT ligands to determine if any of them contributes most significantly toward calcification. Multiple WNT ligands conveying canonical and noncanonical actions, including WNT7b, WNT5a, and WNT2 are related to vascular smooth muscle calcification [37, 38].

The most studied WNT ligand in vascular calcification is WNT3a. WNT3a, through activation of its downstream mediator beta-catenin, can induce RUNX2 and osteocalcin expression and promote calcification in VSMCs [39].

Sheng et al. [40] showed that cholesterol is enriched around the WNT-activated Frizzled receptors and LRP 5/6 co-receptors and plays an essential role in DVL-mediated formation and maintenance of the canonical WNT signaling complex. Cholesterol specifically facilitates the membrane recruitment of the PDZ (Postsynaptic density protein [PSD95]/Drosophila disc large tumor suppressor [Dlg1]/Zonula occludens-1 protein) domain of DVL and its interaction with other proteins [40]. VSMCs from high-fat-fed rats showed higher mRNA expressions of Wnt3a, beta-catenin, and Tcf4 as well as in VSMCs cultured with hyperlipidemic serum [38]. Cholesterol depletion from myoblast membranes induces activation of the WNT signaling pathway and myogenic differentiation [42].

DKK1 slowed vascular calcification by promoting PLD1 degradation via regulating autophagosome formation and maturation. Phospholipase D (PLD) exists widely in biological tissues and can hydrolyze PLC (phosphatidylcholine) to phosphatidic acid (PA) and free choline. PA acts as the second messenger in cells to regulate intracellular calcium [43] (Figure 1).

There is evidence that lack of LDLR may modify osteoblast function, resulting in increased deposition in calcifying vascular tissue [18, 22, 23]. Data increasingly indicate that the WNT/beta-catenin pathway and LDL receptor-related protein 5/6 (LRP5/6) co-receptors are

also involved in osteoblasts differentiation, initiating and promoting calcification processes [18, 44, 45]. Beta-catenin plays a key role in the commitment of early progenitors to osteoblast precursors by mediating WNT signal transduction. Low-density lipoprotein cholesterol, a strong stimulator of atherosclerosis and inflammation, signals LRP5 to initiate WNT signaling in the vasculature and valve interstitial cells. These cells then develop bone formation signaling and cause ectopic bone matrix synthesis and calcification over time [45]. The role of involvement of WNT /beta-catenin pathway components and LRP5/6 in calcification processes in FH patients was confirmed by data on knockout and transgenic animal models [18, 22, 35, 44–48].

LRP5/6 are members of the LDLR family and are composed of structurally related cell surface receptors. They act, in consort with Frizzled receptors, as coreceptors to mediate the Wnt/beta-catenin signaling pathway [49–51]. LRP5 and LRP6 are single-pass transmembrane proteins and are indispensable for Wnt signal transduction [49]. LRP5 is an LDLR co-receptor involved in activation of skeletal bone formation, but it is also implicated in cholesterol metabolism [18, 45, 50, 51]. It is expressed in low concentration in many tissues including the aortic valve. There is increasing data that LRP5 apart from the canonical WNT signaling pathway is active in cardiovascular calcification. Both LRP5 and LRP6 are involved in cardiac disease [52]. LRP5, apart from inducing osteogenic differentiation in heart valves was demonstrated to play a protective role in the injured heart following MI in mice. On the other hand, LRP6 inhibition limited myocardial fibrosis, improved cardiac repair in myocardial infarction, decreased blood pressure in hypertensive animals, and reduced adipogenesis and lipogenesis to prevent elevated serum LDL, triglycerides, and glucose levels [53, 54].

LRP5 is expressed in low levels also in the aortic valve, and upregulation of LRP5 in hypercholesterolemic rabbit aortic valve confirms that the LRP5/Wnt pathway is implicated in aortic stenosis progression. Rajamannan et al. [55] found that hypercholesterolemic AoV calcification is mediated in part by the LPR5/beta-catenin pathway and is attenuated by atorvastatin. In their study, the cholesterol diet induced complex bone formations in the calcified AoVs, with an increase in the number of LRP5 receptors, osteopontin, and p42/44 expression.

A recent review by Bundy et al. [44] discussed the potential role of the canonical WNT signaling pathway in vascular calcification and the WNT ligands that specifically aid in VSMC transdifferentiation.

FACTORS INFLUENCING CALCIFICATION PROCESSES

Many local and systemic factors influence the calcification process, including hyperlipidemia, hypertension, systemic inflammatory diseases, kidney disease, and diabetes [53, 54]. Also, medical therapies, such as statins and warfarin, exhibit pro-calcific effects on the vessel wall [5, 57].

Serum lipids play an important role in vascular calcification. Several clinical studies documented associations between LDL and coronary artery and aortic valve calcification [57–62]. High LDL-C levels were also associated with increased calcification progression in patients with known aortic calcification. In the CARDIA study, LDL-C, male sex, and the body mass index were significant risk factors for CAC and calcification progression [60]. The role of LDL-C was confirmed by the increased calcification of valves and arteries in patients with heterozygous LDLR null familial hypercholesterolemia [16, 17, 20, 58]. On the other hand, HDL (high-density lipoprotein) appears to have beneficial effects on vascular calcification through effects on bone preosteoclasts [57].

Higher apo B levels, apolipoprotein present in LDL and other liver-delivered lipoproteins, were associated with CAC prevalence, incidence, and progression. Apo B discordance, relative to LDL-C or non-HDL-C, was inconsistently associated with CAC prevalence and progression [62].

Other factors that might be responsible for the development of coronary and aortic valve calcification in patients FH include Lp(a) and circulating PCSK9 level [63–67]. Lp(a) is an independent risk factor for aortic valve stenosis and AoVC in the general population as well as in FH patients [63–67]. In the study including 129 heFH patients, AoVC was present in 38.2% of patients. In this study Lp(a) level was significantly correlated with the presence and severity of AoVC, but not with CAC [66]. Lp(a) is a major carrier of phospholipids and their oxidized forms, which are co-expressed with Lp(a) within the stenotic leaflets and promote valvular calcification. Interestingly, Kopytek et al. [68] recently showed that in severe aortic stenosis, oxidized phospholipids are associated with Lp(a) in relation to hypofibrinolysis, which is also linked to the severity of aortic stenosis.

Also, PCSK9, a protein regulating LDLR activity, is involved in premature artery calcification. Alonso et al. [69] selected 161 molecularly defined FH patients, measured CAC with cardiac CT using the Agatson score and correlated these measurements to PCSK9 levels, plasma Lp(a) levels, and apo(a) levels. They found that both plasma PCSK9 levels and Lp(a) were independently predictive of elevated coronary artery calcium scores. According to their findings, circulating PCSK9 levels were significantly lower in patients without coronary artery calcification while patients with the highest CAC scores had the highest levels of PSCK9 and Lp(a) [66]. The study by Poggio P et al. [70], indicates that PCSK9 is also involved in aortic valve calcification. On the contrary, Acena A. et al [71] described the independent role of low PCSK9 levels in progression of aortic stenosis in patients with ischemic heart disease. Interestingly, recent data suggest an association between PCSK9 serum levels and recurrent cardiovascular events in FH patients [72] (Table 3).

Inflammation is a key feature of arterial and aortic valve calcification. Clinical, animal, and *in vitro* studies implicate

Table 3. Factors influencing vascular calcification processes

Factor	Effect on calcification	Mechanism of action
LDL-C	Stimulatory	Oxidized low-density lipoprotein stimulates vascular calcification by driving osteoblastic differentiation of vascular smooth muscle cells and inhibiting osteoclast differentiation
VLDL-C	Stimulatory	
HDL-C	Inhibitory	High-density lipoprotein exerts beneficial effects on vascular calcification through effects on bone preosteoclasts
Lp(a)	Potentially casual	Lp(a) is a vehicle for oxidized phospholipids and oxysterols, which potentiate inflammation and atherosclerosis
Treatment with statin	Increase plaque calcification	Statins and high-intensity exercise promote calcification without increasing risk
Treatment with PCSK9-I	Increase plaque calcification	

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein a; PCSK9-I, proprotein convertase subtilisin-kexin type 9 inhibitor; VLDL-C, very low-density lipoprotein cholesterol

hyperlipidemia-induced inflammation in the genesis and progression of vascular calcification.

Diabetes mellitus is also one of the important factors involved in vascular calcification [12]. FH and DM significantly increase the risk and progression of arterial and aortic valve calcification, by inducing oxidative stress and inflammatory state. In FH patients, deficiency or dysfunction of LDL receptors results in increased plasma residence time of LDL in the circulation and, in consequence, increased exposure of vascular tissue to LDL particles and increased oxidative modifications of LDL, inflammatory state, and pathological conditions leading to calcification. In DM increased accumulation of advanced glycoxidation end products (AGEs) in aortic valves leads to enhanced valvular oxidative stress, inflammation, and expression of coagulation factors and, in consequence, calcification markers. Interestingly, AGE levels are better predictors for vascular calcification than HbA1c [57, 73].

Several studies confirmed the involvement of inflammatory cytokines, such as TNF alfa, Il-6, Il-1beta, CRP, and PTX3 in calcification processes [74–77]. Moreover, observations made in human aortic valves of diabetic patients with aortic stenosis demonstrated that the number of pro-inflammatory proteins impacts stenosis progression [78]. These data indicate the importance of inflammation status for the severity of aortic calcification. Data from genetic studies further confirm the role of inflammation in calcification: polymorphisms of inflammation factor genes (Interleukin-6 receptor gene, C-reactive protein gene) were associated with an attenuated systemic inflammatory state and less severe aortic stenosis or, conversely, might predispose to larger aortic valve calcification. Therefore, they potentially can be novel genetic risk markers of disease progression [79, 80]. Interestingly, Plunde and Back [81] described the important role of omega-6 fatty acid arachidonic acid that gives rise to the mediators prone to elicit a pro-inflammatory response and enhance calcification-related mechanisms in aortic valves.

Recent data, published by Sánchez-Duffhues et al. [77] indicate, that the pro-inflammatory cytokines, TNF alfa, and Il-1 beta, induce endothelial cell transformation to osteogenic differentiation. The authors suggest that the bone morphogenetic protein type II receptor (BMPR2) BMPR2-JNK signaling axis is a key pathway regulating inflammation-induced endothelial cell transformation and contributing to calcification.

GlycA, a novel composite biomarker of systemic inflammation, reflects posttranslational glycosylation of acute phase reactants and is measured by nuclear magnetic resonance spectroscopy. GlycA has been associated with a greater prevalence of coronary artery calcium, cardiovascular disease (CVD) events, and mortality. In cross-sectional analysis, in the Multi-Ethnic Study of Atherosclerosis, GlycA was positively associated with prevalent aortic valve calcification as well as descending thoracic aorta and other extra-coronary calcification [82].

Biomarkers that play a role in the pathophysiology of cardiac calcification can be measured in plasma samples for early detection and disease prevention. These include fetuin-A (AHSG), matrix Gla protein (MGP), osteoprotegerin (OPG), Klotho, fibroblast growth factor 23 (FGF23), nucleotide pyrophosphatase/phosphodiesterase-1 (NPP1) [25]. A loss of local and circulating calcification inhibitory proteins, such as MGP, fetuin-A, and OPG, also contribute significantly to the formation of vascular calcification [83, 84].

DETECTION OF CORONARY AND AORTIC VALVE CALCIFICATION

Coronary artery calcium imaging, according to the American Society for Preventive Cardiology, is included on the list of imaging tests helpful with the diagnosis and prognosis of CVD [85]. CT angiography without contrast infusion is used for assessment of CAC and atherosclerotic plaque characterization. It is a noninvasive procedure and patient radiation exposure is 1mSv [83]. Improvements in technology, especially high-speed multislice CT scans, allow objective measurement of both the density and extent of coronary calcification, usually calculated by using the Agatston method et al. [86]. For calcification assessment, the Agatston coronary calcium score, as well as the aortic valve calcification score, is calculated. Another noninvasive imaging biomarker of active coronary atherosclerotic mineralization recently suggested by Moss et al. [87] is positron emission tomography (PET) computed tomography using 18-F fluorodeoxyglucose (FDG-PET/CT) and 18F-sodium fluoride-tracers [86]. This analysis is useful for early detection of early calcification [5, 6, 87]. ^{18}NaF- PET/CT is also useful in aortic valve sclerosis detection. This imaging

system using PET detects smaller calcium deposits that are below CT resolution (200–500 µm) and intravascular ultrasound (200 µm lateral resolution). ^{18}F-NaF PET/CT imaging, which has higher sensitivity for calcium minerals, is used in human and animal studies to identify high-risk vulnerable lesions. Abdelbaky et al. [88] have found unequivocal evidence that early aortic valve inflammation may predispose to valve sclerosis using this technique.

Interestingly, another method, recently described — circulating microvesicles (cMV) — appeared to indicate vascular atherosclerotic plaques and calcification. Circulating microvesicles are released when cells are activated. Chiva-Blanch et al. [89] found that endothelial-, granulocyte-, neutrophil- and platelet-derived cMV discriminate and map coronary atherosclerotic plaque and calcification in asymptomatic patients with FH. In their study, the Agatston coronary calcium score correlated with granulocyte-, platelet-, and endothelial-derived cMV. Circulating microvesicles could be useful biomarkers to better characterize and individualize cardiovascular risk prediction in FH patients.

TREATMENT OF VASCULAR CALCIFICATION

There is no treatment to decrease vascular calcification. Statin therapy might increase, decrease, or cause no changes in coronary calcification [22, 61, 90, 91]. Statins and high-intensity exercise promote calcification without increasing risk [61]. Statins and other LDL-lowering therapies markedly diminish the progression of atherosclerosis in FH patients; however, statins do not seem to reduce the rate of progression of coronary calcification despite a beneficial effect on the progression of atherosclerosis [92, 93]. Statins may also increase calcification associated with plaque quiescence/healing. There is a possibility that statins increase calcification and CAC scores by reducing plaque volume and increasing the density of plaque calcium leading to plaque stabilization [94]. Statins may also limit the progression of vascular calcification by reducing inflammation in atheroma associated with the decrease in LDL-C [95]. Summing up, strategies to prevent aortic valve and aorta calcification with statins have not been met with clinical success, and novel approaches are required.

The SEAS study examining the role of combined simvastatin and ezetimibe therapy in aortic stenosis involved 1873 patients with mild-to-moderate asymptomatic aortic stenosis. The authors [96] found that during a median follow-up of 52.2 months, simvastatin and ezetimibe reduced the incidence of ischemic cardiovascular events but not events related to aortic valve stenosis. However, secondary analysis from the SEAS trial showed that these drug combinations reduced the need for aortic valve replacement in patients with mild aortic stenosis and high LDL-C levels (>4.0 mmol/l), but not in patients with moderate aortic stenosis [97].

Plunde and Back suggested the need for clinical trials of high-dose EPA supplements as a treatment for aortic valve calcification, considering that fatty acids serve as substrates for many lipid mediators involved in the resolution of inflammation. Aortic valves incorporate omega-3 polyunsaturated fatty acid, and high omega-3 fatty acids are associated with slower progression of aortic valve stenosis [81].

Therapy with inhibitors of PCSK9: monoclonal antibodies alirocumab and evolocumab in statin-treated patients resulted in substantial reductions in atherogenic lipoprotein cholesterol-carrying particles and a decrease of CAC rate progression in comparison to statin monotherapy [89–91].

As previously mentioned, Lp(a) causal in ischemic heart disease is also associated with increased risk of calcification. Current treatment options for high Lp(a) include PCSK9 inhibitors that reduce its levels by 25%–30% on average [98, 99]. The new drugs lowering Lp(a) include antibodies against Lp(a), and therapies with ASO (antisense oligonucleotides) and siRNA (small interfering RNA), which currently are under clinical trials [100]. Therapies with ASO and siRNA olpasiran and pelacarsen reduce circulating Lp(a) levels by 85%–90%. Cholesteryl ester transfer protein (CETP) inhibitors also significantly reduce atherogenic lipoproteins, apolipoprotein B, small LDL particles, and Lp (a), and increase HDL-C. Obicetrapib, a next-generation, oral, once-daily, low-dose CETP inhibitor was characterized in clinical trials by an excellent safety and tolerability profile and markedly lowered atherogenic lipoproteins. Moreover, the REVEAL trial demonstrated that adding CETP inhibitor anacetrapib to intensive statin therapy reduced the risk of major coronary events, and this effect increased with longer follow-up duration. A recently published article by Bortnick AE showed in a multiethnic population that HDL-C, HDL-P, large HDL-P, and apoC3-lacking HDL-C were inversely associated with long-term incidence and progression of AVC. These data raise the possibility, that drugs increasing HDL-C, such as CETP inhibitors, could be a potential therapy for AoC [101].

Therapies using PCSK9 inhibitors, antisense oligonucleotides targeting apo(a) and thus lowering Lp(a) or cholesteryl transfer protein inhibitors and their role in reducing the risk of aortic stenosis progression have been described in detail in a recent review [102–105].

The findings on the role of inflammatory factors in arterial and AoVC raise the question about inhibitors of the IL-6 pathway, such as the IL-6 receptor antagonists: tocilizumab and sarilumab (106). Experimental data indicate that aortic calcification can be inhibited by an IL-1β mAb in LDLR-deficient mice [107, 108].

Apart from inflammation markers also the beta-catenin-dependent pathway is a potential target in the prophylaxis and treatment of vascular complications.

CONCLUSION AND FUTURE RESEARCH

There are still many controversies and unresolved questions concerning arterial calcification – although CAC severity is a strong predictor of cardiovascular morbidity and mortality, is it a healing process of vulnerable plaque? Or does it

increase the risk of plaque rupture? What is the role of statins and lipid-lowering drugs in calcification processes and in preventing the development of calcification? What is the role of LDLR defect and the WNT/beta-catenin pathway? So far there have been no convincing data on whether and how to treat vascular calcification and how the treatment will affect cardiovascular risk.

There is a need to estimate the role of CAC determination value in clinical practice in FH patients also in Poland, as there are specialized centers able to diagnose genetic background and treat FH patients with PCSK9 inhibitors [109, 110].

Article information

Conflict of interest: None declared.

Funding: UJ CM N41/DBS/000982

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Outcomes for patients with implanted cardioverter--defibrillators admitted to the Emergency Department due to electrical shock during the pre-pandemic and COVID-19 era

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Editorial
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DOI: 10.33963/v.kp.98604

Received:
July 19, 2023

Accepted:
December 19, 2023

Early publication date:
December 29, 2023

ABSTRACT

Background: Implantable cardioverter-defibrillators (ICD)/cardiac resynchronization therapy with defibrillation (CRT-D) recipients may be susceptible to the arrhythmic effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Aims: We aimed to evaluate characteristics and outcomes of patients hospitalized for ICD/CRT-D shocks during the pandemic compared to the pre-pandemic period.

Methods: This retrospective study analyzed medical records of patients hospitalized for ICD/CRT-D shock in the pre-pandemic (January 1, 2018–December 31, 2019) and pandemic periods (March 4, 2020–March 3, 2022). Survival data were obtained on October 24, 2022.

Results: In total, 198 patients (average age 65.6 years) had 138 pre-pandemic and 124 pandemic visits. Of these patients, 115 were hospitalized during pre-pandemic, 108 during the pandemic, and 25 in both periods. No significant differences were noted in age, sex, number of shocks, or appropriateness of therapy between these periods. During the pandemic, during 14 hospital stays of patients with SARS-CoV-2, 8 (57.1%) received electrical shocks, compared to 12 (10.9%) with negative SARS-CoV-2 tests (P <0.001). The in-hospital mortality rate was 2 of 115 patients hospitalized during the pre-pandemic and 7 of 108 during pandemic periods (4 patients with and 3 without SARS-CoV-2 [P = 0.10]). During the follow-up, there were 66 deaths. Cox regression analysis showed that survival decreased with age and heart failure decompensation in medical history but increased with higher ejection fraction. The pandemic alone was not a survival predictor. However, SARS-CoV-2 infection, older age, and heart failure decompensation in medical history predicted worse outcomes during the pandemic period.

Conclusions: The pandemic did not increase the number of hospital visits due to ICD/CRT-D discharges. SARS-CoV-2 infection predicts increased mortality in patients with ICD/CRT-D shocks.

Key words: cardiac resynchronization therapy, COVID-19, hospitalization, implantable cardioverter defibrillator, pandemic

INTRODUCTION

Coronavirus disease 19 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first cases were recognized in December 2019 in Wuhan, China [1]. In Poland, the first case of COVID-19 disease was documented on March 4, 2020 [2]. Since then, the number of infected patients increased rapidly [3, 4]. The symptoms of respiratory damage pre-

WHAT'S NEW?

The global COVID-19 pandemic has profoundly affected healthcare systems, necessitating significant changes in patient care worldwide. Patients with implantable cardioverter-defibrillators or cardiac resynchronization therapy with defibrillation, who require meticulous monitoring and specialized attention, are particularly vulnerable. This study investigated the impact of the pandemic on hospitalization admissions in this patient cohort and showed that despite the pandemic, hospitalization rates remained unaffected. However, patients with concurrent SARS-CoV-2 infection experienced elevated rates of in-hospital shock incidents and mortality. These findings advance our understanding of the pandemic's influence on specific patient populations and offer valuable insights for future healthcare planning and resource allocation during comparable crises.

dominate, but signs of cardiovascular involvement are frequent [5, 7]. Direct cardiac injury, autonomic dysfunction, stress myocardiopathy, vascular thrombosis, electrolyte disturbances, and release of proinflammatory cytokines are often encountered in patients with SARS-CoV-2 infection. Increased metabolic demand, combined with the abovementioned factors, could evoke cardiac arrhythmias, which are usual extrapulmonary manifestations of the disease [7]. Patients with chronic conditions are particularly vulnerable to a severe disease course and increased risk of death [8, 9]. Many of them have an implanted cardioverter-defibrillator (ICD) or a cardiac resynchronization therapy defibrillator (CRT-D), and COVID-19 caused in these patients appropriate shocks triggered by ventricular arrhythmias and inappropriate shocks triggered by atrial fibrillation (AF) with a rapid ventricular response [10–12]. Furthermore, sinus tachycardia, often encountered in COVID-19, could be responsible for that inappropriate shock triggering [13]. However, a lower percentage of lethal ventricular arrhythmias in the general population during the pandemic era compared to the pre-pandemic period was indicated by a decrease in the percentage of shockable first recorded rhythm in patients with cardiac arrest [7]. The results of analyses on ICD shocks during the pandemic are contrasting [14, 15]. The electrical shock occurrence in ICD/CRT-D recipients could be increased by overall psychological stress [16, 17]. In contrast with these assumptions, lockdowns and decreased physical activity reduce the occurrence of shocks [10–12].

This retrospective study aimed to evaluate Emergency Department (ED) admissions related to high-energy therapy, examining patients' clinical characteristics and outcomes during both the pre-pandemic and COVID-19 pandemic periods. Secondary aims included assessing the incidence of SARS-CoV-2 infections in these patients and comparing the clinical data and outcomes between those with and without SARS-CoV-2 infection. The findings contribute valuable insights into the impact of the COVID-19 pandemic on high-energy therapy patients, highlighting potential implications for patient management during infectious outbreaks.

METHODS

The study was designated as a retrospective analysis of medical records of patients with ICD/CRT-D admitted to 2 high-volume hospitals due to high-voltage therapy. Admission to the ED was considered the same as admission to the hospital. A total of 36 patients (13.1%) were discharged home from the ED.

At the beginning of the COVID-19 pandemic, patients were mainly admitted to Infectious Disease Hospitals [3, 4]. By the beginning of September 2020, most patients requiring hospitalization were admitted to the nearest hospitals [18]. Only those patients requiring tertiary care procedures were referred to designated hospitals.

All admissions of these patients to the EDs during two 24-month periods were evaluated: 138 admissions in the pre-pandemic era (January 1, 2018–December 31, 2019) and 124 visits during the pandemic period (March 4, 2020–March 3, 2022).

Age, sex, therapy appropriateness, number of shocks, symptoms before shock that are presumed to provoke factors comorbidities, the cause of ICD/CRT-D implantation, and SARS-CoV-2 swab test results in the pandemic era were gathered from electronic records. The time of the ICD intervention was assessed as before hospital admission or before and during hospitalization. The presence of dyspnea, fatigue, chest pain, vomiting, fever, or hemorrhage before the electrical shock was defined as the presence of symptoms not related to arrhythmia or ICD/CRT-D high-voltage therapy unless otherwise indicated. Loss of consciousness during electrical shock was considered arrhythmia-related. The presence of electrical shocks during hospitalization was assessed based on the medical recordings. Furthermore, the following procedures: ventricular ablation, supraventricular arrhythmia ablation: (pulmonary vein isolation, tricuspid isthmus ablation, ablation of the atrioventricular junction, ablation of the slow pathway of the atrioventricular node), coronary artery catheterization, coronary angioplasty, amiodarone or lidocaine administration during hospitalization were noted. The medical records of the patients were searched for general anesthesia of the patients aiming to treat electrical shocks.

In the case of the patients who died in the hospital, the first recorded rhythm during the last cardiac arrest was noted.

The therapy for COVID-19 was conducted as recommended by Polish experts [19, 20].

The ED at the University Hospital and the ED at the 4th Military Hospital are 2 of 4 EDs in Wrocław, a principal

city of the Lower Silesia voivodeship with approximately 800 000 inhabitants.

During the third and fourth wave of the pandemic, the 4th Military Hospital was designated as the regional center for the treatment of patients with SARS-CoV-2 infection who needed treatment with pacemaker implantation, ablation, coronary angiography, angioplasty, or cardiac surgery.

The main outcome was all-cause mortality. Survival until hospital discharge was assessed based on the hospital records, and medium-term survival was assessed on the basis of the data obtained from the Ministry of Digitalization on October 24, 2022. The patients lost to follow-up were assessed as alive at the last contact (censored data).

Statistical analysis

Statistical analyses were carried out with standard statistical software (Statistica version 13, TIBCO Software Inc., Palo Alto, CA, US). Continuous variables were presented as mean and standard deviation for normally distributed data and as the median and interquartile range (IQR) for non-normally distributed data. Student's t-test and the Mann-Whitney U test were used for the statistical analysis of the differences, respectively. Categorical variables were presented as numbers and percentages and compared with the chi-squared test with Yates correction if necessary.

Survival after the hospital stay was assessed as survival until hospital discharge and one-month and 6-month survival. For these analyses, all visits were taken into account. For medium-term survival analysis, only the patient's last visit was considered. A Cox regression model was used to perform univariable and multivariable analyses. The covariates of the multivariable regressions were selected based on univariable regression results. Two models were built. The stepwise multivariable regression result was presented. The first model included demographics, past medical history data that were significant in the univariable analysis, the pandemic period, and used invasive procedures during hospitalization. The second model included demographics, number of shocks, and symptoms before shock(s).

Furthermore, the third model was built to assess the survival of patients for whom the last visit was during the pandemic period. The model included all the variables relevant to the first model and the presence of SAR-CoV-2 infection. *P* less than 0.05 was considered significant.

RESULTS

Demographics

The study group consisted of 198 patients (36 women, 162 men) aged 65.6 (standard deviation 12.8 years, range of 20–90 years.)

Hospital visits during pre-pandemic and pandemic period

During the study period, 149 patients had one visit due to electrical shock, 36 had 2 visits, 11 had 3 visits, and 2 had 4 visits. A group of 25 patients were admitted to the EDs during the pre-pandemic and pandemic era, and 173 patients were admitted only during the pandemic or pre-pandemic era. The first visit of 115 patients was in the pre-pandemic era, and 83 patients' first visit was during the pandemic era. The last admission to the hospital during the study period was during the pre-pandemic era in 90 (45.5%) cases, whereas 108 (54.5 %) patients were admitted during the pandemic. A total of 115 patients had at least one admission to the hospital before the pandemic, and 108 patients had at least one admission during the pandemic.

There were 262 admissions during the study period: 138 (52.7%) admissions before the pandemic and 124 (47.3%) during the pandemic. The 14 visits involving patients with a positive test for SARS-CoV-2 infection occurred in 14 different patients: in 12 cases as the only visit, in one case as the first visit but not the last visit, and in one case as neither the first nor the last visit during the study period.

The number of admissions before the pandemic and during the pandemic in the 4th Military Hospital was 89 and 91, respectively, whereas the number of admissions to the University Hospital was 49 and 33, respectively ($P = 0.21$).

Clinical characteristics

A comparison of clinical characteristics of the patient visits before and during the pandemic is presented in Table 1. There were no significant differences in age, sex, shock count, appropriateness of the therapy, or hospital survival.

In Table 2, a comparison of the clinical characteristics of 90 patients' whose last visit was during the pre-pandemic and 108 patients whose last visit was during the pandemic era was presented.

Table 3 presents a comparison of clinical characteristics of visits during the pandemic of patients with and without SARS-CoV-2 infection. The patients with SARS-CoV-2 infection had hospital shocks more often and had higher hospital mortality. Furthermore, the patients with SARS-CoV-2 infection more often had complaints before electrical discharge than did the patients without that infection. Dyspnea was reported by patients with SARS-CoV-2 infection nearly 3 times more frequently than by patients without SARS-CoV-2 infection. Among 14 patients with SARS-CoV-2 infection, the admission was *via* Emergency Medical Services (EMS) in 3 cases, transfer from an outpatient clinic in 3 cases, transfer from another hospital department in 5 cases, and of their own accord in 3 cases.

The comparison of patients with and without COVID-19 during the pandemic era is presented in Table 4. The patients admitted with COVID-19 disease had more often symptoms not related to ICD/CRT-D discharge and higher levels of C-reactive protein.

Before the pandemic, 115 patients were admitted at least once, and 2 of them died. During the pandemic,

Table 1. Comparison of the details of patients' visits before and during the pandemic

	Pre-pandemic era n = 138	Pandemic era n = 124	*P*-value
Age, years, median (IQR)	68 (61–74)	67 (61–73)	0.30
Male, n (%)	114 (82.6)	102 (82.3)	0.94
Secondary prevention, n (%)	49 (33.5)	46 (37.1)	0.62
CRT-D, n (%)	32 (23)	29 (23)	
ICD, n (%)	105 (76)	90 (1)	
S-ICD, n (%)	1 (1)	5 (4)	0.18
Number of shocks before admission, median (IQR)	2.5 (1–6)	2 (1–6)	0.76
Appropriate, n (%)	98 (71.0)	91 (73.4)	0.67
Non-appropriate, n (%)	34 (24.6)	30 (24.2)	0.93
Appropriate and non-appropriate, n (%)	6 (4.4)	3 (2.4)	0.39
IHD, n (%)	97 (70)	80 (65)	0.13
HCM, n (%)	2 (1)	9 (7)	
DCM, n (%)	36 (26)	32 (26)	
Others, n (%)	3 (2)	3 (2)	
ICD/CRT-D discharges during hospitalization, n (%)	16 (12)	20 (16)	0.29
Arrival by EMS, n (%)	88 (64)	61 (49)	0.12
Chest pain before the shock, n (%)			
Ventricular ablation, n (%)	25 (18.1)	14 (11.3)	0.12
Supraventricular arrhythmia ablation, n (%)	3 (2.2)	3 (2.4)	0.92
Coronary angiography, n (%)	57 (41.3)	41 (33.1)	0.17
Coronary angioplasty, n (%)	16 (11.6)	12 (9.7)	0.62
Amiodarone, n (%)	42 (30.4)	39 (31.5)	0.86
Lidocaine, n (%)	3 (2.2)	8 (6.5)	0.16
External cardioversion, n (%)	2 (1.5)	3 (1.4)	0.90
In hospital mortality, n (%)	2 (1.4)	7 (5.5)	0.13
6-month mortality, n (%)	13 (9)	17 (14)	0.28

Abbreviations: CRT-D, cardiac resynchronization therapy defibrillator; DCM, dilated cardiomyopathy; EMS, Emergency Medical Services; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; IHD, ischemic cardiomyopathy; IQR, interquartile range; S-ICD, subcutaneous ICD

Table 2. Comparison of 90 patients whose last visit took place in the pre-pandemic period and 108 whose last visit took place during the pandemic (only the parameters related to the last visit of each patient were analyzed)

	Pre-pandemic era n = 90	Pandemic era n = 108	*P*-value
Age, years, median (IQR)	68 (61–73)	67 (61–73)	0.57
Male, n (%)	74 (82)	88 (81)	0.89
Secondary prevention, n (%)	35 (39)	40 (37)	0.52
CRT-D, n (%)	69 (77)	76 (70)	0.40
ICD, n (%)	20 (22)	28 (26)	
S-ICD, n (%)	1 (1)	4 (4)	
Number of shocks before admission, median (IQR)	2.5 (1–6)	2.5 (1–7)	0.45
Appropriate, n (%)	62 (69)	78 (72)	0.37
Non-appropriate, n (%)	23 (26)	28 (26)	
Appropriate and non-appropriate, n (%)	5 (6)	2 (2)	
IHD, n (%)	59 (66)	70 (65)	0.69
HCM, n (%)	2 (2)	6 (6)	
DCM, n (%)	26 (29)	29 (27)	
Others, n (%)	3 (3)	3 (3)	
ICD/CRT-D discharges during hospitalization, n (%)	8 (9)	16 (15)	0.20
Arrival by EMS, n (%)	57 (63)	55 (51)	0.23
Ventricular ablation, n (%)	14 (16)	13 (12)	
Supraventricular arrhythmia ablation, n (%)	2 (2)	1 (1)	0.87
Coronary angiography, n (%)	35 (39)	34 (31)	0.28
Coronary angioplasty, n (%)	10 (11)	9 (8)	0.51
Amiodarone, n (%)	26 (29)	34 (31)	0.69
Lidocaine, n (%)	1 (1)	7 (6)	0.12
External cardioversion, n (%)	0 (0)	2 (2)	0.60
In hospital mortality, n (%)	2 (2)	7 (7)	0.27
6-month mortality, n (%)	13 (15)	16 (15)	0.89

Abbreviations: see Table 1

Table 3. Comparison of the details of patients' visits with and without coronavirus disease (COVID-19)

	Non-COVID-19 n = 110	COVID-19 n = 14	*P*-value
Age, years, median (IQR)	67 (61–73)	67 (58–67)	0.82
Sex, male, n (%)	89 (80.9)	13 (92.9)	0.46
Number of shocks before admission, median (IQR)	2 (1–7)	2 (1–4)	0.53
Shocks			
• appropriate, n (%)	81 (73.6)	10 (71.4)	0.86
• non-appropriate, n (%)	26 (23.6)	4 (28.6)	
• both, n (%)	3 (2.7)	0 (0)	
ICD/CRT-D discharges during hospitalization, n (%)	12 (10.9)	8 (57.1)	<0.001
Arrival by EMS, n (%)	58 (52.7)	3 (21.4)	0.06
In-hospital mortality, n (%)	3 (2.7)	4 (28.6)	<0.001
Ventricular ablation, n (%)	13 (11.8)	1 (7.1)	0.94
Supraventricular ablation, n (%)	2 (1.8)	1 (7.1)	0.77
Coronary angiography, n (%)	39 (35.5)	2 (14.3)	0.20
Coronary angioplasty, n (%)	12 (10.9)	0 (0)	0.42
Amiodarone, n (%)	32 (29.1)	7 (50.0)	0.11
Lidocaine, n (%)	6 (5.5)	2 (14.3)	0.49
External cardioversion, n (%)	2 (1.8)	1 (7.1)	0.77

Abbreviations: see Table 1

Table 4. Comparison of patients with and without coronavirus disease (COVID-19)-during the pandemic era

	Non-COVID-19 n = 110	COVID-19 n = 14	*P*-value
Symptoms not related to ICD/CRT-D discharge, n (%)	35 (31.8)	10 (71.4)	0.009
C-reactive protein, ng/ml, median (IQR)	2.7 (0.6-8.2) n = 103	13.4 (1.9–36) n = 14	0.007
Potassium (mEq/l), median (IQR)	4.1 (3.8–4.3) n = 107	4.1 (3.8–4.4) n = 14	0.87
NT-proBNP, pg/ml	1988 (622-4958) n = 97	4253 (1463-6834) n = 14	0.11
IHD, n (%)	72 (65.5)	8 (57.1)	0.75
HCM, n (%)	6 (5.5)	3 (21.4)	0.10
DCM non-IHD, n (%)	29 (26.4)	3 (21.4)	0.94
Long QT, n (%)	2 (1.8)	0	0.54
AF, n (%)	72 (65.5)	11 (78.6)	0.50
DM, n (%)	37 (33.6)	3 (21.4)	0.54
CKD, n (%)	21 (19.1)	2 (14.3)	0.94
COPD, n (%)	6 (5.5)	1 (7.1)	0.72
Stroke, n (%)	15 (13.6)	0 (0)	0.30
Cancer, n (%)	10 (9.1)	0 (0)	0.51

Abbreviations: AF, atrial fibrillation (chronic, paroxysmal, persistent); CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus, NT-proBNP, N-terminal pro-B-type natriuretic peptide; other — see Table 1

108 patients were admitted at least once, and 7 of them died ($P = 0.10$).

Implanted devices

The distribution of the implanted devices in the pre-pandemic and pandemic periods is presented in Tables 1 and 2. There were 6 admissions in 5 patients with implanted subcutaneous ICD (S-ICD) — one admission during the pre-pandemic period and 5 admissions during the pandemic period. Three admissions were related to inadequate electrical shocks. All the patients with implanted S-ICD admitted during the pandemic had negative SARS-CoV-2 tests.

Follow-up

All but 2 patients who were lost to follow-up were followed until October 24, 2022. Survival for these patients was assessed as one day, and their survival data were considered censored. The median time of follow-up from the first visit to the hospital due to electrical shock during the study period was 712 (IQR, 360–1125) days. The median time of follow-up from the last visit to the hospital due to electrical shock was 558 (IQR, 309–982) days.

In-hospital mortality

The total in-hospital mortality was 9; including 2 patients died during the pre-pandemic period and 7 during the pandemic period. Among patients who died in the hospital during the pandemic period, 4 had COVID-19 disease. None of the patients who died had incessant ventricular arrhythmia. The deaths were due to multiorgan failure in 7 cases, and the first recorded rhythm during their last cardiac arrest was asystole in 3 cases, pulseless electrical

activity in 3 causes, and ventricular fibrillation in one patient in whom after defibrillation asystole occurred, and there was no return of any electrical activity. One patient who was brought by EMS during ongoing resuscitation had asystole on admission. The analysis of the memory of his ICD revealed that the electrical shocks were triggered probably by chest compressions and the cardiac arrest was not caused by ventricular arrhythmia.

Medium-term mortality

During the 30 days after the last visit, 8 patients died: 1 before the pandemic era and 7 during the pandemic. These numbers constituted 0.7% of the patients who had at least one visit before the pandemic and 6.5% of the patients with at least one visit during the pandemic ($P = 0.059$).

During the 6-month follow-up, 29 (15%) patients died: 13 (15%) with the last visit before the pandemic and 16 (15%) with the last visit during the pandemic ($P = 0.92$).

During the follow-up, 42 (47%) patients whose last visit was before the pandemic died as well as 24 (22%) patients whose last visit was during the pandemic. However, the follow-up duration of the non-survivors during the pandemic was significantly lower than before the pandemic (126.5 [IQR, 21–202.5] vs. 446 [IQR, 144–721] days; $P < 0.001$).

In Table 5, the univariable Cox regression analysis is presented.

The multivariable proportional hazards Cox regression analysis of the first model presented in Table 6 revealed that medium-term survival depends on the patient's age, heart failure (HF) decompensation in the medical history, and ejection fraction, but not on the period (pandemic vs. pre-pandemic) of the study.

The analysis of the second model which included demographics, number of shocks before admission, period of the study (pandemic vs. pre-pandemic), and symptoms before the shocks demonstrated that survival was decreased when electrical shocks were preceded by dysponea (HR, 3.428; 95% CI, 2.090–5.624; $P < 0.001$) or diarrhea (HR, 9.719; 95% CI, 4.075–23.176; $P < 0.001$)

The analysis of medium-term survival only of the patients whose last visit was during the pandemic period indicated that survival in this subgroup was related to the patient's age, HF decompensation in the medical history, and the presence of Sar-CoV-2 infection (Table 7).

DISCUSSION

Cardiac arrhythmias were found in 10%–20% of hospitalized COVID-19 patients [21]. Cardiac involvement and/or the effects of fever, inflammation, and hypoxia caused by any critical illness may account for this association [22]. Also, patients' underlying susceptibility to arrhythmia may modulate their occurrence. The most common arrhythmia found during COVID-19 was AF, whereas ventricular tachyarrhythmias were reported less frequently [7]. AF with rapid ventricular response and ventricular tachyarrhythmia in patients with ICD/CRT-D may lead to shock delivery, prompting patients to attend the ED.

The study's first finding was that the number of admissions to the ED due to ICD/CRT-D electrical shocks has not increased during the pandemic. The finding is in contrast with the results of the retrospective analysis of Adabag et al. [14], who reported an increase in the number of device high-energy interventions. Contrary to Adabag et al., O'Shea et al. [15] reported fewer electrical shocks during the pandemic. Furthermore, other authors found no significant difference in the occurrence of ICD therapies between pre-pandemic and pandemic periods [23]. Notably, in our study, we investigated the number of ED admissions, not the total number of patients experiencing electrical shocks. Therefore, the reason for the slightly decreased number of ED admissions may not reflect changes in the total number of electrical shocks in that population. Patients' reluctance to attend the ED may have decreased the number of admissions [24].

Furthermore, the number of electrical shocks unrelated to ventricular arrhythmia increased during the last phase of life [25]. During the pandemic, transportation to a tertiary care center for patients with multiorgan failure was considered unnecessary. Patients with an implanted ICD/CRT-D often have pre-existing HF [26]. The mortality rate during the pandemic of patients with pre-existing heart disease increased [27]. Therefore, it can be presumed that the size of the susceptible population may have decreased with each pandemic wave. Finally, the timing should be taken into account. In a report by Tajstra et al. [28], in Poland, during the early pandemic phase, the number of high-energy interventions did not change compared to the reference period, which may have been related to the low number of infected patients. Contrary to this report, Ducceschi et al. [29] reported that in Italy, the second-most affected country in the world after China, at the beginning of the pandemic, the percentage of patients with ventricular tachycardia/ventricular fibrillation doubled.

The second finding was that the percentage of patients with SARS-CoV-2 infection among patients with ICD/CRT-D shocks was about 10%. The percentage of patients with SARS-CoV-2 infection was higher than in the general population of ED patients in the same region, which during the third wave was reported to be 6.5% [30]. This finding aligns with the assumption that the occurrence of shocks increases during the infection.

The third finding was that patients with SARS-CoV-2 infection admitted to the ED due to electrical shock had higher in-hospital and medium-term mortality than those without the infection. This finding is concordant with reports of other authors who found that patients with acute cardiovascular disorders and concomitant SARS-CoV-2 infection have a worse prognosis than those without SARS-CoV-2 infection [31–33].

Comparing the clinical presentation of patients with and without COVID-19, we found that patients with SARS-

Table 5. Univariable Cox regression analysis for median-term survival

	Variable	HR (95% CI)	*P*-value
Demographics	Age (1 year)	1.038 (1.017–1.060)	<0.001
	Male sex	1.399 (0.740–2.643)	0.30
Studied period	Pandemic period	0.793 (0.485–1.297)	0.36
Location	University Hospital	1.133 (0.713–1.802)	0.60
Symptoms before and during CV	Lack of symptoms preceding CV	0.397 (0.256–0.617)	<0.001
	TLOC at CV	0.999 (0.515–1.939)	0.10
	Pain before CV	0.567 (0.179–1.797)	0.34
	Dyspnea	3.069 (1.887–4.991)	<0.001
	Fatigue	2.158 (1.230–3.785)	0.007
	Infection	1.872 (0.900–3.891	0.09
	Bleeding	7.348 (2.658–20.319	<0.001
	Diarrhea	7.334 (3.126–17.208)	<0.001
Probable cause	Acute heart ischemia	0.570 (0.140–2.319)	0.43
	Heart failure decompensation	4.376 (2.445–7.831)	<0.001
	Electrolytes imbalance	1.656 (0.721–3.807	0.24
	Secondary prevention	1.067 (0.808–1.408	0.65
HVT details	HVT total number	0.970 (0.915–1.029)	0.31
	Inappropriate HVT	0.823 (0.491–1.377)	0.46
Disease underlying ICD/CRT-D implantation	Ischemic cardiomyopathy	1.123 (0.696–1.813)	0.634
	Non-ischemic	1.001 (0.608–1.648)	0.10
	HCM	1.042 (0.328–3.310)	0.94
Concomitant diseases	CKD	1.364 (0.788–2.360)	0.27
	DM	1.978 (0.618–1.549)	0.93
	COPD	2.112 (1.116–3.997)	0.02
	Cancer	2.975 (1.477–5.990)	0.002
	Stroke	0.896 (0.448–1.793)	0.76
Echocardiography	EF	0.943 (0.920–0.967)	<0.001
Medical history	Heart failure decompensation	2.886 (1.860–4.478)	<0.001
	AF/AFL	1.875 (1.146–3.067)	0.01
	RBBB	0.439 (0.578–3.577)	0.43
	LBBB	2.232 (1.269–3.924)	0.005
ECG on admission	AF	1.393 (0.896–2.164)	0.14
	VT	2.431 (0.979–6.033)	0.06
In-hospital procedures	Ventricular ablation	0.930 (0.503–1.718)	0.82
	Supraventricular ablation	0.435 (0.060–3.125)	0.41
	Coronary angiography	0.784 (0.495–1.241)	0.30
	Coronary angioplasty	0.487 (0.197–1.203)	0.12
	Amiodarone	1.710 (1.092–2.677)	0.02
	Lidocaine	1.086 (0.342–3.445)	0.90
	External cardioversion	All patients who had external cardioversion survived, and HR could not be calculated	

Abbreviations: AFL, atrial flutter; CI, confidence interval; CV, electrical shock; HR, hazard ratio; HVT, high-voltage therapy; LBBB, left bundle branch block; RBBB, left bundle branch block; TLOC, transient loss of consciousness; VT, ventricular tachycardia; other — see Tables 1 and 4

Table 6. Stepwise multivariable Cox regression analysis for survival in the model 1 (only the parameters related to the last visit of each patient were analyzed)

	HR (95% CI)	*P*-value
Age (per year)	1.025 (1.001–1.049)	0.045
EF (per 1%)	0.953 (0.928–0.979)	<0.001
Cardiac decompensation in MHx	1.960 (1.185–3.244)	0.009

Abbreviations: EF, ejection fraction; MHx, medical history; other — see Table 5

Table 7. Stepwise multivariable Cox regression analysis for survival in the subgroup of patients who had the last visit during the pandemic in model 3 (only the parameters related to their last visit were analyzed)

	HR (95% CI)	*P*-value
SARS-CoV-2 infection	3.604 (1.322–9.822)	0.012
Age (per year)	1.052 (1.006–1.100)	0.025
Cardiac decompensation in MHx	2.600 (1.137–5.947)	0.025

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; other — see Tables 5 and 6

-CoV-2 infection rarely had an ICD/CRT-D electrical shock that was not preceded by symptoms of infection. Moreover, the patients with a SARS-CoV-2-positive test had higher C-reactive protein levels. Furthermore, the hospital observations indicated a higher number of ICD/CRT-D discharges in patients with SARS-CoV-2 infection than in those with a negative test. These findings indicate that the predisposing factor in patients with COVID-19 is related to the infection and persists after admission, resulting in further ICD/CRT-D shocks. These findings concur with the assumption of Adabag et al. [14] that the missing links between the substrate of HF and ICD/CRT-D discharges are in the transient factors, like viral infections, which can exacerbate the patient's condition and trigger an arrhythmia.

Furthermore, the assessment of the timing of the electrical shocks in patients with SARS-CoV-2 indicates that the electrical shocks are triggered after the onset of infection symptoms. This finding aligns with the case report of Mitacchione et al. [34] presenting the timeline of SARS-CoV-2 infection, ventricular arrhythmia, and electrical shocks. These authors found that ventricular arrhythmia occurred at the onset of the infection, 20 days before hospital admission, but the electrical storm occurred on the 8th day of hospitalization [34]. Hypoxia-induced intracellular calcium overload leading to early afterdepolarization was considered to be the mechanism of ventricular arrhythmia [34]. Also, Kasinadhuni et al. [35] reported an electrical storm event in a patient on the 5th day of SARS-CoV-2 infection. The patient's electrolyte level was within normal limits. Electrolyte disturbances seem to be less critical in ventricular arrhythmia occurrence in patients with SARS-CoV-2 infection. In the present study, dyselectrolytemia was found in a similar percentage of patients with and without the infection. SARS-CoV-2 infection may trigger ventricular arrhythmias via cytokines like interleukin-6, interleukin-1, or tumor necrosis factor-α, which can modulate K^+ and/or Ca^{2+} channels and prolong the potential duration of their action [36].

The frequency of cardiologic procedures like catheter ablation, coronary catheterization, and angioplasty did not differ between the pre-pandemic and pandemic periods. During the pandemic, temporary deferment of non-urgent elective electrophysiological procedures was recommended [37]. However, invasive procedures in patients with electrical shocks during the COVID-19 pandemic were considered life-saving and, therefore, were performed.

The mortality rate increased during the pandemic in the whole world [37]. In 2020 in Poland, the excess of deaths was about 15%, whereas, for example, in Austria, it was 7.6% [38]. The difference could have resulted from a higher disease burden in Polish society than the average for European Union countries. Other factors related to excess mortality could have been difficult access to healthcare services during the pandemic and an ineffective pro-vaccination campaign. However, our data indicate that the increased in-hospital death rate in patients admitted due to electrical shocks was related only to SARS-CoV-2 infection.

An additional finding of the study is that the number of patients with S-ICD was higher in the pandemic period in comparison to the period before the pandemic, which is concordant with data presented by Kempa et al. [39] that showed increasing number of S-ICD implantations in Poland.

Limitations

The main limitation of the study is its retrospective character. Furthermore, based on the recorded data, multiple shocks could not be distinguished because one episode from multiple shocks of recurrent ventricular tachyarrhythmias met the electrical storm criteria. During the pandemic, in EDs, it was not possible to record all data.

The impact of the lockdown on easy access to drug prescriptions, cardiovascular drug compliance, and patients' decision to call an ambulance or transfer to the ED cannot be validated. Another limitation is that the prevalence of electrical shocks may be underestimated due to lack of remote control and monitoring of implantable electronic devices.

Moreover, the studied groups were relatively small. Because of the small size of the group of COVID-19 patients, the impact of COVID-19 therapy was not analyzed in this study.

CONCLUSIONS

The admissions to the ED during the SARS-CoV-2 pandemic for ICD/CRT-D shocks remained on the same level as before. During the 2 years of the COVID-19 pandemic, among patients with ICD/CRT-D discharges treated in the hospital, about 10% had a positive SARS-CoV-2 smear test. Patients with SARS-CoV-2 infection had more frequent symptoms unrelated to arrhythmia or ICD/CRT-D discharge before admission, electrical discharges from ICD/CRT-D during hospitalization, and higher mortality than non-COVID patients. Patients with SARS-CoV-2 infection also had higher C-reactive protein levels but did not differ in other studied laboratory parameters from those without the infection.

Article information

Conflict of interest: None declared.

Funding: None.

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Impact of chronic total occlusion on prognosis in cardiogenic shock due to unprotected left main coronary artery culprit lesion. Insights from the Polish Registry of Acute Coronary Syndromes

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DOI: 10.33963/v.phj.98889

Received:
August 30, 2023

Accepted:
January 11, 2024

Early publication date:
February 23, 2024

ABSTRACT

Background: Notwithstanding readily available revascularization, significant advancements in mechanical circulatory support, and pharmacological progress, cardiogenic shock (CS) secondary to unprotected left main culprit lesion-related acute myocardial infarction (ULMCL-related AMI) is associated with very high mortality. In this population, chronic total occlusion (CTO) is relatively frequent.

Aims: This study sought to assess the association between the presence of CTO and 12-month mortality in patients with CS due to ULMCL-related AMI.

Results: The study included consecutive patients admitted for AMI-related CS with ULMCL who underwent percutaneous coronary intervention (PCI) and were enrolled in the prospective Polish Registry of Acute Coronary Syndromes (PL-ACS) between January 2017 and December 2021. The patients were stratified into two groups based on the presence of at least one CTO. The primary endpoint was all-cause death at 12 months. Of the 250 included patients, 60 (24%) patients had one or more CTOs of a major coronary artery (+CTO), and in 190 (76%) patients, the presence of CTO was not observed (–CTO). The 12-month mortality rates for the +CTO and –CTO patients were 85% and 69.8%, respectively (P log-rank = 0.03). After multivariable adjustment for differences in the baseline characteristics, the presence of CTO remained significantly associated with higher 12-month mortality (hazard ratio, 1.423; 95% CI, 1.027–1.973; P = 0.034).

Conclusions: Our analysis showed that in patients with CS due to ULMCL-related AMI treated with PCI, the presence of CTO is associated with worse 12-month prognosis.

Key words: acute myocardial infarction, cardiogenic shock, chronic total occlusion, prognosis

INTRODUCTION

Cardiogenic shock (CS) complicating acute myocardial infarction (AMI) is a critical clinical situation. Unfortunately, despite tremendous efforts and progress in its treatment, including pharmacotherapy advancements, rapid access to high-quality revascularization, and availability of mechanical circulatory support (MCS), CS remains the leading cause of death in AMI patients, with in-hospital mortality as high as 40%–50% [1–5]. Mortality is further increased with rates of up to 70% in cases of refractory CS [6].

Unprotected left main culprit lesion-related acute myocardial infarction (ULMCL-related AMI) is associated with a faster presentation

WHAT'S NEW?

The presence of chronic total occlusion (CTO) in patients with cardiogenic shock (CS) secondary to unprotected left main (LM) coronary artery culprit lesion-related acute myocardial infarction (AMI) treated with percutaneous coronary intervention (PCI) is independently related to higher 12-month mortality. Patients with AMI-related CS, just after diagnostic catheterization with a detected culprit lesion in the LM, should be stratified by the presence of CTO. Additional research is needed to understand the safety and efficacy of CS treatment in terms of the extent of revascularization and/or escalation therapy using mechanical circulatory support (MCS) based on the presence of CTO stratification.

of CS, more severe systemic organ failure, worse outcomes even in cases of successful revascularization [7], and very high mortality (up to 75%) [8].

It has been demonstrated that the presence of chronic total occlusion (CTO) of an artery other than the infarct-related one in patients hospitalized for AMI and AMI-related CS is strongly associated with higher rates of in-hospital and long-term mortality than in patients without CTO [9–13]. To the best of our knowledge, there is lack of data evaluating the presence of CTOs in patients with CS due to ULMCL-related AMI.

Thus we aimed to analyze the impact of CTO on long-term prognosis in this patient population using data from a large national multi-center registry.

METHODS

Design of the registry

We used data from the Polish Registry of Acute Coronary Syndromes (PL-ACS). The methodology and analysis have been previously described [14]. In brief, the PL-ACS registry is one of the largest in Europe. It is an ongoing, nationwide, multi-center, prospective, observational study of consecutively hospitalized Polish patients suffering the entire spectrum of acute coronary syndromes. The registry is a joint initiative of the Silesian Center for Heart Diseases and the Polish Ministry of Health. The National Health Fund, a nationwide public health insurance institution in Poland, provides logistical support.

Data on long-term all-cause mortality, including the exact date of death, were obtained from the National Health Fund by January 2022. Follow-up time was censored at one year or the end of follow-up time (whichever came first).

Study population and definitions

Between January 1, 2017, and December 31, 2021, a total of 4954 patients with AMI-related CS were enrolled in the PL-ACS. In this cohort, 321 consecutive patients had culprit lesions located in the LM and underwent LM percutaneous coronary intervention (PCI). Patients after coronary artery bypass grafting and/or missing medical history were excluded. Finally, 250 patients with ULMCL-related AMI CS were analyzed and stratified into two groups based on the presence of at least one CTO lesion (+CTO group, n = 60, 24% vs. –CTO group, n = 190, 76%) (Figure 1).

The ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) were defined according to the Fourth Universal Definition of Myocardial Infarction [15]. CS was defined as 1) systolic blood pressure <90 mm Hg (in the absence of hypovolemia and after proper fluid resuscitation) for at least 30 min or the need for pharmacological support to maintain systolic blood pressure above 90 mm Hg; and 2) signs and symptoms of end-organ hypoperfusion. The definition of ULMCL was at the discretion of the interventional cardiologist performing PCI, based on angiographic criteria such as the presence of thrombus, ulceration, degree of stenosis, distal flow, and anatomical characteristics of the rest of the coronary tree. CTO was defined as any 100% stenosis of the coronary artery on the index angiography, which the operators did not consider as the culprit lesion responsible for the index AMI based on clinical, angiographic, electrocardiographic, echocardiographic, or previous angiography findings. The primary outcome of interest was all-cause 12-month mortality. Secondary outcomes included the incidence of mechanical complications, stroke, major bleeding, resuscitated cardiac arrest, and death during the index hospitalization. The study was approved by the institutional review committee.

Statistical analysis

The continuous variables were presented as medians and interquartile ranges. The categorical variables were presented as percentages. Differences between categorical variables in the baseline characteristics, angiographic characteristics, and in-hospital outcomes were compared using Pearson's χ^2 test or Fisher's exact test, where appropriate. Quantitative variables were compared using the Wilcoxon rank sum test. The cumulative 1-year incidence of all-cause death in patients stratified by the presence of CTO was depicted with Kaplan-Meier curves. The log-rank test was used to compare mortality rates between groups. Additionally, landmark analysis was performed with a landmark set at 30 days (one month). Moreover, we have performed some sensitivity analyses, i.e., survival analysis in the subset of patients who underwent PCI for non-culprit lesion during the index hospitalization, the comparison of 12-month mortality between patients with CTO and those with subtotal stenoses (70%–99%) in the non-culprit vessels, in patients stratified by the location of CTO (right vs. left coronary artery) and in patients

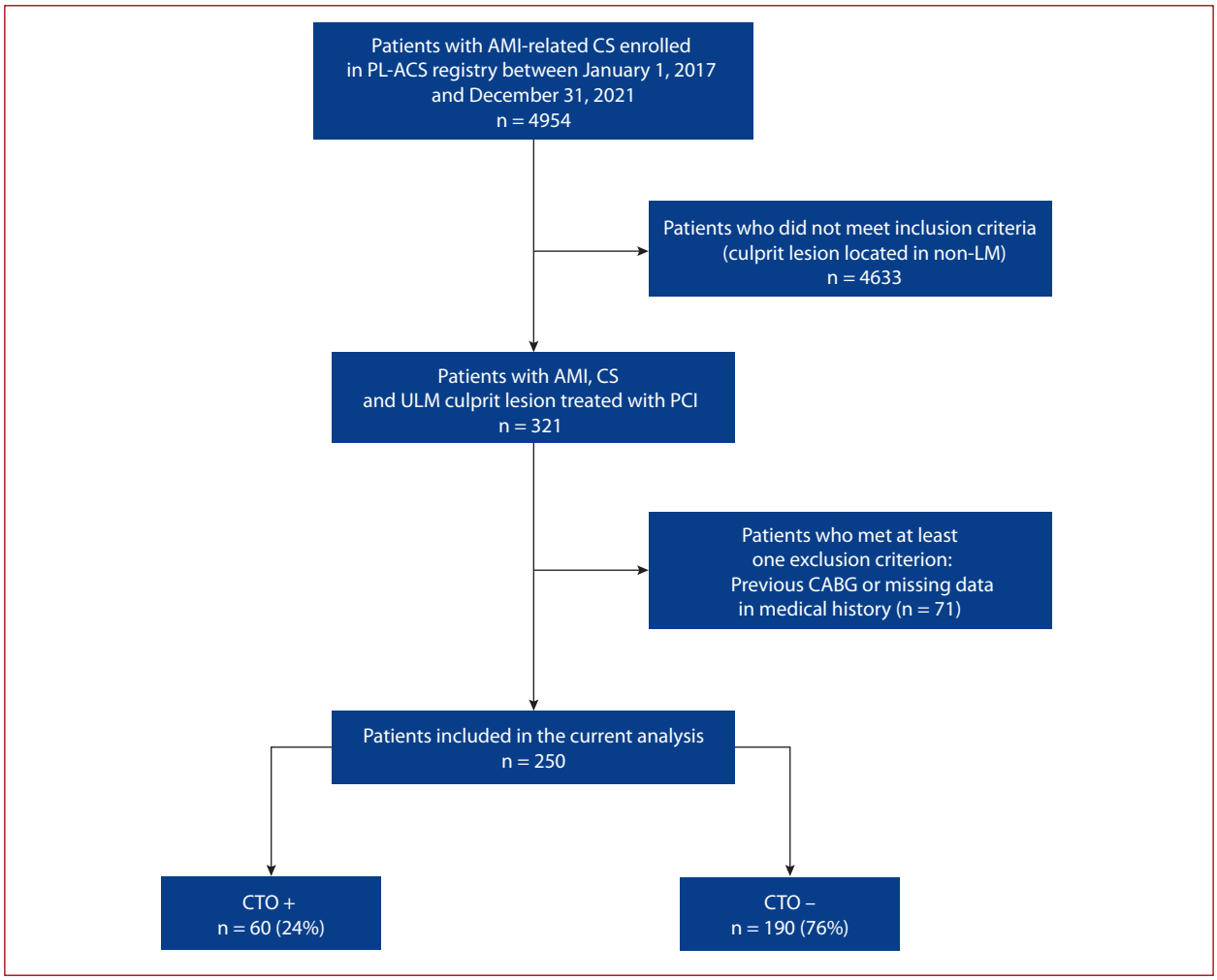

Figure 1. Study flowchart

Abbreviations: AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CS, cardiogenic shock; CTO, chronic total occlusion; LM, left main; PCI, percutaneous coronary intervention; PL-ACS, Polish Registry of Acute Coronary Syndromes; ULM, unprotected left main

stratified by the myocardial infarction presentation (STEMI vs. NSTEMI). The interaction between the presence of CTO and myocardial infarction classification was assessed using the likelihood ratio test. The unadjusted and adjusted Cox proportional-hazards models were created to analyze the relationship between CTO and 12-month mortality. The proportional hazards assumption was tested using the Schoenfeld residuals. The multivariable analysis was performed using the data set with missing values imputed by the random forest algorithm (using the missForest package). Clinically relevant baseline clinical characteristics variables with P <0.05 in the univariable models (chronic kidney disease, peripheral vascular disease, age, obesity, previous stroke) were included in the multivariable model. The level of statistical significance was set at P <0.05 (two-tailed). All statistical analyses were performed using R version 4.2.2 (R Core Team [2022]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria) and RStudio (RStudio Team [2020]. RStudio: Integrated Development for R. RStudio, PBC, Boston, MA, US).

RESULTS

In the whole population of patients with CS complicated by AMI, the rate of ULMCL was 6.5%. The baseline clinical characteristics of the study groups are presented in Table 1. The patients with CTO had a higher prevalence of diabetes and STEMI vs. NSTEMI than the patients without CTO. The angiographic and periprocedural characteristics are listed in Table 2. CTO patients had a higher frequency of multivessel coronary disease, higher prevalence of totally occluded ULMCL, lower rates of Thrombolysis In Myocardial Infarction (TIMI) 3 after PCI, and more often underwent PCI of non-CTO lesions during index hospitalization. The PCI of CTO during index hospitalization of 15 (25%) patients was reported, with a success rate defined as TIMI flow 3 in 5 (33%) patients. The in-hospital secondary outcomes are presented in Table 3. A total of 68% of the +CTO patients and 47% of the –CTO patients (P = 0.004) died during the index hospitalization. The follow-up for death was available for 249 of 250 patients, and the median follow-up time was 6 (1–306) days. At 12 months, a significant difference in the all-cause mortality rate was recorded: n = 51 (85%)

Table 1. Baseline clinical characteristics

Variable	Group			
	Overall n = 250[a]	CTO+ n = 60[a]	CTO– n = 190[a]	*P*-value[b]
Sex, male	184 (74%)	49 (82%)	135 (71%)	0.10
Age, years	70 (63–80)	69 (65–83)	71 (62–80)	0.45
Smoking				0.67
Current smoker	58 (32%)	12 (29%)	46 (32%)	
Former smoker	70 (38%)	18 (44%)	52 (36%)	
Never smoked	56 (30%)	11 (27%)	45 (31%)	
Hypertension	137 (61%)	36 (68%)	101 (59%)	0.26
Hyperlipidemia	65 (33%)	14 (31%)	51 (33%)	0.80
Diabetes	73 (33%)	24 (46%)	49 (28%)	0.02
Obesity	46 (20%)	9 (18%)	37 (20%)	0.70
Previous myocardial infarction	57 (24%)	15 (27%)	42 (23%)	0.52
Previous PCI	49 (20%)	11 (18%)	38 (20%)	0.72
Peripheral vascular disease	36 (15%)	8 (14%)	28 (15%)	0.80
Atrial fibrillation	31 (13%)	4 (6.8%)	27 (15%)	0.11
Chronic heart failure	35 (15%)	10 (17%)	25 (14%)	0.52
Previous stroke	21 (8.5%)	7 (12%)	14 (7.4%)	0.28
Chronic kidney disease	30 (12%)	10 (17%)	20 (11%)	0.22
Ejection fraction (%)	30 (20–40)	28 (20–35)	30 (20–40)	0.35
CA before admission	78 (31%)	18 (31%)	60 (32%)	0.87
Pain-to-admission time, hours	672 (240–2160)	720 (300–1740)	636 (240–2160)	0.52
ACS type				**<0.001**
STEMI	114 (46%)	16 (27%)	98 (52%)	
NSTEMI	136 (54%)	44 (73%)	92 (48%)	
SBP, mm Hg	90 (80–110)	90 (80–118)	90 (80–110)	0.75
DBP, mm Hg	60 (50–70)	60 (50–70)	60 (50–70)	0.58
HR, 1/min	90 (75–100)	94 (80–100)	90 (74–104)	0.39

[a]Median (interquartile ranges) or frequency (%); [b]Pearson's χ^2 test, Wilcoxon rank sum test, Fisher's exact test

Abbreviations: ACS, acute coronary syndrome; CA, cardiac arrest; DBP, diastolic blood pressure; HR, heart rate; NSTEMI, non-ST-segment elevation myocardial infarction; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction; other — see Figure 1

Table 2. Angiographic and periprocedural characteristics

Variable	Group			
	Overall n = 250[a]	CTO+ n = 60[a]	CTO– n = 190[a]	*P*-value[b]
Door-to-catheter time, minutes	28 (10–90)	30 (12–73)	26 (10–90)	0.52
Multivessel disease				<0.001
1VD or isolated LM	135 (54%)	3 (5.0%)	132 (69%)	
2VD	57 (23%)	22 (37%)	35 (18%)	
3VD	58 (23%)	35 (58%)	23 (12%)	
LAD CTO	23 (9.2%)	23 (38%)	0 (0%)	**<0.001**
Cx CTO	21 (8.4%)	21 (35%)	0 (0%)	**<0.001**
RCA CTO	35 (14%)	35 (58%)	0 (0%)	**<0.001**
TIMI flow in LM before PCI				**<0.001**
0	78 (31%)	38 (63%)	40 (21%)	
1	26 (10%)	3 (5.0%)	23 (12%)	
2	32 (13%)	4 (6.7%)	28 (15%)	
3	114 (46%)	15 (25%)	99 (52%)	
Vascular access				**0.003**
Radial	99 (40%)	16 (27%)	83 (44%)	
Femoral	145 (58%)	39 (66%)	106 (56%)	
Other	5 (2.0%)	4 (6.8%)	1 (0.5%)	
LM PCI	250 (100%)	60 (100%)	190 (100%)	NA
Non-culprit vessel PCI	143 (57%)	42 (70%)	101 (53%)	**0.022**
TIMI flow in LM after PCI				**0.001**
0–2	53 (24%)	15 (47%)	38 (20%)	
3	168 (76%)	17 (53%)	151 (80%)	
Glycoprotein IIb/IIIa inhibitor	98 (39%)	21 (36%)	77 (41%)	0.49
IABP	28 (11%)	9 (15%)	19 (10%)	0.28
Advanced MCS	1 (0.4%)	0 (0%)	1 (0.5%)	1.0
CTO PCI during index admission	15 (6.0%)	15 (25%)	0 (0%)	**<0.001**
CABG during index admission	4 (1.6%)	0 (0%)	4 (2.1%)	0.57

[a]Median (interquartile ranges) or frequency (%); [b]Wilcoxon rank sum test, Pearson's χ^2 test, Fisher's exact test

Abbreviations: Cx, circumflex artery; IABP, intra-aortic balloon pump; LAD, left anterior descending artery; MCS, mechanical circulatory support; NA, not applicable; RCA, right coronary artery; TIMI, Thrombolysis In Myocardial Infarction; VD, vessel disease; other — see Figure 1

Table 3. In-hospital outcomes

Variable	Group			
	Overall n = 250[a]	CTO+ n = 60[a]	CTO– n = 190[a]	*P*-value[b]
Mechanical complications	6 (2.4%)	0 (0%)	6 (3.2%)	0.34
Stroke	5 (2.0%)	2 (3.4%)	3 (1.6%)	0.33
Major bleeding	8 (3.2%)	4 (6.8%)	4 (2.1%)	0.093
Resuscitated cardiac arrest	89 (36%)	28 (47%)	61 (32%)	0.032
Death	130 (52%)	41 (68%)	89 (47%)	0.004

[a]Frequency (%); [b]Fisher's exact test, Pearson's χ^2 test

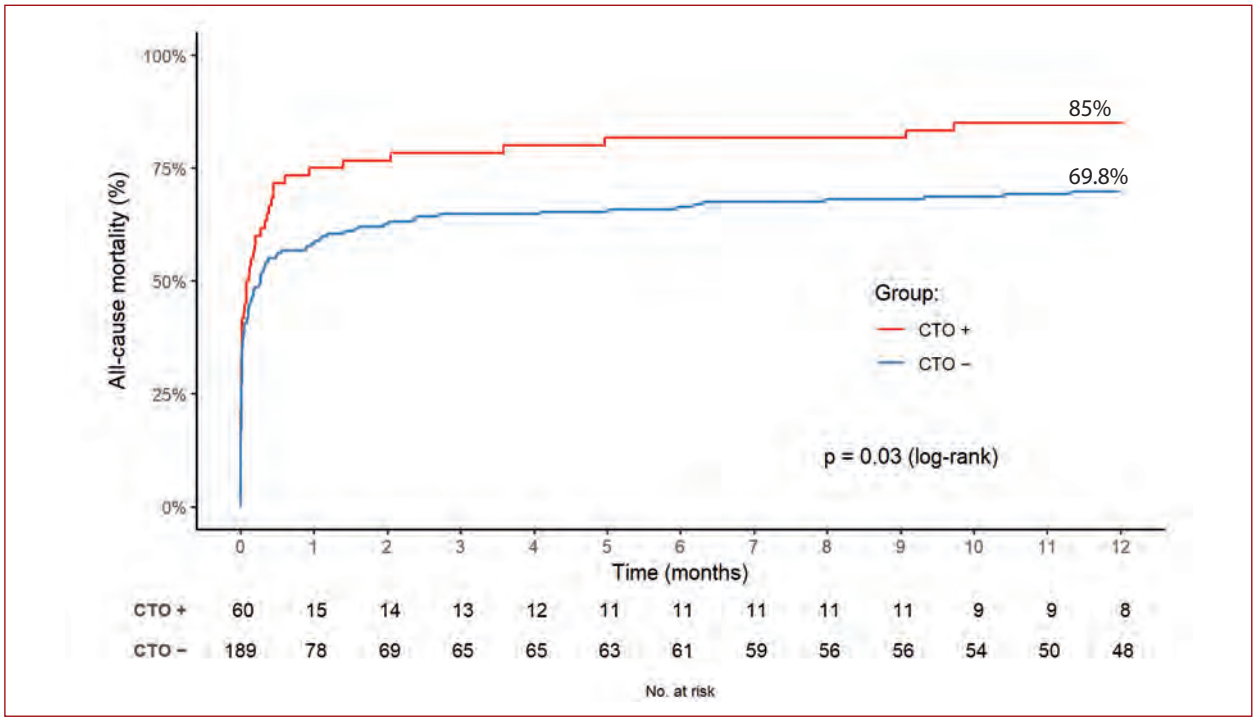

Figure 2. Kaplan–Meier curves presenting the incidence of all-cause 12-month mortality in groups stratified by the presence of chronic total occlusion (CTO) in non-culprit vessels

Abbreviation: see Table 1

of the +CTO and n = 132 (69.8%) of the –CTO (log-rank *P*-value of 0.03) (Figure 2). Most deaths occurred within the first 30 days following the index admission: n = 45 (75%) in the +CTO and n = 110 (58.3%) in –CTO groups (log-rank *P*-value of 0.04) (Figure 3). Similar observations were made in the subgroup of patients who underwent PCI in a non-CTO coronary artery during index hospitalization (12-month mortality of 83.3% in +CTO and 66.3% in the –CTO patients, the log-rank *P*-value of 0.04) (Supplementary material, *Figure S1*). Moreover, patients with CTO were at higher risk of all-cause death when compared to patients without CTO but with angiographically significant lesions (70%–99% stenosis) in the non-culprit vessel (85.0% vs. 69.9%, log-rank *P*-value of 0.02) (Supplementary material, *Figure S2*). Further analysis showed similar 12-month mortality in +CTO patients, irrespective of CTO location in the right or left coronary artery (log-rank *P*-value of 0.42) (Supplementary material, *Figure S3*). The effect of CTO on 12-month mortality was also comparable in STEMI and NSTEMI patients (*P*-value for the interaction of 0.62) (Supplementary material, *Figure S4*). The relationship between the baseline clinical characteristics and 12-month mortality in the univariable analysis is presented in Supplementary material, *Table S1*. In the multivariable analysis, the presence of CTO was independently associated with increased risk of 12-month mortality (hazard ratio 1.423; 95% CI, 1.027–1.973; *P* = 0.034) (Figure 4).

DISCUSSION

Cardiogenic shock complicated by AMI is one of the most severe and challenging acute clinical settings, requiring the greatest medical attention. The prevalence of CS ranges between 4%–10% [2, 3, 16]. Despite the current advances in multilevel treatment approaches, CS continues to entail an unacceptable early and long-term mortality risk [17], which has not changed over the last decade [18].

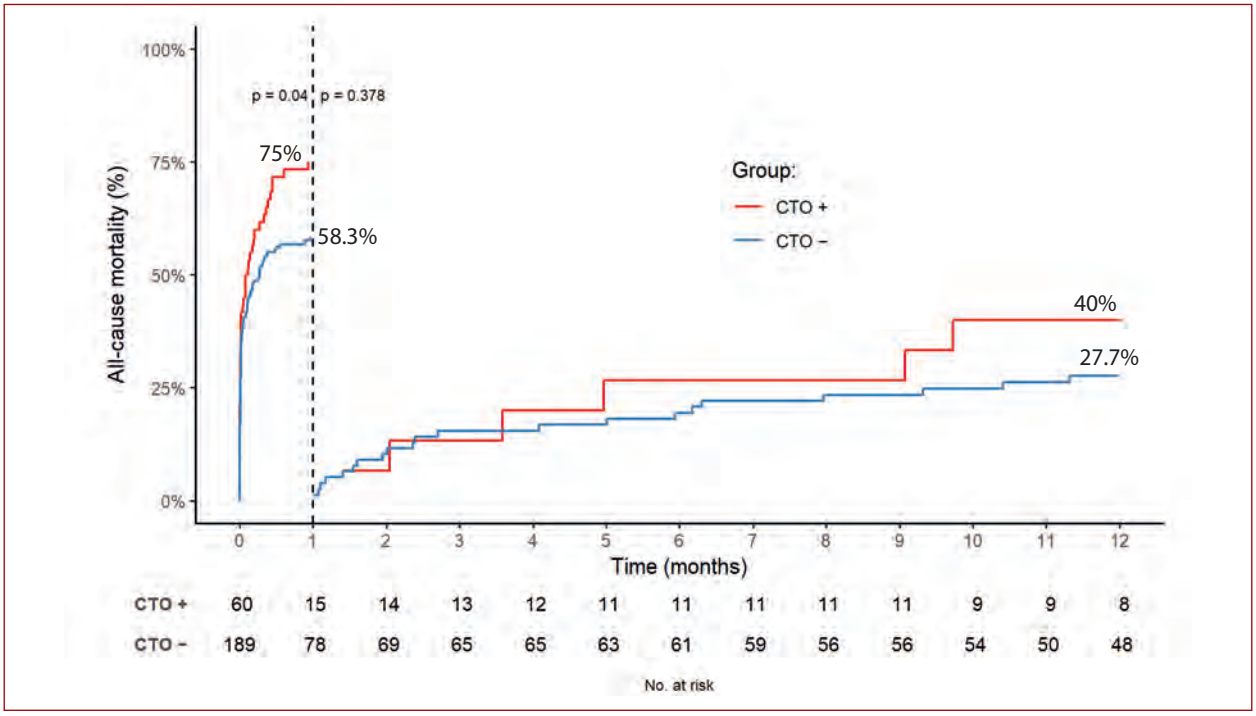

Figure 3. The results of landmark analysis for 12-month all-cause mortality in patients stratified by the presence of chronic total occlusion (CTO)

Abbreviation: see Table 1

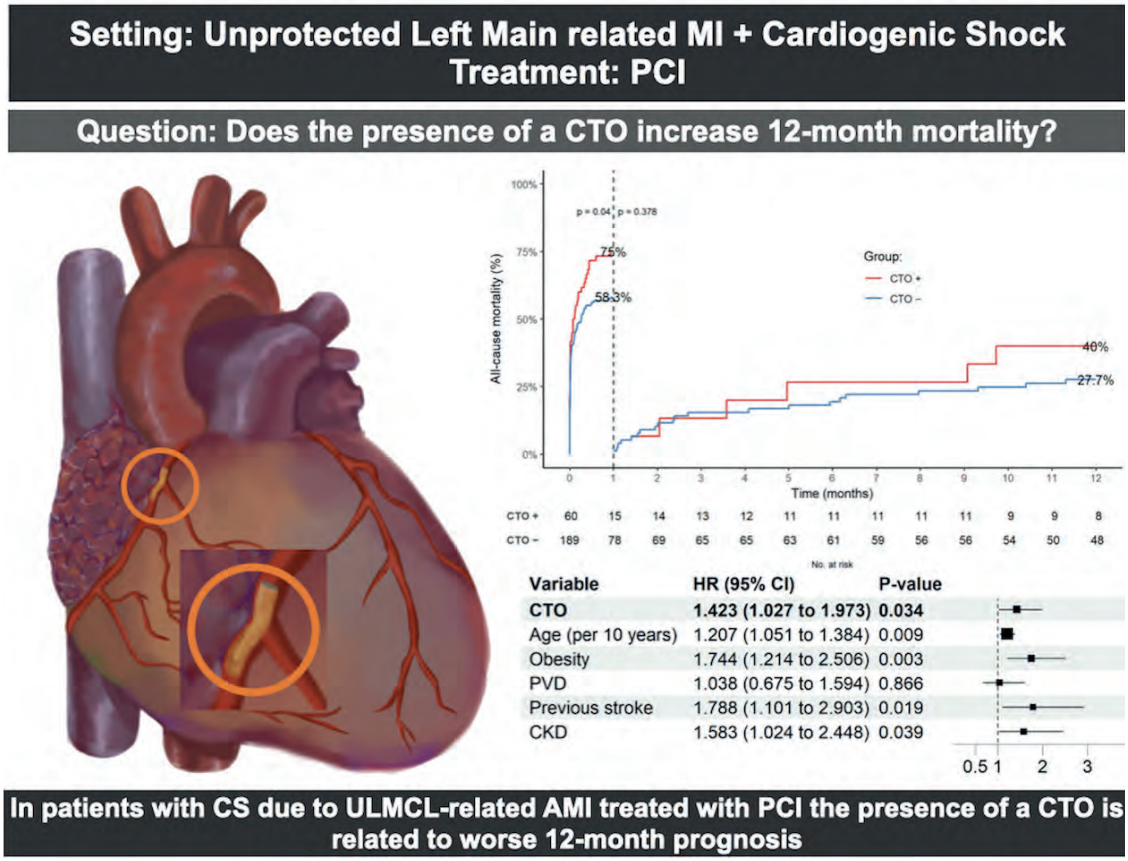

Figure 4. Multivariable analysis of the entire study population outcomes. Forest plot presenting hazard ratios (HR) and 95% confidence intervals (CI) for the variables included in the multivariable Cox regression model for 1-year all-cause mortality

Abbreviations: CKD, chronic kidney disease; CTO, chronic total occlusion; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral artery disease

Presently, coronary revascularization in the acute phase of CS related to AMI has been shown as the only factor modifying prognosis positively [19]. Therefore, prompt coronary angiography to detect a culprit lesion-related AMI complicated by CS is mandatory. Patients with CS complicated by AMI and a culprit lesion located in the left coronary main artery form a particular subgroup in this setting, with higher risk of mortality even after adjusting for confounding clinical and procedural characteristics [8, 20]. Additionally, in CS patients, CTO of an artery other than the culprit vessel is relatively common [12, 13]. We have, therefore, hypothesized that the presence of CTO may be a marker of worse prognosis, which may be useful for risk stratification in patients with AMI complicated by CS related to ULMCL.

The current practice guidelines for managing heart failure published by the European Society of Cardiology and the guidelines for myocardial revascularization created by both the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery do not recommend any strategy of treatment in the subpopulation of patients with CS due to ULMCL-related AMI and concomitant CTO in an artery other than the culprit lesion [21, 22]. To the best of our knowledge, there are no published data concerning the impact of CTO on the short- and long-term prognosis in this group of patients.

Therefore, our study aimed to evaluate the role of CTO in predicting long-term mortality in patients with CS secondary to ULMCL-related AMI. The main findings from this investigation can be summarized as follows: first, CTO was relatively frequent in this cohort of patients (24%); second, the presence of CTO in patients with CS due to ULMCL-related AMI was associated with increased risk of long-term mortality, also after adjustment for potential confounders in the multivariable analysis; third, most deaths occurred within the first 30 days following the index admission, and the relationship between CTO and worse outcomes was particularly noticeable within this period.

The presence of CTO in a vessel other than the culprit one in patients with CS is relatively high, with a recorded prevalence of 25%–30% [13, 23], consistent with the rate reported in this study. The reason why concurrent CTO is associated with worse prognosis in patients with CS secondary to ULMCL-related AMI is unknown and may be partially explained by the higher risk profile of CTO patients (higher prevalence of diabetes, higher percentage of multivessel coronary disease, lower rate of PCI success as assessed by TIMI flow). However, after adjustment for differences in baseline characteristics by multivariable Cox regression analysis, CTO remains an independent predictor of 12-month mortality.

Similarly, in the published sub-analysis of the IABP--SHOCK II (Intraaortic Balloon Pump in Cardiogenic Shock) trial of the prognostic impact of CTO in a non-infarct related artery (non-IRA) in STEMI, Saad et al. [24] demonstrated that CTO in a non-IRA was an independent predictor of one-year mortality. Interestingly, CTO in a non-IRA was a predictor of ventricular arrhythmias requiring defibrillation at 30-day follow-up, which is in line with our findings of a higher rate of in-hospital resuscitated cardiac arrest in the CTO group as compared to non-CTO.

These last interactions may shed some light on the discussion of the potential mechanism underlying increased mortality in patients with CTO after AMI complicated by CS due to ULMCL. Nombela-Franco et al. [25], in the VACTO (Ventricular Arrhythmias and Chronic Total Coronary Occlusion) Primary Study, showed the prognostic importance of CTO in the incidence of appropriate implantable cardioverter-defibrillators (ICD) interventions for ventricular arrhythmia and its impact on poor survival in a cohort of patients receiving ICD treatment for primary prevention of sudden cardiac death from ischemic cardiomyopathy. Consistently, Di Marco et al. [26] showed that the presence of CTO was associated with higher scar burden and was an independent predictor of ventricular tachycardia recurrence after successful ventricular tachycardia ablation.

Current practice guidelines recommend that prophylactic implantations of the ICD for the primary prevention of sudden cardiac death in patients with MI and depressed left ventricular contractility should be delayed for at least 40 days [21]. According to our findings, emphasizing that most patients died within the first 30 days following the index admission, we can postulate that in patients with CS-complicated AMI secondary to ULMCL, the presence of concomitant CTO may provide an additional vital parameter for risk stratification and may be a matter of other investigations in this group of patients.

Finally, some studies showed that in stable patients undergoing unprotected left main PCI, CTO of the right coronary artery (RCA) may be associated with increased risk of periprocedural complications and mortality [27, 28]. This may be because during unprotected left main PCI, a large region of myocardium is jeopardized, and in the absence of a patent RCA, hemodynamic deterioration is more likely [28]. However, not all studies found a negative effect of the lack of RCA flow on outcomes, which may be partially explained by differences between studies in left main PCI complexity, clinical characteristics of included patients, or clinical context [28, 29]. Indeed, our study showed that in the setting of CS, the prognosis of patients with ULMCL and any CTO is poor, irrespective of CTO location.

Our study underlines the prognostic value of concurrent CTO in the very high-risk population of patients with CS due to ULMCL-related AMI. However, owing to the observational nature of our study, the causal relationship between CTO and worse outcomes cannot be confirmed. Moreover, even if, intuitively, CTO revascularization might seem beneficial in patients with CS, there are no data supporting such an approach. Despite significant technical progress, CTO PCI remains a complex procedure with success strongly related to the operator's skills and a relatively higher rate of periprocedural complications, which seems

to be of special importance in the setting of CS [30]. Moreover, PCI of ULM in the absence of RCA support, differed neither in the prevalence of periprocedural complications nor in long-term survival, as compared to PCI with RCA support [31]. Notably, the landmark CULPRIT-SHOCK (Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock) trial showed no benefit of immediate complete revascularization compared with culprit-lesion-only PCI in STEMI patients with CS [23]. Importantly, in this trial, no modifying effect of CTO on this finding was observed [13].

Acute myocardial infarction is the most essential reason for CS development, resulting in a subsequent sudden and significant decrease in myocardial contractility. This leads to a vicious circle of reduced cardiac output (CO), hypotension, coronary perfusion worsening, and further ischemic deterioration of myocardial function with inadequate critical organ perfusion [31]. Thus, several MCS devices have been developed aiming to break the circle and change the unfavorable prognosis in CS complicated by AMI. Furthermore, apart from augmentation of CO with the subsequent improvement of systemic perfusion, MCS can also reduce the burden of myocardial ischemia [32]. However, it is challenging to determine the appropriate time to escalate therapy to an MCS device or determine which MCS device should be used. Again, we speculate that the presence of CTO might help improve the selection of patients with CS secondary to ULMCL-AMI who may benefit from MCS, but further studies regarding this issue are needed.

Limitations

There are several limitations to our analysis that should be acknowledged. Due to the observational character of the study, the causal relationship between the presence of CTO and higher mortality cannot be confirmed. Despite data adjustment in the multivariable analysis, the results could still be biased by potentially important parameters that were not available in the registry. Additionally, owing to the limited sample size, this analysis was underpowered to evaluate the association between successful CTO recanalization and outcomes in the present analysis. Finally, as it is a single-country study, it may not apply to other populations.

CONCLUSIONS

In a large registry, we found that in patients with CS secondary to unprotected left main coronary artery culprit lesion-related AMI treated with PCI, the presence of CTO is associated with higher 12-month mortality.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: None declared.

Funding: None.

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Is the 2016 ESC diagnostic algorithm useful for assessing the prevalence of chronic heart failure in population-based studies?

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DOI: 10.33963/v.phj.98958

Received: October 10, 2023

Accepted: January 15, 2024

Early publication date: February 19, 2024

ABSTRACT

Background: Chronic heart failure (CHF) is a major healthcare problem. However, there are no epidemiological studies assessing the prevalence of CHF in the general population with diagnosis based on algorithms recommended for clinical practice.

Aim: The aim of the HF-Pomorskie survey was to assess the prevalence of three basic components of the 2016 ESC diagnostic algorithm for CHF (symptoms, N-terminal pro B-type natriuretic peptide [NT-proBNP], and abnormalities on echocardiography) and to determine whether this algorithm may be applicable to studies in general population samples.

Methods: The study was performed in a representative sample of 313 adults (170 women and 143 men) aged between 20 and 90 years (mean 55.2 years [15.3]) in Northern Poland. A questionnaire to determine New York Heart Association [NYHA] class, laboratory tests including NT-proBNP, as well as transthoracic echocardiography and spirometry examinations were performed in all subjects.

Results: Dyspnea (NYHA class II–IV) was reported by 13.7% of recruited participants. Dyspnea and elevated levels of NT-proBNP (>125 pg/ml) were found in 7.7% of all examined subjects, while dyspnea, elevated NT-proBNP levels accompanied by systolic or diastolic abnormalities on echocardiography occurred in 4.8%. In the group without dyspnea (86.3% of all examined subjects), every sixth subject had an elevated level of NT-proBNP. On the other hand, 5.8% of studied subjects reported a previous diagnosis of CHF, which was confirmed using the current ESC algorithm in 78% of them.

Conclusions: The prevalence of CHF assessed by the 2016 ESC diagnostic algorithm in a representative sample of adults was equal to 4.8%. The clinical algorithm for the diagnosis of CHF is fully applicable to the representative surveys in the general population. However, due to logistic and economic factors, echocardiography examination and NT-proBNP determination can be limited to patients reporting dyspnea or previous diagnosis of CHF.

Key words: epidemiology, ESC guidelines, heart failure, NT-proBNP, NYHA scale

WHAT'S NEW?

The growing incidence of chronic heart failure (CHF) has been highlighted by the World Health Organization and the European Society of Cardiology (ESC). There are only a few studies assessing the epidemiology of CHF and its symptoms in Europe, and there are no such studies in the general population in Poland, which is one of the regions of high cardiovascular risk in central and Eastern Europe. However, estimating the prevalence of CHF in the population is a challenge. The available ESC recommendations apply mainly to newly diagnosed patients, but confirming the diagnosis is difficult. Our study explored whether the ESC diagnostic algorithm (symptoms, natriuretic peptides) could be used in a population study. The conclusions of this research have very broad scientific and practical implications for prevention, which should be a priority in Poland, Europe, and around the world.

INTRODUCTION

Chronic heart failure (CHF) is a large problem not only in cardiology but also in the whole healthcare system. Along with pneumonia, it is one of the main reasons for hospital admissions among elderly patients. Nevertheless, epidemiological data on this disease are scarce and imprecise e.g., the number of patients with CHF in Poland is estimated from 600 000 to even more than a million [1, 2]. The methods of assessing the prevalence of heart failure (HF) with non-acute onset are also debatable. It seems obvious that the patient's declaration and physical examination are not enough, but should transthoracic echocardiography (TTE) or B-type natriuretic peptide (BNP) level be performed in every screened subject? According to the 2016 and 2021 guidelines of the European Society of Cardiology (ESC), diagnosis requires the presence of symptoms and confirmation of myocardial dysfunction or structural changes on TTE [3, 4]. This algorithm is relatively easy to apply in clinical settings; however, in the case of epidemiological studies, there is a question of who should be tested and what tests should be performed. Consideration should also be given to which group of subjects should be screened for CHF, e.g., should the study protocol in a population-based sample be narrowed down to symptomatic groups only?

Previous reports have pointed out that myocardial dysfunction may precede the onset of symptoms for a long time. As a result, recommendations for preventive management in asymptomatic left ventricular systolic dysfunction (LVSD) were added to the 2016 ESC guidelines [4]. Early implementation of treatment with, among others, angiotensin-converting enzyme inhibitors may slow down the development of the disease and delay the onset of symptoms [5–8]. A thorough understanding of the epidemiology of CHF and LVSD is essential in planning health policy to prevent an excessive number of disease exacerbations and hospital admissions, especially in the wake of the 2019 coronavirus pandemic.

The study aimed to assess the prevalence of the main components of the CHF diagnostic algorithm proposed by the ESC for clinical practice and to determine whether this algorithm may be applicable to studies in general population samples.

METHODS

The HF-Pomorskie Study is an observational study of a representative group of residents from the Pomeranian Province in Poland. The study aimed to assess the prevalence of CHF in this region. The study included people aged 20 years or older, who were also randomly selected for the WOBASZ II population study. The processes of sample drawing, data collection methodology, and blood sampling were described in detail in our previously published article [9, 10].

The HF-Pomorskie Study was carried out among the residents of the Pomeranian Province. In the first stage, 2 small communes (fewer than 8000 residents), 2 medium-sized communes (8000–40 000 residents), and 2 large communes (40 000–200 000 residents) were chosen by drawing lots. Then, 100 women and men from each commune and, additionally, 100 people from the capital of the province were randomly selected using a personal identification number (PESEL) and invited to participate. Overall, 700 individuals were invited to participate in the study. Of those, 148 addresses were incorrect, or an individual could not be contacted. The age and sex of the participants corresponded to the 2014 population structure of the Pomeranian Province. Letters of invitation to participate in the survey were sent to the randomly selected participants. In each of the 7 communes, a research center was established, where participants were invited to visit. A detailed study design was developed, taking into account the elements of the CHF diagnostic algorithm according to the ESC guidelines. Each patient completed a questionnaire and had laboratory blood tests.

To assess the premises for the use of the diagnostic algorithm, two independent experts analyzed the database to look for cases of CHF symptoms, NT-proBNP levels, and TTE findings.

Transthoracic echocardiography, spirometry, and ECG were performed on 313 participants. One of them reported that she had previously been diagnosed with HF with reduced ejection fraction (EF) and had the result of a recent echocardiography (performed 3 months before the enrolment). As the diagnosis of HF was unquestionable, this patient was included in the analysis, and the data from the echocardiography performed outside the project were entered into the database.

A MasterScreen Pneumo device (CareFusion, Germany) was used for spirometry, which was performed in accordance with the guidelines of the American Thoracic Society/European Respiratory Society [11]. Obstruction was diagnosed when the forced expiratory volume/forced vital capacity ratio, was below the lower limit of normal (i.e., below the 5th percentile) [12].

Blood samples were collected from participants, after fasting, at their homes or at the research center. The collected material was centrifuged immediately; then, the obtained plasma was frozen and transported to the central laboratory where parameters of interest, including NT-proBNP levels, were determined. The natriuretic peptide levels were measured using an Immulite 1000 analyzer (Siemens Healthcare Diagnostics, Germany) by immuno-chemiluminescence, and the elevated plasma levels of NT-proBNP were defined according to the ESC recommendations. The threshold was >125 pg/ml [3].

Data on the prevalence of symptoms, comorbidities, and exposure to tobacco smoke were obtained from the questionnaire.

Recordings and measurements were made in line with the 2016 recommendations of the European Association of Cardiovascular Imaging and the American Society of Echocardiography [13].

All examinations were performed on a Siemens Acuson S2000 device, using a vector head. The geometry of the left and right ventricles and both atria were assessed as well as the general and segmental contractility of the LV in standard projections, using the 2D, M-mode, and Doppler modes, as recommended.

To detect potential systolic dysfunction, end-diastolic and end-systolic volumes were assessed using the disk summation method according to a modified Simpson rule.

Based on left ventricular ejection fraction (LVEF), patients with HF with preserved EF, HF with mid-range EF, and HF with reduced EF were identified. Due to the increasing importance of HF with preserved systolic function (LVEF >50%), diastolic function of the LV was assessed.

The following parameters were measured to assess LV diastolic function: the ratio of mitral inflow E-wave velocity to A-wave velocity (E/A ratio), velocity of mitral annulus movement assessed by tissue Doppler (E'), E/E' ratio, left atrial volume index, and the maximum wave velocity of tricuspid regurgitation.

Statistical analysis

Statistical analysis was performed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). The results were presented as percentages, mean values with standard deviations or medians, and quartile/interquartile ranges. The proportions were compared through a chi-square test. The distribution of the NT-proBNP level was compared using the Kruskal-Wallis test. For all statistical analyses, the level of significance was set at 0.05. The HF-Pomorskie Study was approved by the Bioethics Committee at the Medical University of Gdansk (No. NKBBN/421/2013). Each participant gave their informed consent before enrolment in the study. The investigation conformed with the principles outlined in the Declaration of Helsinki.

Table 1. Participant characteristics in the HF-Pomorskie Study (n = 313)

	HF-Pomorskie n (%) (n 313)
Sex	
Women	170 (54.3)
Men	143 (45.7)
Age	
18–64	215 (68.7)
≥65	98 (31.2)
BMI, kg/m^2	
<25	111 (35.5)
25–29.9	107 (34.2)
≥30	95 (30.4)
Comorbidities (self-reported)	
Hypertension	80 (25.1)
Diabetes	34 (10.8)
Chronic coronary syndrome (History of ischemic heart disease + prior myocardial infarction)	34 (10.8)
Hypercholesterolemia	182 (57.2)
History of chronic kidney disease and/or GFR <60 ml/min/1.73 m^2	27 (8.5)
Atrial fibrillation	20 (6.3)
Chronic obstructive pulmonary disease	53 (16.6)
Current smoker	89 (28.2)
Ex-smoker	101 (31.7)
Never smoker	123 (40.1)

Abbreviations: BMI, body mass index; GFR, glomerular filtration rate

RESULTS

The study was conducted between 2014 and 2016 and included 313 patients (170 women and 143 men) aged between 20 and 90 (mean age 55.2 [15.3]). The response rate was 56.7%. Table 1 presents the characteristics of the participants in the HF-Pomorskie Study.

Diagnostic algorithm

All participants of the study were assessed for the presence of HF symptoms according to the ESC diagnostic algorithm; the results are presented in Figure 1. The symptomatic group was composed of people who reported dyspnea (13.7%), defined as New York Heart Association (NYHA) class II–IV (Table 2). The distribution of the NT-proBNP level (between NYHA II, III, and IV) was statistically significant (P = 0.015). More than half of the patients in this group (55.8%, n = 24) had an increased level of NT-proBNP. Finally, CHF diagnosis was confirmed in every 3rd patient with dyspnea (39.5%) based on TTE. In the group without dyspnea, which was the majority of the study population, every 6th (15.9%) patient had elevated levels of NT-proBNP. For two patients in the asymptomatic group, TTE showed reduced EF (≤40%), and a diagnosis of LVSD was made.

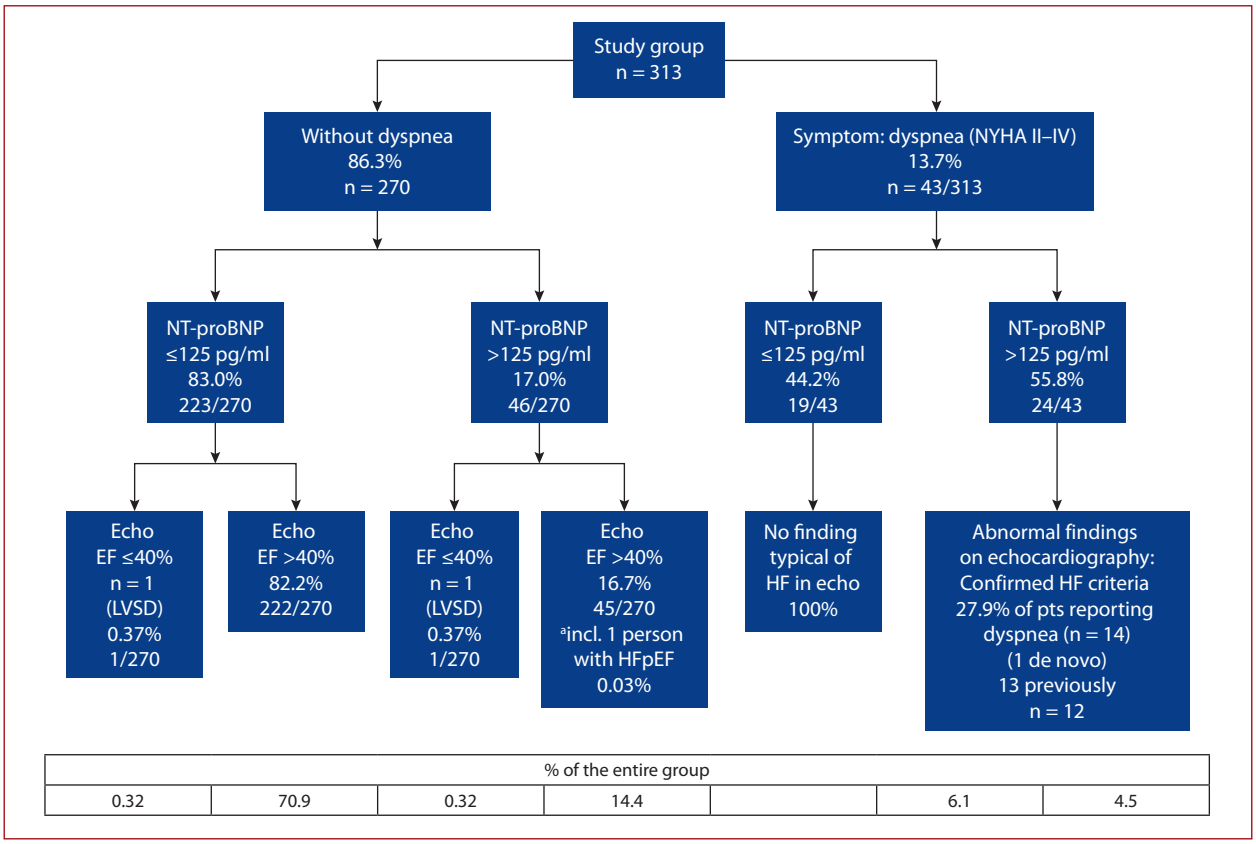

Figure 1. Components of the diagnostic algorithm (symptoms, NT-proBNP, and abnormalities on echocardiography) in the study group

[a]A patient after myocardial infarction, chronic treatment with ACE-I, and beta-blocker did not report dyspnea (NYHA I), with slightly elevated NT-proBNP levels. Transthoracic echocardiography findings: segmental abnormal contractility with normal EF
Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; EF, ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LVSD, left ventricular systolic dysfunction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association

All participants underwent a spirometry test to deepen the diagnosis of dyspnea. In the whole group, obstruction was found in 15.9% (n = 50), and in the group of patients reporting dyspnea, obstruction was found in 30.2% (n = 13; *P* <0.05 for both) (Figure 2).

Natriuretic peptides

Plasma NT-proBNP was measured in all participants. The median of NT-proBNP was 58.5 pg/ml (30.0–116.0). Values ≥125 pg/ml were found in 22.4% (n = 70) of the whole study population.

In the group of patients with dyspnea, increased levels of natriuretic peptides were demonstrated in more than half (55.8%) of patients, and HF was confirmed by TTE findings in 45.8% of patients with NT-proBNP >125 pg/ml and every fourth patient with dyspnea (25.6%).

In the group of patients with CHF, the NT-proBNP median was 539.5 pg/ml (157.3–1704.8) and 88.9% of people had NT-proBNP levels above the cut-off value (>125 pg/ml). In the group of patients with decreased EF, the NT-proBNP levels above the cut-off value were demonstrated in all patients (median 1364.0 pg/ml [1162.0–1455.0]).

In the group of patients with asymptomatic LV dysfunction, one patient did not have symptoms indicative of CHF — the NT-proBNP value was above 125 pg/ml.

CHF prevalence

In the examined group, 5.75% of patients (n = 18) had been previously diagnosed with HF. All cases were analyzed individually by two independent experts. The diagnosis reported in the interview was confirmed in 4.15% (n = 13) of cases. These were the patients whose self-reported CHF was confirmed by TTE.

In the remaining patients, previously diagnosed CHF was not confirmed. One patient was newly diagnosed with HF. Ultimately, the study found an overall prevalence of HF of 4.8%.

Additionally, 0.64% (2 patients) were diagnosed for the first time. In total, CHF was diagnosed in 4.79% of the participants, mostly in men (90.9%). The mean age in this group was 66.2 years (10.4). The mean body mass index (BMI) in this group was 28.5 kg/m^2 (3.8). Subgroup analysis by BMI showed that 9.1% had a BMI <25 kg/m^2 (normal), 54.5% had a BMI of 25–29.99 kg/m^2 (overweight), and 36.4% had a BMI >30 kg/m^2 (obese).

To describe this group, participants were divided according to the LVEF value. In the HF group, there were 6 patients (1.92%) with reduced EF, 3 (0.96%) with intermediate EF, and 6 (1.92%) with preserved EF. In the CHF group, 35.7% had hypertension, 21.4% had previously diagnosed diabetes, 35.7% had chronic obstructive pul-

Table 2. Distribution of patients reporting dyspnea in the study group

Dyspnea	Total NYHA II–IV	NYHA II (n)	NYHA III (n)	NYHA IV (n)
Percentage of people with dyspnea in the study group n = 313	43 (13.7%)	28 (8.9%)	12 (3.8%)	3 (1.0%)
NT-proBNP level, pg/ml, median (Q1–Q3)	143.0 (70.25–296.0)	98.0[a] (63.0–168.0)	220.0[a] (120.25–1235.25)	1364.0[a] (795.5–2433.0)
Percentage of patients with NT-proBNP >125 pg/mL, n = 44	24 (54.5%)	13 (44.8%)	8 (66.7%)	3 (100%)

[a]$P = 0.015$

Abbreviations: see Figure 1

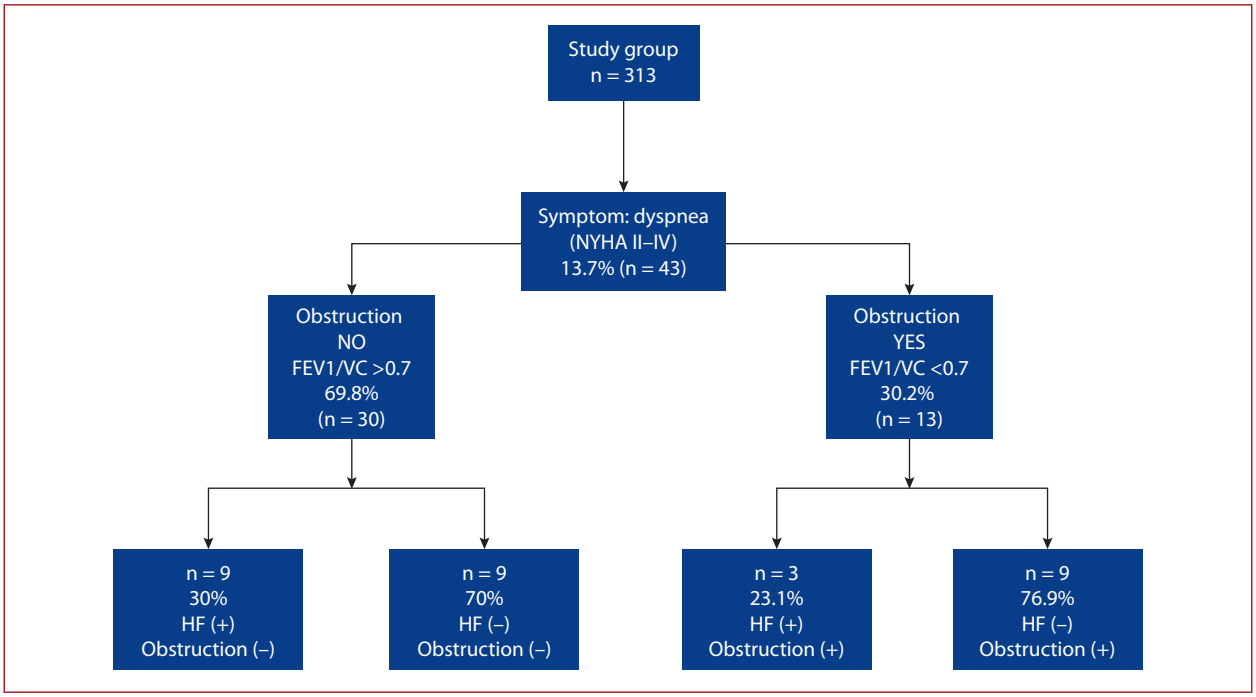

Figure 2. Obstruction in spirometry and heart failure in patients reporting dyspnea (NYHA II–IV)

Abbreviations: FEV1, Forced Expiratory Volume during the first second of expiration; VC, vital capacity; other — see Figure 1

monary disease (COPD) or obstruction in spirometry, and 35.7% had previously diagnosed chronic kidney disease or eGFR ≤60 ml/min/1.73 m^2.

There were 3 participants in the study group without prior diagnosis of HF, whose TTE test showed a reduction in LVEF of more than 50%. One person who reported dyspnea was diagnosed with HF. In the other two patients, asymptomatic LV dysfunction (LVSD) was diagnosed due to the lack of symptoms.

Almost 4% (3.83%) of the studied population had asymptomatic diastolic dysfunction.

DISCUSSION

The HF-Pomorskie Study was designed to analyze the prevalence of specific CHF symptoms and CHF itself in a selected province in Poland and to assess the usefulness of a diagnostic algorithm recommended by cardiology societies. The above analysis focused not only on the assessment of CHF prevalence but also on establishing recommendations for the most favorable screening design for a population-based study.

It should be noted that the ESC diagnostic algorithm applies only to newly diagnosed CHF. It is much more difficult to confirm the diagnosis in people who are already undergoing treatment. This is largely due to the reduction in the severity of symptoms and the levels of natriuretic peptides in patients who are optimally treated. However, this problem arises only in the case of screening, whereas in clinical practice it is a desired effect.

CHF prevalence

In the HF-Pomorskie Study, the prevalence of self-reported CHF was 5.75%. All patients underwent TTE, and this diagnosis was confirmed in 4.5% (n = 14) of them, and *de novo* diagnosis was made in 0.3% (1 patient). Finally, CHF was diagnosed in 4.8% of the study group.

These findings seem to be consistent with the results of European studies that form the basis of the epidemiological data. So far, the most frequently cited data were published in the Rotterdam Heart Study (CHF prevalence 3.9%) and the EPICA study (CHF prevalence 4.36%) [14, 15]. These studies are considered to have the strongest methodologies.

The Hamburg City Health Study published in 2022 seems to be the best-planned screening study reported in the literature at the moment. Among the 7000 participants (45–78 years old), the prevalence of CHF was 4.83% and LVSD 1.12%. In that study, like in HF-Pomorskie, a detailed medical history was taken, the level of natriuretic peptides was assessed, and echocardiographic examinations were performed [16].

It should be noted that there is a pilot HF registry project conducted in 12 countries. It includes both outpatients and hospitalized patients. Although not a population-based study, still it provides useful details about this group of patients [17, 18].

The NATPOL 2011 study was the only attempt to analyze the prevalence of HF in a representative sample of adults in Poland. Based on interviews with patients, the self-reported prevalence of CHF was 4.3%. TTE was not performed, which certainly reduced the value of the data obtained. To verify the reported percentage of diagnoses, the authors analyzed the public medical insurer's database (National Health Fund) for the ICD10 code I50 (corresponds to CHF), and the percentage of confirmed diagnoses was 3.0%. The data obtained in the above studies should be treated with caution, as they do not reflect the actual situation in Poland [19]. However, it can be assumed that the number of CHF patients reported recently (600 000–700 000) is certainly underestimated [1, 2].

Correale et al. [20] presented an overview of comorbidities in HF patients. In their study, the proportion of patients with diabetes and chronic kidney disease was similar to HF-Pomorskie. The exception was COPD – in the HF Pomorskie study it was 35.7%, whereas Correale et al. reported 15.0% [20]. In our study, we included patients with self-reported COPD and additionally obstruction in spirometry. Thanks to performing echocardiography in all participants, it was possible to estimate the number of patients with LVSD, which was 0.64% of the study group. We had expected that the clinical problem of LVSD was more widespread. It seems, however, that population-based testing to detect LVSD is not cost-effective and does not meet the criteria for screening even though estimating the prevalence of this disease seems to be important for health policy planning. It may be worth considering searching for LVSD in a narrower group of patients with other CVD risk factors, e.g., diabetes or hypertension. However, due to the small number of participants, further analyses were not possible in this study.

Assessment of symptom severity

Dyspnea, which is often reported as a decrease in exercise tolerance and increased weakness is a nonspecific symptom and patients often do not associate it with HF. In our study, dyspnea was reported by 13.7% of the participants. In this group, HF was diagnosed in every 4th person (27.8%). At the same time, when analyzing the group reporting dyspnea, every 3rd patient was diagnosed with airway obstruction in spirometry, but only 25% of participants with such obstruction suffered from HF. This indicates the need for performing spirometry in patients with dyspnea because most of these cases do not have a cardiac cause. At the same time, this group requires further pulmonary function tests. It is also worth noting that for almost one-third of participants reporting dyspnea (29.3%), its underlying cause was not found. Similar results were obtained in the NATPOL 2011 study by Undrunas et al. [21] who analyzed the frequency of self-reported dyspnea in a representative group of 2413 people. The dyspnea equivalent (NYHA II–IV) was reported by 10.1% of participants, and in this group, the diagnosis of CHF was reported only by every 9th patient (13.1%) [21]. Dyspnea, as a symptom, is subjective and non-specific. There is probably a group in which this symptom can be associated with obesity or a low level of physical activity.

For many decades, the NYHA classification has been used to assess the severity of symptoms of HF. Its main disadvantages are subjectivity and lack of precision. The study by Raphael et al., which analyzed the reproducibility of the NYHA symptom classification, showed only 54% agreement between cardiologists assessing the same patient [22]. In a similar study, Goldman et al. found that the repeatability of symptom assessment using the NYHA classification by two independent cardiologists was only 56% [23].

Natriuretic peptides

The next step according to the ESC diagnostic algorithm was the analysis of natriuretic peptides. Since 1993, their role has been increasing in successive editions of the ESC recommendations for CHF management. Currently, it is recommended that this parameter should be initially measured in every patient with suspected CHF. This test appears to be widely available and easy to perform. However, in Poland, there are healthcare facilities where it is easier to perform TTE than to assess the natriuretic peptide concentration [23]. Although the measurement of this parameter could significantly facilitate initial differential diagnosis of dyspnea in the outpatient setting, primary care physicians working in Poland's public healthcare system are not able to order it.

In the group of patients who did not report dyspnea, increased levels of NT-proBNP were found in 15.9%, and a previous diagnosis of CHF was confirmed in one patient. These results indicate that elevated levels of natriuretic peptides are common in that population and may be related to non-cardiac causes, e.g. chronic kidney disease or COPD. Nonetheless, it is certainly a useful screening tool.

Limitations

The main limitation of our study is its sample size. The cost of a study designed according to the ESC guidelines and analyzing the prevalence of LVSD in a representative group is enormous; therefore, our study group was limited to approximately 300 people. A thorough analysis of

our research question would require inclusion of several thousand people in the study. However, the use of three-stage randomization allowed for effective analysis of the distribution of variables even in that small group.

We did not analyze ECG in this group. ECG abnormalities are widespread in CHF patients [25]. It can be used in the CHF diagnostic algorithm, similar to chest X-rays. In the guidelines, both examinations have a class I C recommendation [3, 4]. Nevertheless, natriuretic peptides and echocardiography had a decisive role when CHF was suspected.

Another limitation is that spirometry was performed without assessing bronchodilator reversibility; therefore, it allowed us to identify a group of people with obstructive disorders but did not allow us to diagnose COPD.

Summary of findings

A diagnostic algorithm designed for clinical practice (according to the ESC criteria) is useful for assessing the prevalence of CHF in population-based surveys. However, such a study requires significant financial resources and extensive involvement of specialized equipment and qualified personnel. Moreover, imaging diagnostics should be limited to selected participants (those reporting symptoms and those with elevated NT-proBNP levels).

The prevalence of CHF among the residents of the Pomeranian Province was 4.8%, including newly diagnosed cases (0.3%).

Almost all CHF patients, both treated and newly diagnosed, had elevated levels of natriuretic peptides.

The percentage of people who self-reported CHF was 5.75%. It should be noted, however, that after careful evaluation of their medical history and current state, in 1% of cases, the CHF diagnosis could be considered doubtful, and in another 2.0% it was disputable.

In the general population, dyspnea, defined as NYHA class II–IV, was reported by 13.7% of participants. Every third patient with dyspnea had features of obstruction in spirometry, and every fourth patient had an elevated level of NT-proBNP.

CONCLUSIONS

The use of the clinical algorithm for the diagnosis of CHF in population-based studies is possible; however, imaging tests and NT-proBNP should be limited to patients reporting dyspnea or with prior diagnosis of CHF for its verification. The extensive use of TTE and determination of NT-proBNP levels to identify patients with asymptomatic LVSD or LV relaxation disorders do not seem justified.

It is sometimes difficult to assess the validity of a prior diagnosis of CHF, especially in pharmacologically treated patients with acute coronary syndrome.

The inclusion of spirometry in the screening for CHF in the population seems to be justified not only to differentiate CHF from lung diseases but also because of the coexistence of CHF with lung diseases.

We must still remember that in the clinical management of suspected HF, we should follow the ESC recommendations. If possible, we should measure natriuretic peptides in each patient, and in the next step, we perform an imaging test, e.g., echocardiography.

Article information

Acknowledgments: This study was partially funded by a Polish Cardiac Society Grant and by statutory grants from the Medical University of Gdansk. It was also partly funded by Siemens Healthcare Sp z o.o. — a partner of the project — who provided an unrestricted educational grant for echocardiography examinations and NT-proBNP level analyses. These funding agencies had no involvement in the design or conduct of the study, nor were they involved in the collection, management, analysis, or interpretation of the data or drafting of the manuscript.

Special thanks to Dr. Janusz Springer for the final corrections.

Conflict of interest: None declared.

Funding: Polish Cardiac Society Grant.

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First-year follow-up costs of myocardial infarction management in Poland from the payer's perspective

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DOI: 10.33963/v.phj.99006

Received:
August 10, 2023

Accepted:
January 18, 2024

Early publication date:
February 2, 2024

ABSTRACT

Background: Myocardial infarction (MI) remains a major burden for healthcare systems. Therefore, we intended to analyze the determinants of cost management of patients hospitalized for MI in Poland.

Methods: Data on patients hospitalized and discharged with the diagnosis of acute MI were derived from the public payer claims database. Adult patients, reported between October 1, 2017 and December 31, 2019, were included. Costs of hospitalization for acute MI and cumulative one-year follow-up were analyzed.

Results: The median (IQR) of the total direct cost was €3804.7 (2674.1–5712.7) per patient and 29% (€1113.6 [380.5–2490.4]) of these were costs related to the use of post-hospitalization healthcare resources. The median cost of cardiovascular disease management was €3624.7 (2582.1–5258.5), and 26% of this sum were follow-up costs. The analysis of the total cost for individual years showed a slight increase in median costs in subsequent years: €3450.7 (2407.8–5205.2) in 2017, €3753.8 (2642.6–5681.9) in 2018, and €3944.9 (2794.8–5844.4) in 2019. Male sex, heart failure, atrial fibrillation, diabetes, kidney disease, chronic obstructive pulmonary disease, and history of stroke in addition to hospitalization in a department other than cardiology or internal disease were independently related to the cost of MI patient management.

Conclusions: The high cost of management of MI patients was independently related to sex, heart failure, atrial fibrillation, diabetes, kidney disease, chronic obstructive pulmonary disease, and history of stroke as well as hospitalization in other than cardiology or internal disease department.

Key words: acute myocardial infarction, healthcare costs, invasive management

WHAT'S NEW?

We present a pioneering study that comprehensively captures and quantifies hospitalization and post-hospitalization costs of managing myocardial infarction (MI), which were not previously explored in Poland. The identification of cost predictors and sex disparities highlights the necessity for tailored and evidence-based approaches to confront economic challenges posed by MI. By focusing attention on optimal healthcare management programs, we can promote more sustainable outcomes and mitigate the financial burden on both the healthcare system and affected individuals.

INTRODUCTION

Cardiovascular disease (CVD) remains a major threat to public health worldwide [1]. Notably, ischemic heart disease, including its most important manifestation (i.e., myocardial infarction [MI]) is the main cause of mortality, contributing to 16% of the world's total deaths [2]. In addition, patients with acute MI often incur high medical expenditures following the event. These expenditures include frequent rehospitalization, multiple drug prescriptions, and device-related therapies as well as cardiac rehabilitation [3]. MI is also related to substantial indirect costs, resulting from either premature mortality or MI-related disability limiting return to work. In addition, contemporary societies are under the pressure of increasing general health-related expenditures [4]. Therefore, identification of factors associated with the increased cost of management could help in planning a strategy for cost reduction and more affordable healthcare as well as save more lives.

Over 80 thousand patients suffer from acute MI in Poland yearly with one-year mortality exceeding 17% [5]. Moreover, almost half of all patients are rehospitalized for various reasons within one year following MI [5–7]. However, there are a few scientific reports available that have estimated costs related to CVD entities such as MI, heart failure (HF), hypertension, and percutaneous coronary intervention (PCI) in Poland [6–9]. In addition, only a few reports have analyzed factors related to resource use in patients hospitalized for MI. Therefore, the present analysis aimed to explore the determinants of the management cost of patients hospitalized for MI in Poland.

METHODS

Study population

We included all adult (≥18 years of age) patients who had been discharged from the hospital with the diagnosis of acute MI between October 1, 2017 and December 31, 2019 in Poland. We classified hospitalization for MI according to ICD-10 codes I21 or I22 as the main diagnosis at any hospital ward. The index hospitalization for MI was defined as a continuous hospital stay, including all possible transfers between wards or hospitals for any reason until a patient's discharge home or death.

Patient histories were determined using claims data. A patient was coded as having a disease (e.g. hypertension or chronic kidney disease) if the disease was reported by any hospital or outpatient clinic. The follow-up period was defined as one year after discharge or the period from discharge to the patient's death. Hospitalization was defined as admission to a healthcare facility lasting >24 hours unless the patient died within 24 hours.

Ethics committee approval was not needed as we analyzed a fully anonymous national database. Informed consent was not required.

Cost analysis

We focused on direct costs (including hospitalization and post-hospitalization costs) from the payer's perspective. In addition, we only considered costs associated with management of cardiovascular diseases. The original costs are given in Polish zloty (PLN), and we converted them into Euro (EUR), by adopting the EUR to PLN exchange rate of 4.61, which is the value for the date of the last observation day (Dec 31, 2020). Resources used by healthcare providers and financed by the National Health Fund were identified. Total costs included costs of all services provided for the patient, which were calculated starting from the index hospitalization to the end of the follow-up period. Follow-up costs encompassed all expenses incurred after hospital discharge after MI and for one year or until the patient's demise. Costs associated with CVD management included an additional restriction on the ICD-10 code.

Statistical analysis

Categorical variables were described as proportion and compared using the χ^2 test. Continuous variables were expressed using mean and median values and compared using the Mann-Whitney test. Dispersion of variables was measured using the standard deviation (SD) and interquartile range (IQR). We used a multivariable linear regression model to examine the associations between related clinical factors and costs. Additionally, the Box-Cox method was employed to find the optimal transformation of the response variable. To report the most significant independent predictors, we ran a variable selection procedure using backward elimination and the Bayesian Information Criterion (BIC). The BIC criterion consists of two terms; the first one is related to the sum of squared residuals and measures the quality of model fit while the second one is related to the number of variables in the model and can be interpreted as a penalty for the complexity of the model. The method involves finding a subset of independent variables that

minimizes the criterion. The coefficient of determination (R^2) and F test were used to assess the goodness of fit of the model. We used the Spearman coefficient to measure the strength of correlations between single variables. We assumed a significance level of 0.05 in all statistical tests. All statistical analyses were performed using R statistical software (version 4.0.3). In particular, we used R packages: stats and ggplot2.

RESULTS

Overall, 154 108 MI patients were included in the analysis, with 56 095 (36.4%) females and 98 013 (63.6%) males (Table 1). The mean (SD) age was 68.1 (11.9) years, whereas the median (IQR) age was 68.0 (60.6–76.8). The majority of patients had been hospitalized in cardiological departments (88.1%). Invasive management (at least coronary angiography) was performed in 90.4% of patients, percutaneous coronary intervention (PCI) in 74.3%, and coronary artery bypass grafting (CABG) in 4.0% (Table 1).

In-hospital mortality was 8.64%. Post-discharge one-year all-cause mortality was 8.7%. The mean number of hospital stays within one year following discharge was 1.20 (0.47). The median number of consultations with the cardiologist within one year following discharge was 1.09 (0.00–2.23). The median number of consultations with a primary healthcare physician within one year following discharge was 10.28 (6.67–14.89). Patients with diabetes consulted a diabetologist 0.71 (1.29) times, on average, the median was 0.00 (0.00–1.14).

The median total cost was €3804.7 (2674.1–5712.7) per patient and 29% (€1113.6 [380.5–2490.4]) of this was cost related to using post-hospitalization resources. The median cost of CVD management was €3624.7 (2582.1–5258.5), of this sum, 26% of costs were related to post-hospitalization expenditures (Table 2). The analysis of the total cost for individual years shows a slight increase in median costs in subsequent years: €3450.7 (2407.8–5205.2) in 2017, €3753.8 (2642.6–5681.9) in 2018, and €3944.9 (2794.8–5844.4) in 2019 (Table 3).

Table 4 presents the subgroup analysis of the total costs of medical care in patients hospitalized for MI. History of dialysis, CABG during the index hospitalization, chronic kidney disease, and HF were related to higher management costs. Males incurred significantly larger total costs compared to female patients. Patients who were hospitalized in a cardiology department cost significantly less when compared with patients hospitalized in other departments. The Spearman correlation coefficient between age and the total

Table 1. Characteristics of the analyzed group

Variable	Number (%)
Age, years, mean (SD)	68.1 (11.9)
Sex, n (%)	
Females	56 095 (36.4)
Males	98 013 (63.6)
Heart failure, n (%)	33 329 (21.6)
Hypertension, n (%)	115 757 (75.1)
Atrial fibrillation, n (%)	19 103 (12.4)
Diabetes, n (%)	47 956 (31.1)
History of myocardial infarction, n (%)	10 789 (7.0)
History of CABG, n (%)	1571 (1.0)
History of PCI, n (%)	17 623 (11.4)
History of stroke, n (%)	4977 (3.2)
Chronic kidney disease, n (%)	12401 (8.0)
History of dialysis, n (%)	1555 (1.0)
Chronic obstructive pulmonary disease, n (%)	17 495 (11.4)
History of cancer, n (%)	38 569 (25.0)
Index hospitalisation, n (%)	
Coronary angiography, n (%)	139 389 (90.4)
Percutaneous coronary intervention, n (%)	114 446 (74.3)
CABG, n (%)	6233 (4.0)
Department, n (%)	
Cardiology	135 803 (88.1)
Internal medicine	13 467 (8.7)
Other	4838 (3.1)
Type of hospital, n (%)	
District	50 664 (32.9)
Community	39 778 (25.8)
Teaching	24 792 (16.1)
Other	38 874 (22.2)

Abbreviations: CABG, coronary artery bypass graft; SD, standard deviation; PCI, percutaneous coronary intervention

Table 2. Summary of the costs (in Euros) per patient

Type of cost	Median (IQR)	Mean
Hospitalization costs	2290.7 (2082.4–3205.7)	2699.5
Post-hospitalization costs	1113.6 (380.5–2490.4)	2302.7
Hospitalization and post-hospitalization costs	3804.7 (2674.1–5712.7)	5002.2
Post-hospitalization costs associated with cardiovascular causes	929.2 (217.3–2027.3)	1828.1
Hospitalization and post-hospitalization costs associated with cardiovascular causes	3624.7 (2582.1–5258.5)	4536.8

Patients with missing cost values were excluded from the analysis

Abbreviations: IQR, interquartile range; other — see Table 1

Table 3. Summary of the costs by year of discharge from the hospital (in Euros)

Year of discharge from the hospital	Median (IQR)	Mean
Costs of hospitalization for acute myocardial infarction		
2017	2105.8 (1915.8–2659.8)	2336.4
2018	2290.7 (2082.4–2973.0)	2621.9
2019	2359.3 (2082.4–3310.4)	2791.0
2017–2019	2290.7 (2082.4–3205.7)	2699.5
Costs of the management in the post-discharge period		
2017	997.3 (280.9–2377.6)	2176.3
2018	1116.9 (399.1–2524.6)	2318.5
2019	1131.1 (387.3–2480.1)	2318.0
2017–2019	1113.6 (380.5–2490.4)	2302.7
Total costs		
2017	3450.7 (2407.8–5205.2)	4537.3
2018	3753.8 (2642.6–5681.9)	4975.7
2019	3944.9 (2794.8–5844.4)	5144.6
2017–2019	3804.7 (2674.1–5712.7)	5002.2

Patients with missing cost values were excluded from the analysis

Abbreviations: see Tables 1 and 2

cost was not statistically significant (r = –0.005; *P* = 0.12). Age remained not significantly related to the costs in multivariable analysis both when we used age as a continuous variable and when we constructed age categories (Table 4). The abovementioned relationships remained unchanged in multiple regression analysis using a Box-Cox transformation on dependent variables to correct cost data which had skewed distribution [10]. This allowed us to obtain a model that is better fitted to the data (R^2 = 0.2232) when compared to the model based on the original response variable (R^2 = 0.1316) (Figure 1).

The subgroup analysis of the postdischarge costs of medical care is presented in Table 5. The high cost of management was related to dialysis, chronic kidney disease, and HF in the history. Male sex was also related to significantly higher costs. The multivariable analysis confirmed that kidney disease, sex, history of HF, diabetes, atrial fibrillation, hypertension, chronic obstructive pulmonary disease, cancer, and stroke as well as invasive management in the acute phase of MI and type of department where the patient was hospitalized were independently related to management costs following discharge.

The management cost of patients hospitalized for acute MI was correlated with the number of comorbidities (Figure 2). Both, the total cost as well as the post-hospitalization cost correlated with the number of comorbidities (Spearman correlation r = 0.20; *P* <0.001 and r = 0.16; *P* <0.001).

DISCUSSION

To the best of our knowledge, this is the first study that captured and quantified the hospitalization and post-hospitalization costs related to MI in Poland. The number of hospital admissions and cost of hospitalization of acute MI patients put a substantial economic burden on the healthcare system. Our analysis focused on the country's National Health Fund data and demonstrated that more than 90% of total hospitalization and post-hospitalization expenditure was related to cardiovascular healthcare. Importantly, the mean post-hospitalization cost, €2302.7, incurred in the first year following discharge was only slightly lower compared to the mean cost of acute MI patient hospitalization (€2669.5). Our findings align with the annual costs reported in the Soroka Acute Myocardial Infraction II (SAMI II) retrospective study from a tertiary medical center. In that study, annual per-patient costs throughout the first year following MI (€5592) were significantly higher compared with the preceding year (€3120) [11]. Additionally, we observed that the mean per-person annual cost of hospitalization in Poland was comparable to that incurred in Sweden in relation to CVD patients [12].

Analyzing clinical data, our results showed that co-morbidities rather than age were cost predictors. Specifically, the co-morbidities identified as predictors of increased hospitalization cost in studies of MI patients were diabetes, hypertension, and chronic kidney disease as well as HF, atrial fibrillation, and stroke. These comorbidities may affect the course of coronary artery disease and, as a result, may increase therapy-related costs, which stresses the need for optimal and coordinated care in the first year following MI [13, 14].

Our results demonstrated that men are more likely than women to generate high management costs. CVDs are highly prevalent in men compared to women, which may explain the underuse of clinical procedures in women and overuse in men. Another explanation can be a higher complication rate in men and, therefore, higher costs of usually expensive procedures tackling complications [15]. On the other hand, women are more willing than men to

Table 4. Variables related to the total costs (in Euros) in univariable and multivariable analyses

Variable	Total cost			
	Univariate, median (IQR)	*P*-value	Mutivariable regression, β (95% CI)[a]	*P*-value
Age				
<50 years	3290.6 (2487.4–4539.8)	<0.001	Reference	
50–60 years	3724.3 (2746.5–5393.5)		–	–
60–70 years	3989.7 (2850.6–6085.6)		–	–
70–80 years	4072.3 (2770.3–6289.5)		–	–
≥80 years	3460.9 (2305–5151)		–	–
Sex				
Male	3969 (2846.1–6037.5)	<0.001	0.023 (0.022, 0.025)	<0.001
Female	3531 (2388.5–5204.9)		Reference	
Heart failure				
Yes	3998.8 (2562.2–6575.9)	<0.001	0.023 (0.021, 0.025)	<0.001
No	3766.7 (2698.6–5519.3)		Reference	
Hypertension				
Yes	3855.5 (2668.6–5849.6)	<0.001	–	–
No	3678.9 (2689.9–5300.6)		Reference	
Atrial fibrillation				
Yes	3850.9 (2501.6–6192.3)	0.241	0.007 (0.005, 0.010)	<0.001
No	3798.8 (2698.1–5650.7)		Reference	

→

Table 4 (cont.). Variables related to the total costs (in Euros) in univariable and multivariable analyses

Variable	Total cost			
	Univariate, median (IQR)	*P*-value	Mutivariable regression, β (95% CI)[a]	*P*-value
Diabetes				
Yes	4128.5 (2838–6440.6)	<0.001	0.020 (0.018, 0.021)	<0.001
No	3691.1 (2618.3–5410)		Reference	
History of myocardial infarction				
Yes	3641.9 (2443.6–5989.4)	<0.001	–0.013 (–0.017, –0.010)	<0.001
No	3813.4 (2695.2–5692.3)		Reference	
History of PCI				
Yes	3879 (2647.1–6384.1)	<0.001	0.009 (0.006, 0.012)	<0.001
No	3795.7 (2677.9–5638.1)		Reference	
History of CABG				
Yes	3666.3 (2448.1–6059.1)	0.198	–	–
No	3805.5 (2676.8–5709.7)		Reference	
History of stroke				
Yes	4124 (2681.2–6304.7)	<0.001	0.013 (0.008, 0.017)	<0.001
No	3796.4 (2673.8–5689.3)		Reference	
Chronic kidney disease				
Yes	4481.4 (2880–8240)	<0.001	0.025 (0.022, 0.028)	<0.001
No	3765.5 (2662.3–5569)		Reference	
History of dialysis				
Yes	17368.1 (9718.1–21201.8)	<0.001	0.280 (0.273, 0.287)	<0.001
No	3782.6 (2663.6–5629.7)		Reference	
Chronic obstructive pulmonary disease				
Yes	3955.7 (2712.6–6091.5)	<0.001	0.008 (0.006, 0.011)	<0.001
No	3786.5 (2670.4–5664)		Reference	
Cancer in the history				
Yes	3896.6 (2689.8–5959.6)	<0.001	0.010 (0.008, 0.012)	<0.001
No	3774.1 (2669.2–5629.8)		Reference	
Coronary angiography during the index hospitalization				
Yes	3877.5 (2798.6–5779.2)	<0.001	0.032 (0.029, 0.035)	<0.001
No	2700.2 (1453.3–4863.6)		Reference	
PCI during the index hospitalization				
Yes	3961.8 (3028.9–5520.1)	<0.001	0.113 (0.111, 0.115)	<0.001
No	2546.7 (1301.2–6653.1)		Reference	
CABG during the index hospitalization				
Yes	8071.4 (6883.5–10,144.4)	<0.001	0.252 (0.248, 0.256)	<0.001
No	3707.5 (2621.8–5356)		Reference	
Department of cardiology				
Yes	3791.4 (2702.8–5627.2)	0.045	–0.050 (–0.055, –0.046)	<0.001
No	3951.4 (2430.4–6412.4)		Reference	
Department of internal medicine				
Yes	3710.5 (2260.9–5824.5)	<0.001	–0.027 (–0.032, –0.022)	<0.001
No	3810.5 (2708.2–5701.7)		Reference	
Other department				
Yes	4725.7 (2933.7–7964.9)	<0.001	–	–
No	3785.7 (2668.9–5644.4)		Reference	
Teaching hospitals				
Yes	4284 (2913.6–6912)	<0.001	–	–
No	3732.1 (2622.9–5492.6)		Reference	
District hospitals				
Yes	3667.3 (2598.2–5495.5)	<0.001	–0.017 (–0.019, –0.015)	<0.001
No	3874.6 (2714.7–5817.9)		Reference	
Community hospitals				
Yes	3587.9 (2457–5388.3)	<0.001	–0.018 (–0.02, –0.016)	<0.001
No	3875.6 (2761.8–5816.5)		Reference	
Other hospitals				
Yes	3960.3 (2871.4–5578)	<0.001	0.009 (0.007, 0.010)	<0.001
No	3754.7 (2612.9–5765.9)		Reference	

[a]Estimated coefficient in the model based on variables selected using the Bayesian Information Criterion (BIC)

Abbreviations: see Table 1

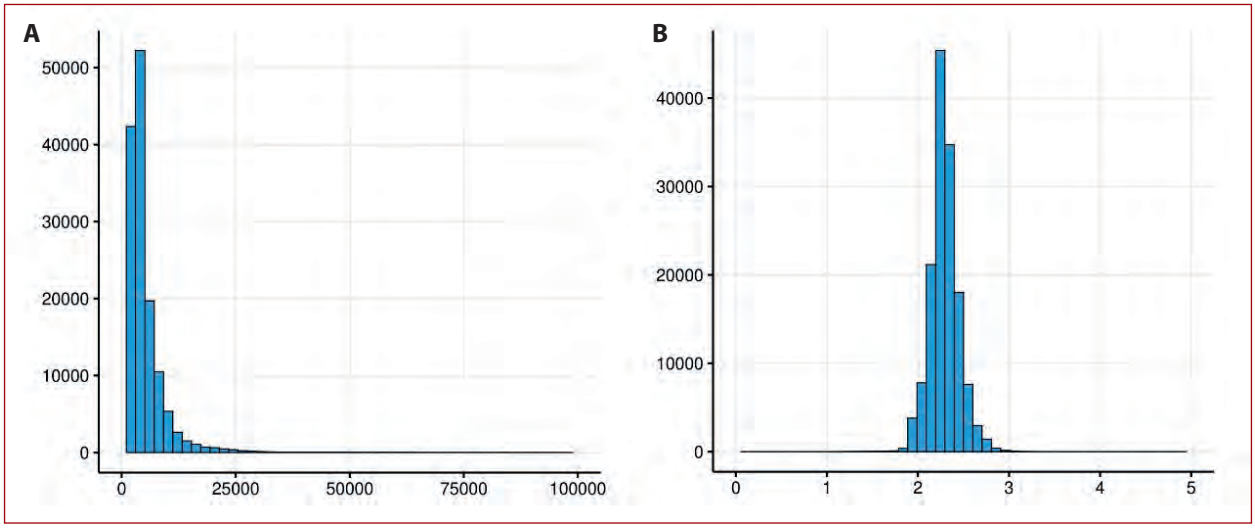

Figure 1. Distribution of the total cost (**A**) and distribution of the total cost after Box-Cox transformation (**B**). The optimal value of parameter λ = 0.1 in Box-Cox transformation

Table 5. Subgroup analysis of the costs (in Euros) of management in the post-discharge period

Variable	Post-hospitalization cost			
	Univariate, median (IQR)	*P*-value	Multivariable regression, β (95% CI)[a]	*P*-value
Age				
<50 years	780.7 (245.8–1532.7)	<0.001	Reference	
50–60 years	1024.5 (382.7–2143.5)		–	–
60–70 years	1154.3 (431.2–2618.9)		–	–
70–80 years	1250 (446.3–2887.5)		–	–
≥80 years	1072.8 (241.1–2420.8)		–	–
Sex				
Males	1147 (422.1–2620.6)	<0.001	0.040 (0.036, 0.043)	<0.001
Female	1049.2 (292.4–2272)		Reference	
Heart failure				
Yes	1432.3 (521.4–3569.6)	<0.001	0.039 (0.035, 0.044)	<0.001
No	1054.9 (352.6–2249.7)		Reference	
Hypertension				
Yes	1160.6 (401–2634.2)	<0.001	0.014 (0.01, 0.018)	<0.001
No	974 (331.5–2049.2)		Reference	
Atrial fibrillation				
Yes	1357.9 (480.4–3276.2)	<0.001	0.019 (0.014, 0.024)	<0.001
No	1093.2 (369.2–2388.7)		Reference	
Diabetes				
Yes	1297 (485.2–3064.5)	<0.001	0.037 (0.033, 0.040)	<0.001
No	1036.7 (341–2252)		Reference	
History of myocardial infarction				
Yes	1256.6 (381.7–3272.3)	<0.001	–0.022 (–0.03, –0.015)	<0.001
No	1103.5 (380.3–2444.3)		Reference	
History of PCI				
Yes	1339.7 (440.1–3460)	<0.001	0.021 (0.014, 0.027)	<0.001
No	1095.1 (373.1–2390)		Reference	
History of CABG				
Yes	1234.8 (332.7–3534.1)	<0.001	–	–
No	1112.5 (380.9–2482.3)		Reference	
History of stroke				
Yes	1460 (525.6–3307)	<0.001	0.022 (0.013, 0.031)	<0.001
No	1103.4 (376.7–2463)		Reference	
Chronic kidney disease				
Yes	1835.3 (736.2–5122.1)	<0.001	0.052 (0.045, 0.058)	<0.001
No	1079.8 (359.1–2345)		Reference	

Table 5 (cont.). Subgroup analysis of the costs (in Euros) of management in the post-discharge period

Variable	Post-hospitalization cost			
	Univariate, median (IQR)	*P*-value	Multivariable regression, β (95% CI)[a]	*P*-value
History of dialysis				
Yes	14695.1 (6500.3–17999.5)	<0.001	0.437 (0.421, 0.453)	<0.001
No	1103.4 (372.7–2425.4)		Reference	
Chronic obstructive pulmonary disease				
Yes	1302.1 (514.9–2995)	<0.001	0.025 (0.020, 0.030)	<0.001
No	1095.7 (365.4–2429.4)		Reference	
History of cancer				
Yes	1246.1 (472.8–2859.2)	<0.001	0.040 (0.036, 0.043)	<0.001
No	1073.2 (346.3–2367.2)		Reference	
Coronary angiography during the index hospitalization				
Yes	1109.1 (380.2–2457.2)	<0.001	–0.014 (–0.02, –0.008)	<0.001
No	1168.2 (382.3–2829.4)		Reference	
PCI during the index hospitalization				
Yes	1149.6 (445.9–2434.1)	<0.001	0.041 (0.036, 0.045)	<0.001
No	944.1 (202.2–2760.8)		Reference	
CABG during the index hospitalization				
Yes	1013.6 (519.4–1719)	<0.001	–	–
No	1119.9 (375.6–2526.2)		Reference	
Department of cardiology				
Yes	1103 (376.1–2421.3)	<0.001	–0.044 (–0.053, –0.035)	<0.001
No	1254.9 (424.5–3071.2)		Reference	
Department of internal medicine				
Yes	1199.8 (410.4–2913)	<0.001	–0.022 (–0.033, –0.011)	<0.001
No	1104.3 (378.4–2454.5)		Reference	
Other department				
Yes	1413.5 (471–3620.3)	<0.001	–	–
No	1104.5 (378.1–2460.6)		Reference	
Teaching hospitals				
Yes	1116.6 (433.6–2606)	<0.001	–	–
No	1112.7 (365.2–2469.4)		Reference	
District hospitals				
Yes	1103.4 (374.7–2463.4)	0.003	–0.015 (–0.020, –0.011)	<0.001
No	1117.9 (383.3–2502.6)		Reference	
Community hospitals				
Yes	1136.7 (315–2580.6)	0.768	–0.019 (–0.023, –0.014)	<0.001
No	1105.5 (402.6–2456.2)		Reference	
Other hospitals				
Yes	1103.4 (408.4–2354.7)	0.098	–	–
No	1116.7 (373.1–2533.4)		Reference	

[a]Estimated coefficient in the model based on variables selected using the Bayesian Information Criterion (BIC)

Abbreviations: see Table 1

adapt their lifestyle and adhere to medications to avoid surgery [16].

The likelihood of incurring high management costs was associated with a number of co-morbidities. Similarly, a multi-country analysis of costs related to CVD in patients with atrial fibrillation reported that co-morbidities, such as diabetes and stroke, were identified as predictors of costs in the Polish population [17]. Pre-existing HF was related to significantly higher costs in our analysis. This finding is in line with other analyses showing high costs of management of HF patients [18].

Since the economic burden of acute MI is high, efforts to provide effective public health activities and effective medical management could result in significant health-related cost savings and increased productivity. It applies also to MI-related complications and post-acute MI hospitalization which can be substantially lowered with effective treatment coordination and prevention.

Limitations

Although our study focused on Polish residents, our findings remain relevant to other healthcare systems. However, the present analysis has some limitations. First, the design of the present study precludes any claims on cause-and-effect relations. Indeed, we can only confirm statistical associations between the analyzed variables and cost management, rather than a causal relationship. Second, we were not able to estimate the indirect costs of MI nor the

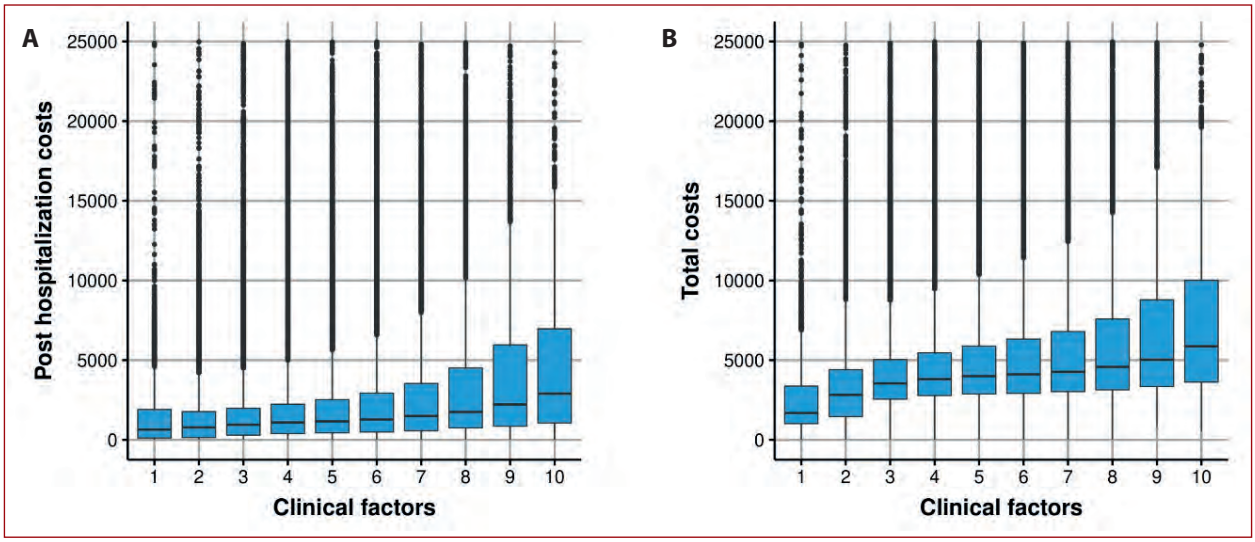

Figure 2. Total costs (**A**) and post-hospitalization costs (**B**) calculated in Euros in relation to several clinical factors (male sex, hypertension, diabetes, atrial fibrillation, heart failure, cancer in the history, stroke in the history, myocardial infarction in the history, chronic kidney disease in the history, chronic obstructive pulmonary disease, history of percutaneous coronary intervention, percutaneous coronary intervention during the index hospitalization, invasive management during the index hospitalization, previous dialysis, history of coronary artery bypass grafting, coronary artery bypass grafting) present simultaneously in the patient

socio-economic status of patients due to lack of available data. Moreover, we have no data on lifestyle habits of the analyzed patients. The inclusion of such additional information would possibly allow for a more effective analysis of the impact of the considered variables on costs. Third, we could not analyze costs of drugs utilized in the post-discharge period. Therefore, the presented cost estimates should be seen as understated. Finally, the results are based on the robustness of the public databases that generally suffer from reporting bias resulting from the specificity of financing claims. On the other hand, a major advantage of the present study is the analysis of a large, nationwide database including all patients hospitalized for MI between October 1, 2017 and December 31, 2019 in Poland. Thus, the data regarding used resources provide an overview of current everyday practice.

CONCLUSIONS

Male sex, HF, atrial fibrillation, diabetes, kidney disease, chronic obstructive pulmonary disease, and history of stroke as well as hospitalization in departments other than cardiology or internal disease are independently related to the cost of management of MI patients. Age was not independently related to the cost of management of MI patients.

Article information

Conflict of interest: None declared.

Funding: None.

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Do children with asymptomatic ventricular preexcitation have similar quality of life as healthy children?

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DOI: 10.33963/v.phj.99291

Received:
September 28, 2023

Accepted:
February 1, 2024

Early publication date:
February 22, 2024

ABSTRACT

Background: To our knowledge, no studies have assessed quality of life (QoL) in asymptomatic children with a preexcitation electrocardiogram pattern.

Aim: To evaluate the QoL of children with asymptomatic Wolff–Parkinson–White (WPW) syndrome.

Methods: This study involved QoL assessment of 31 children with asymptomatic preexcitation and 82 healthy children using the WHOQOL-BREF and the Pediatric Arrhythmia Related Score (PARS), a specific questionnaire that we have developed, which is related to patients' feelings and observations concerning arrhythmia.

Results: There were no significant differences between the two groups in all the measured domains; however, there were significant differences regarding general satisfaction with their health condition ($P = 0.01$). There were no differences in general satisfaction with the QoL, but WPW children more often experienced palpitations than the control group ($P < 0.001$) and were more likely to feel sad ($P = 0.046$) and nervous ($P = 0.04$) compared to healthy children.

Conclusions: The children with WPW were more dissatisfied with their health compared to healthy children. Although both groups of children had similar levels of satisfaction with their QoL, some areas of physical and psychological parameters of QoL were worse in WPW children. The PARS questionnaire is a useful tool as a disease-specific QoL instrument, which supplements the general questionnaire and aids in clinical practice and decision-making.

Key words: pediatrics, quality of life, questionnaire, ventricular preexcitation

INTRODUCTION

Wolff–Parkinson–White (WPW) syndrome is an abnormality of the cardiac conduction system characterized by an accessory conduction pathway between the atria and the ventricles [1, 2]. WPW diagnosis is usually based on an electrocardiogram (ECG). During sinus rhythm, the typical resting ECG pattern consists of a short PR interval, slurred upstroke (or downstroke) of the QRS complex ("delta wave"), and wide QRS complex [3–5]. The presence of an accessory pathway may lead to serious consequences ranging from supraventricular tachycardia (SVT) to sudden cardiac death (SCD) [6]. In the pediatric group, an accessory atrioventricular pathway is the most frequent cause of SVT. Moreover, children and adolescents with accessory pathways may be "presymptomatic" as they have not had time to develop symptoms or a sentinel event [7], and SCD may occur even in asymptomatic WPW [8–10].

Reduced quality of life (QoL) is a typical consequence of chronic disease in children and adolescents, hence, children with SVT have a significantly poorer QoL than their healthy peers [11–14]. To our knowledge, no studies have assessed the QoL in children with asymptomatic WPW, and we hypothesized that the QoL of children with asymptomatic WPW is worse than in healthy individuals because of limitations and hazards resulting

WHAT'S NEW?

Quality of life assessment in asymptomatic children with a preexcitation electrocardiogram pattern is a new clinical practice, as to the best of our knowledge, no studies have assessed the quality of life in these children. Quality of life questionnaires should be an important element in clinical practice, as they can be helpful in treatment decision-making.

from WPW diagnosis. Therefore, this study was designed to evaluate the QoL in children with asymptomatic WPW.

METHODS

Participants

The study group included children aged 7–18 with asymptomatic preexcitation and no organic heart disease or other chronic conditions that could interfere with the QoL. All participants lived in Poland and were patients of the Department of Pediatric Cardiology, Poznan University of Medical Sciences, Poland. All patients were approved for electrophysiology studies (EPS) and radiofrequency ablation or cryoablation by a cardiologist with expertise in electrophysiology and electrotherapy. A group of healthy children aged 7–18 with no medical conditions that could impede their QoL was enrolled as the control group by pediatricians during routine check-ups. The inclusion criteria, as in our previous studies assessing QoL [11, 15, 16], was a minimum age of 7 years. All patients and their parents provided written informed consent and each patient underwent a detailed interview and physical examination (both groups). In addition, the study group also had 12-lead resting ECG and echocardiography examinations.

The criterion for recognizing an asymptomatic patient was the lack of symptoms typical of arrhythmia, such as palpitations with abrupt onset and end, shortness of breath or chest pain, and no arrhythmia recorded during electrocardiographic diagnostics. The QoL parameters were assessed in children with preexcitation and compared to the control group. The study protocol was approved by the Bioethics Committee of the University of Medical Sciences, Poznan, Poland.

World Health Organization Quality of Life (WHOQOL) questionnaire

The WHOQOL-BREF instrument comprises 26 items to measure the following domains: physical health (Phd), psychological health (Psd), social relationships, and the environment [17, 18]. The WHOQOL-BREF is a shorter version of the original instrument that may be more convenient for use in large research studies or clinical trials. The questions included in the questionnaire are rated on a five-point Likert scale; the points are calculated in accordance with the established code and transformed to a 4–20 scale and subsequently to a 0–100 scale. The higher the score obtained in one domain, the higher the QoL [17, 18].

WHOQOL-BREF also includes questions that are analyzed individually: question 1 concerns the individual's general perception of QoL, and question 2 concerns the individual's general perception of their health. Considering the patient's age, the question referring to sexual activity in the social domain was removed from the questionnaire.

Pediatric Arrhythmia Related Score (PARS)

The questionnaire regarding patients' feelings and observations associated with arrhythmia (Pediatric Arrhythmia Related Score — PARS) was developed by pediatric cardiologists in collaboration with clinical psychologists and modified for arrhythmia children. This questionnaire was used in our previous studies evaluating QoL in SVT children [11, 15, 16]. The questionnaire contains 32 questions, which are grouped into 3 domains: physical, regarding the symptoms perceived as specific or likely to accompany SVT; medical satisfaction, concerning cooperation with medical care professionals; and psychological, referring to the emotional condition of the studied individuals. The answers are provided using a 1–5 point scale where "1" means "absolutely not" and "5" means "absolutely yes". Each domain is assessed on a 1–5 point scale and numeric results of individual areas are "negatively directed", i.e. the lower the numeric value, the higher the QoL. For this research, only the questions regarding physical and psychological aspects were used, assuming that the questions referring to medical satisfaction are inappropriate in a group of healthy children, who have limited or no contact with medical care professionals. Specific details regarding the PARS questionnaire are available in our previous study [11].

Statistical analysis

Statistica 13 software by TIBCO and PQStat by PQStat Software was used for the statistical analysis with the level of significance $\alpha = 0.05$. The two groups were compared with regard to age, sex, education, and place of living (village/town). The normality of the distribution of variables was assessed by the Shapiro–Wilk test. The Mann–Whitney test was used to compare the variables between the two groups. The Friedman test with the Dunn–Bonferroni multiple comparison test or the Wilcoxon test were applied to test whether the evaluated domains were different. The χ^2 test of independence, Fisher's exact test, or the Fisher–Freeman–Halton test were used to test relationships between categorical variables. Since the variable "sex" could confuse the results of the univariate

Table 1. Patient demographics

	Preexcitation group	Healthy children	*P*-value
Patient No.	31	82	
Age, median (Q1–Q3)	13 (11.0–16.0)	13 (10.0–16.0)	0.95
Sex, n (%)			
Boys	24 (77.4)	38 (46.3)	0.003
Girls	7 (22.6)	44 (53.7)	
Place of living, n (%)			
Village	9 (29.0)	22 (26.8)	0.44
Town	22 (71.0)	60 (73.2)	
Background, n (%)			
1. Junior school	18 (58.1)	34 (41.5)	0. 82
2. Grammar school	4 (13.0)	22 (26.8)	
3. Basic vocational school	2 (6.4)	1 (1.2)	
4. Secondary technical school	2 (6.4)	6 (7.3)	
5. High school	5 (16.1)	19 (23.2)	

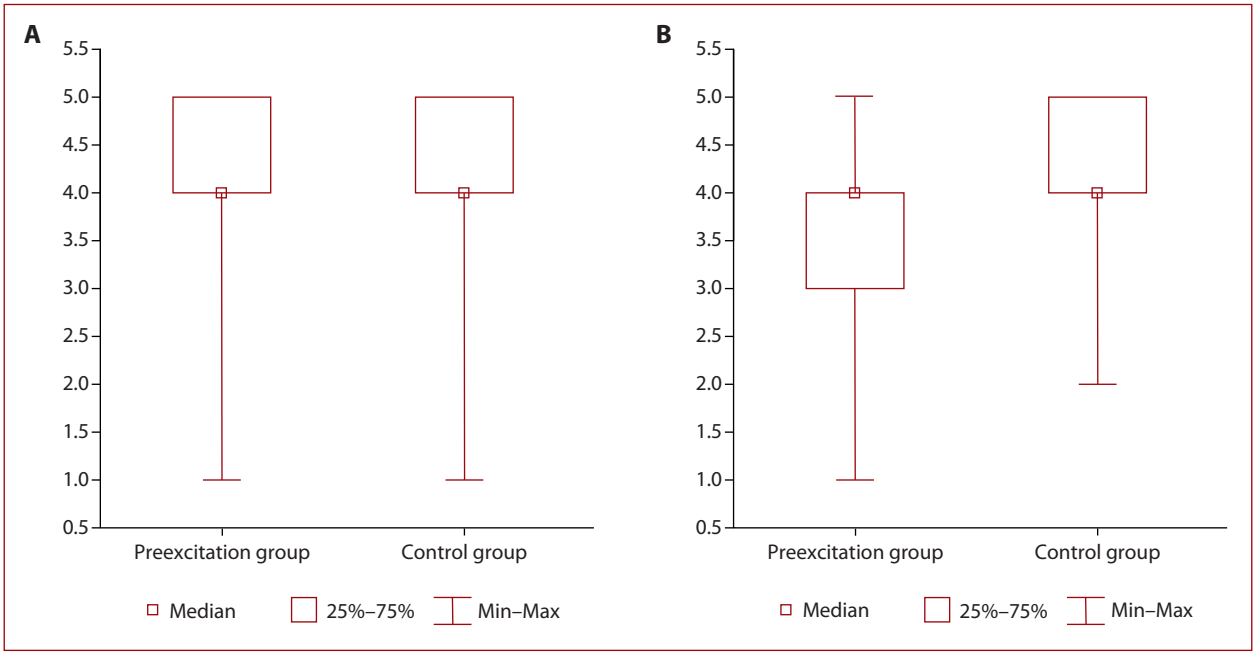

Figure 1. General satisfaction with the quality of life (**A**) and with health condition (**B**): comparison of the preexcitation and healthy groups

analyses (the groups were not homogeneous with respect to sex), a logistic regression model was built to verify the conclusions obtained in the preliminary analyses. In this model, the dependent variable is the occurrence or not of a particular disease, and the independent variables are sex and the question analyzed. In the constructed models, the significance of the variables in the model was tested using the Wald chi-squared test, and the significance of the whole model was tested using the reliability quotient test. To assess correlations between scores in the PARS and WHOQOL-BREF, the Spearman rank correlation coefficient was used.

RESULTS

Of 73 WPW patients aged 7–18 eligible for ablation treatment, 31 were asymptomatic and were included in the study. In all cases, accessory pathways were confirmed during EPS examination. The control group included 82 healthy children. Patient demographics are shown in Table 1.

WHOQOL-BREF

The WHOQOL-BREF analysis showed a few differences between the group of healthy children and WPW patients. Significant differences were found regarding general satisfaction with their health condition ($P = 0.02$), with 67.7% of WPW children being satisfied/very satisfied with their general health compared to 87.9% of healthy children (Figure 1). There were no differences regarding general satisfaction with their QoL ($P = 0.19$) (Figure 1). However, there was a statistically significant difference between the group of healthy children and the WPW children in terms of the social domain ($P = 0.03$), but after adjusting for sex,

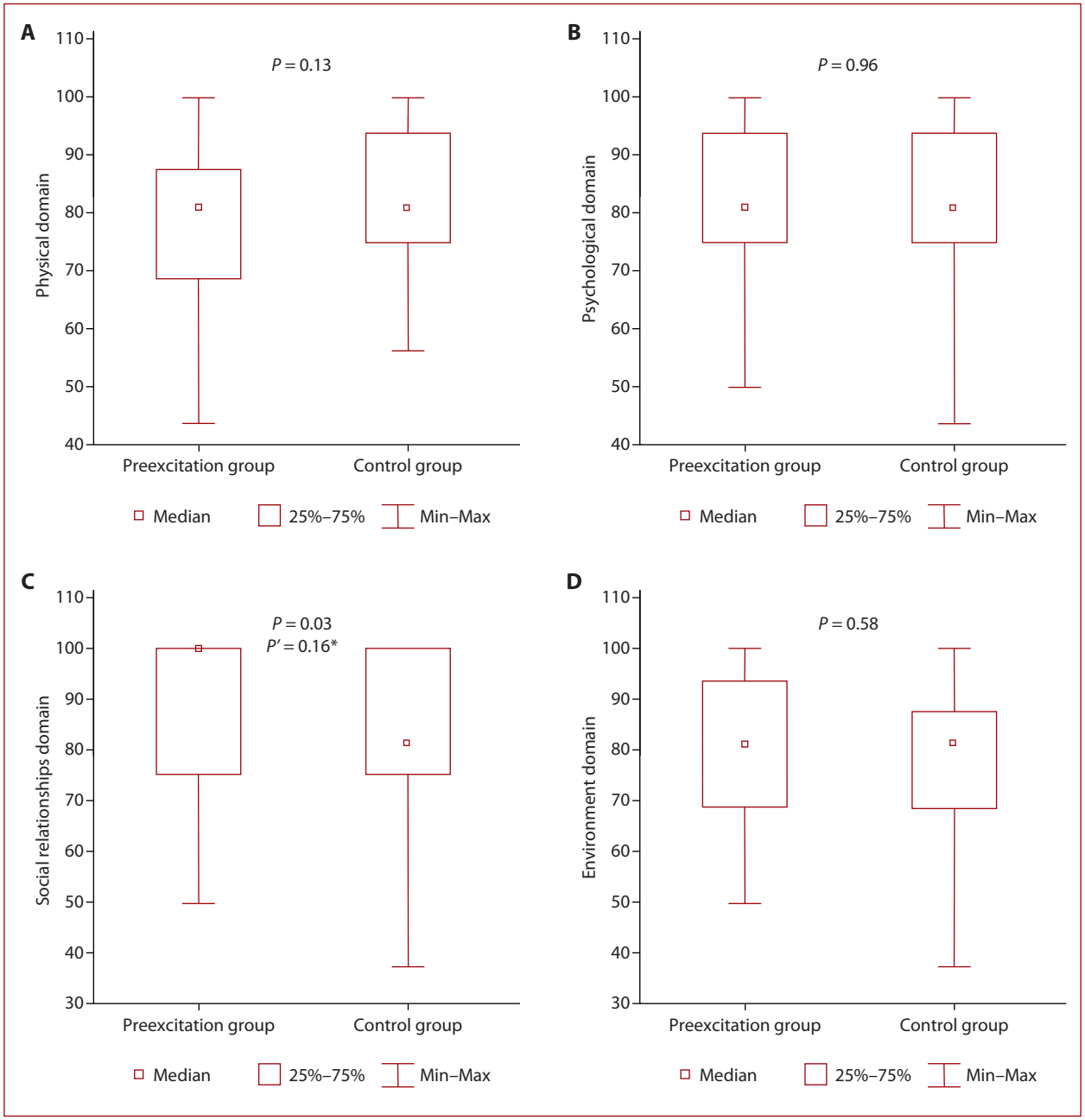

Figure 2. WHOQOL-BREF scores: comparison of the preexcitation and the control groups

**P*-value corrected for sex

the difference was statistically insignificant (Figure 2). There were no significant differences in physical, psychological, and environmental domains (Figure 2). When analyzing each sub-scale of WHOLQOL-BREF, after considering the sex variable in the analysis, a difference was only observed in one sub-scale regarding Phd: dependency on drugs and treatment (P <0.001) (Table 2).

PARS questionnaire

The PARS questionnaire analysis showed no significant differences between the domains (Figure 3), with similar Phd and Psd values for both groups. The analysis of Phd only showed that WPW children more often felt palpitations than the control group and the Psd analysis also showed that the WPW group was more likely to feel nervous compared to the healthy children (Table 3). After adjusting for sex, there was also a significant difference in the response to the question about being sad (Table 3).

Analysis of the WPW group

In the study group, we assessed correlations between the scores obtained in the PARS questionnaire and the WHO: higher QoL regarding Phd and Psd of the PARS relates to the higher evaluation of the QoL in similar domains of WHOQOL. There was a correlation between Phd of the PARS questionnaire and Phd of the WHOQOL-BREF assessment

Table 2. Sub-scales of WHQOL-BREF assessment: comparison of the preexcitation and healthy groups

Sub-scales	Preexcitation group	Healthy children	*P*-value	*P*-value corrected for sex
	Median (Q1–Q3)	Median (Q1–Q3)		
Physical domain				
Pain and discomfort	5.0 (4.0–5.0)	5.0 (3.0–5.0)	0.22	0.35
Dependency on drugs and treatment	5.0 (3.0–5.0)	5.0 (5.0–5.0)	**<0.001**	**<0.001**
Mobility	4.0 (3.0–5.0)	4.0 (4.0–5.0)	0.14	0.05
Work capacity	4.0 (3.0–5.0)	4.0 (4.0–5.0)	0.32	0.29
Energy and fatigue	5.0 (4.0–5.0)	4.0 (4.0–5.0)	**0.049**	0.16
Activities of daily living	4.0 (4.0–5.0)	4.0 (4.0–5.0)	0.66	0.77
Sleep and rest	4.0 (3.0–5.0)	4.0 (4.0–5.0)	0.56	0.96
Psychological domain				
Self-esteem	5.0 (4.0–5.0)	4.0 (4.0–5.0)	0.59	0.84
Negative feelings	4.0 (3.0–5.0)	4.0 (4.0–5.0)	0.99	0.58
Thinking, learning, memory, concentration	4.0 (4.0–4.0)	4.0 (4.0–5.0)	0.20	0.21
Positive feelings	4.0 (4.0–5.0)	4.0 (4.0–5.0)	0.40	0.30
Bodily image and appearance	5.0 (4.0–5.0)	5.0 (4.0–5.0)	0.66	0.92
Meaning of life	5.0 (4.0–5.0)	5.0 (4.0–5.0)	0.44	0.48
Social relationships domain				
Personal relationships	5.0 (4.0–5.0)	4.0 (4.0–5.0)	**0.008**	0.07
Social support	5.0 (4.0–5.0)	4.0 (4.0–5.0)	0.19	0.31
Environment domain				
Financial resources	4.0 (3.0–5.0)	4.0 (3.0–5.0)	0.46	0.88
Freedom, physical safety, and security	5.0 (4.0–5.0)	5.0 (4.0–5.0)	0.88	0.93
Health and social care	4.0 (3.0–5.0)	3.0 (3.0–4.0)	0.08	0.13
Home environment	5.0 (4.0–5.0)	5.0 (4.0–5.0)	0.57	0.87
Opportunities for acquiring new information and skills	5.0 (4.0–5.0)	5.0 (4.0–5.0)	0.55	0.40
Opportunities for recreation/leisure activities	5.0 (4.0–5.0)	5.0 (4.0–5.0)	0.78	0.78
Physical environment (pollution/noise/traffic/climate)	4.0 (3.0–5.0)	4.0 (4.0–5.0)	0.80	0.41
Transport	4.0 (3.0–5.0)	4.0 (3.0–4.0)	0.87	0.99

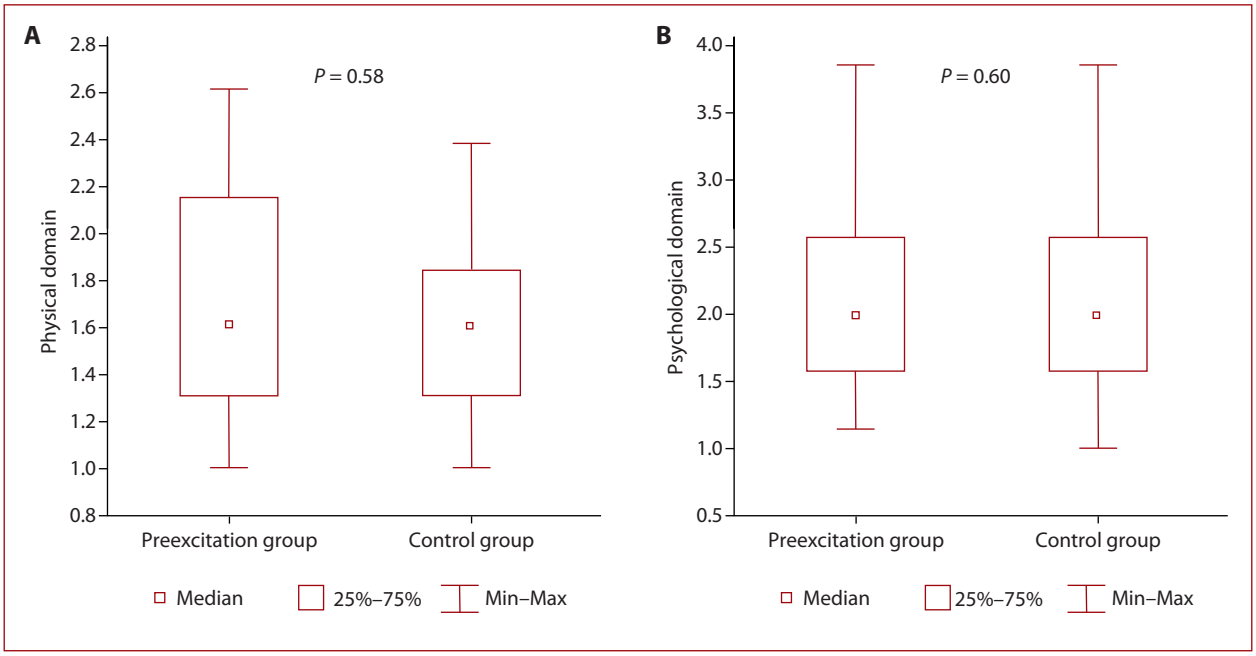

Figure 3. PARS scores: comparison of the preexcitation group and healthy children

(Rs= –0.37; *P* = 0.04). Similarly, there was a correlation between Psd of the PARS questionnaire and Psd of the WHOQOL-BREF assessment (Rs= –0.61; *P* <0.001).

DISCUSSION

Good physical functioning does not always correspond with psychological well-being or health perception, particularly among patients with cardiovascular disorders who are very concerned about their heart condition. Indeed, patients with cardiac conditions may suffer from depression and anxiety, thus requiring psychotherapeutic help [19–21].

This study evaluated QoL in asymptomatic children with WPW and demonstrated that the general QoL of asymptomatic WPW patients is similar to that of healthy children.

Table 3. PARS questions and scores: comparison of WPW and healthy children

Questions	Preexcitation group	Healthy children	*P*-value	*P*-value corrected for sex
	Median (Q1–Q3)	Median (Q1–Q3)		
Physical domain				
1. Do you have dyspnea?	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.23	0.05
2. Do you have palpitations?	2.0 (1.0–3.0)	1.0 (1.0–1.0)	**<0.001**	**<0.001**
3. Do you have pain behind your breastbone?	1.0 (1.0–2.0)	1.0 (1.0–1.0)	0.32	0.28
4. Do you ever faint?	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.97	0.93
5. Do you seem to pass urine more frequently than usual?	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.06	0.06
6. Do you ever have blurred vision? (e.g. scotoma)	1.0 (1.0–2.0)	2.0 (1.0–3.0)	0.27	0.30
7. Do you think you are paler than your friends or do you happen to become pale suddenly?	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.65	0.52
8. Do you experience situations in which you sweat more than your friends?	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.25	0.35
9. Do you ever feel nauseous?	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.60	0.86
10. Do you have headaches?	2.0 (1.0–3.0)	3.0 (2.0–3.0)	0.09	0.13
11. Do you have stomach aches?	2.0 (1.0–3.0)	3.0 (2.0–3.0)	0.08	0.12
12. Do you sometimes feel suddenly cold without a reason?	1.0 (1.0–3.0)	1.0 (1.0–2.0)	0.36	0.08
13. Do you think you are weaker than your peers?	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.96	0.96
Psychological domain				
1. Do you often cry?	1.0 (1.0–3.0)	2.0 (1.0–2.0)	0.78	0.41
2. Is it easy to make you cry?	2.0 (1.0–4.0)	2.0 (1.0–3.0)	0.27	0.09
3. Do you think you are more nervous than your peers?	2.0 (2.0–3.0)	2.0 (1.0–2.0)	**0.04**	**0.049**
4. Do you think you are sadder than your peers?	2.0 (1.0–3.0)	1.0 (1.0–2.0)	0.19	**0.046**
5. Do you think you are happier than your peers?	3.0 (2.0–4.0)	3.0 (2.0–4.0)	0.66	0.96
6. Do you think you are lonelier than your peers?	1.0 (1.0-2.0)	1.0 (1.0–2.0)	0.66	0.86
7. Can you count on your friends?	5.0 (4.0-5.0)	5.0 (4.0–5.0)	0.96	0.82

However, the healthy children reported significantly greater contentment regarding their general satisfaction with their health condition. Both physical and psychological parameters of the QoL were similar in both groups but some areas of physical and psychological parameters of QoL were lower in WPW children. Analyzing each question individually indicated that WPW children felt generally more dependent on treatment; they felt palpitations more often and were more likely to feel sad and nervous compared to healthy children. Although the patients were classified as asymptomatic, some of them reported palpitations based on the PARS questionnaire; this may be explained by the stress related to the diagnosis and their awareness of the resulting risks. The relationship between the described symptoms and arrhythmia was not confirmed in electrocardiographic tests for any of the patients with palpitations. Moreover, when asked about the symptoms, they denied that they were typical, (i.e., abrupt onset and end) and that they were not accompanied by other symptoms suggestive of arrhythmia.

Patients with SVT experience many negative feelings [21, 22], and the limitations resulting from the disease significantly lower the QoL of SVT children. The obligation to take medications as well as arrhythmia symptoms may have an additional negative impact on their QoL and emotional development [11, 23]. Yet, there are insufficient data related to QoL in asymptomatic WPW, so it is important to assess how the limitations related to WPW diagnosis affect the patient's physical, emotional, and social well-being. To our knowledge, this is the first study assessing the QoL in children with asymptomatic WPW.

We believe that asymptomatic WPW can also be challenging, especially in young, active people who want to develop their interests without limitations. One of the limitations resulting from WPW diagnosis is avoidance of physical activity, especially competitive sports [24–27]. For young people, it is often a very significant limitation of their passions, interests, and life goals, which brings about the feeling of being different from their peer group. That perception is reinforced because WPW patients must be supervised and monitored, have regular check-ups, and be aware of unpredictable tachycardia episodes [24, 28, 29]. These issues may also cause QoL deterioration. Moreover, the "heart condition" diagnosis may contribute to the patient's lower QoL, and affect their sense of security or cause fear, as evidenced in our study. Our participants felt more dependent on treatment and more inclined to feel sad and nervous in comparison with healthy children.

For adult competitive/professional athletes with asymptomatic preexcitation, an EPS is recommended to evaluate the risk of SCD [5, 30]. It should be noted that in pediatric patients below 12 years, the risk of SCD is very low, therefore, a conservative approach is recommended [30]. Despite this, prophylactic ablation is advocated by some authors as it reduces the risk of sudden death [31]. According to the 2020 European Society of Cardiology guidelines on sports cardiology and exercise in patients with cardiovascular diseases, it should be emphasized that our knowledge on this subject is still insufficient [30]. Parents and children should be provided with comprehensive information about the risks and potential benefits of ablation treatment versus observation and be informed about related risks of this procedure [24, 32]. Competitive athletes with low-risk pathways identified during EPS not undergoing ablation therapy should be monitored for the

development of new symptoms [24], and the PARS may be a helpful tool to show the real clinical disease status and detect symptomatic patients.

In the previous studies [11, 15, 16], we noticed that the PARS can be particularly useful in everyday clinical practice to detect QoL deterioration, which can be difficult to observe during routine check-ups. It is also useful in deciding about EPS and ablation treatment in non-obvious cases (medical and psychological reasons). The necessity to limit sports activity and the related consequences for QoL may be important factors affecting qualification for ablation in young athletes with WPW. Joint decisions with the athletes are encouraged by the 2020 European Society of Cardiology guidelines on sports cardiology and exercise in patients with cardiovascular diseases, which emphasize the importance of respecting "the autonomy of the individual after provision of detailed information about the impact of sports and the potential risks of complications and/or adverse events" [30].

The influence of arrhythmia and its treatment on QoL is still an underestimated issue in the clinical approach. The published studies on pediatric and adult patients with arrhythmia showed the positive effects of ablation on QoL [12–15, 33]. It is known that arrhythmia, apart from worsening QoL, can also lead to heart failure and cardiomyopathy, which is why successful arrhythmia control is so important. Gardziejczyk et al. [33] show that successful catheter ablation significantly improves clinical status, left ventricular ejection fraction, and health-related QoL of patients with structural heart disease and arrhythmia-mediated cardiomyopathy. We suppose that further analysis needs to be performed to demonstrate long-term consequences of ablation therapy on QoL parameters and also in children with asymptomatic preexcitation patterns on ECG.

QoL evaluation is an important element in current clinical practice as some individuals feel ill and do not function well despite no changes in their body tissues. The Constitution of the World Health Organization defines health "as a state of complete physical, mental, and social wellbeing" [34]. QoL refers to "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns" [35]. Thus, QoL assessment should be a key element in assessing the patient's health condition and making further clinical decisions, including those concerning diagnosis and treatment.

Study limitations

We acknowledge the following limitations of the performed study.

The study group was limited to 31 patients. The small group size was related to the fact that the majority of patients admitted to the Department of Pediatric Cardiology with signs of ventricular preexcitation on ECG recordings, without electrocardiographically confirmed episodes of tachycardia, reported symptoms that could indicate arrhythmia. Therefore, they were excluded from participation in the study. Despite the small group size, this is still the only available study that examines in detail the QoL of children with asymptomatic preexcitation.

The control group and the study group were not homogeneous and differed in terms of sex, which is a limitation of the study. The control group consisted of volunteers. Since sex could be a factor confounding the results of univariate analyses, a logistic regression model was developed to verify the conclusions obtained in preliminary analyses. In this way, we sought to eliminate possible distortions that might arise from differences in the numbers of boys and girls in individual groups.

Although the children in the study group were not on medication and had not been hospitalized for cardiac reasons by the time of completing the questionnaire, they were compared with healthy children in terms of "dependency on drugs and treatment". We believe that this question, which is part of the WHOQOL-BREF questionnaire, allows for assessment of whether the mere diagnosis of ventricular preexcitation features, despite the absence of treatment at the time of completing the questionnaire, may give patients a sense of being limited by a scheduled future treatment (e.g., having an ablation procedure and its effects on their normal physical activity, including sports).

CONCLUSION

In conclusion, general satisfaction with their health condition in WPW children was significantly worse in comparison with healthy children. Although both groups of children were generally satisfied with their QoL, some physical and psychological parameters of QoL were worse in WPW children. The PARS questionnaire is a useful disease-specific QoL instrument that supplements the general questionnaire and helps in clinical practice and decision-making.

Article information

Conflict of interest: None declared.

Funding: None.

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Coronary Artery Ectasia Database — Poland (CARED-POL). The rationale and design of the multicenter nationwide registry

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DOI: 10.33963/v.kp.98261

Received:
October 9, 2023

Accepted:
November 18, 2023

Early publication date:
December 15, 2023

INTRODUCTION

Coronary artery aneurysm or ectasia (CAAE) are a rare vascular pathology diagnosed in 0.15%–5.3% of patients undergoing coronary angiography [1]. According to the anatomy of the expanded segment, CAAE was considered a coronary artery aneurysm (CAA) or coronary artery ectasia (CAE). Giant CAAE is an even less common phenomenon observed in only 0.02% of patients after coronary angiography and usually defined as a 4-fold enlargement of the vessel diameter [1]. CAAEs are often diagnosed incidentally, while symptomatic patients experience various complications of unstable angina, acute myocardial infarction (MI), arrhythmias, or sudden cardiac death. Major adverse cardiovascular events (MACE) occur in up to 10% of CAAE patients per year [2]. MI can be caused by in-aneurysm thrombosis with artery closure or distal embolization [3–5]. As has been shown, CAAE diagnosis is associated both with increased MI incidence and risk of MI recurrence [6]. The most common etiology of CAAE is atherosclerosis, followed by Kawasaki disease or other vasculitis histories, infectious septic emboli, and connective tissue disease. Iatrogenic causes are less common [7]. Although some pathophysiological and clinical risk factors for CAAE development have been identified, detailed pathomechanisms have not yet been known [8–10]. Moreover, so far, the data on Polish patients are limited to case reports, case series, and small groups from major academic centers [8–13]. CAAEs are not analyzed in the main nationwide registers of invasive procedures either [14].

AIM OF THE REGISTRY

The primary purpose of the Coronary Artery Ectasia Database — Poland (CARED-POL) Registry is to comprehensively investigate the current prevalence, morphological characteristics, risk factors for the development and complications of CAAE as well as long-term prognosis in the Polish population.

MATERIAL AND METHODS

Study population

CARED-POL is a multicenter observational nationwide registry of CAAE conducted in cooperation with the Scientific Platform of the Polish Society of Cardiology (NCT06057987). Patients aged >18 years old will be prospectively enrolled, and after giving informed consent, they will be included ambispectively based on angiographic diagnosis of CAA or CAE. CAA is defined as a focal dilatation with a diameter of more than or equal to 1.5 times the adjacent normal coronary segment, while CAE is an analogous lesion but more diffuse, exceeding more than a third of the coronary artery length. CAAs are then classified as either saccular aneurysms (asymmetric outpouchings, transverse diameter exceeds longitudinal diameter) or fusiform aneurysms (circumferential dilations, longitudinal

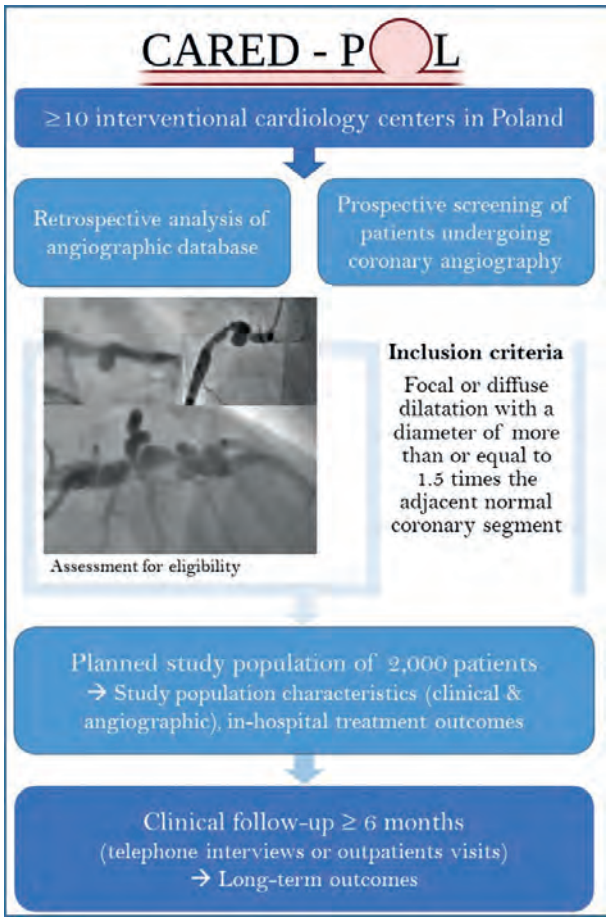

Figure 1. Flowchart of the study design

diameter exceeds transverse diameter). A giant CAAE is diagnosed when the diameter of the artery exceeds 4-fold the diameter of the reference vessel.

Each participating center will enroll patients retrospectively from their internal databases after evaluation of all consecutive coronary angiographies by an experienced interventional cardiologist using quantitative coronary angiography (QCA) [12], but also prospectively for 6 months from joining the CARED-POL Registry. The patient data will be collected from standardized and anonymous forms *via* the Scientific Platform of the Polish Society of Cardiology. We expect that 2000 patients in all participating centers will be included. The study design is summarized in Figure 1.

The study will be conducted in accordance with the Declaration of Helsinki. Ethical approval was granted by the local Bioethics Committee of the Poznan University of Medical Sciences (approval number 687/23).

Data collection and endpoints

The CARED-POL Registry will involve clinical data, angiographic quantitative evaluation of aneurysms, their intracoronary imaging, treatment methods, periprocedural complications in patients undergoing revascularization or invasive aneurysm treatment, and MACE during the in-hospital period. A minimum of 6-month follow-up *via* outpatient visits, medical records, or telephone interviews will be assessed. The primary study endpoints will be all-cause death, re-hospitalization for unstable angina, and MI. The secondary endpoints will be heart failure, bleeding, stroke, embolic events, and any cause for repeat coronary angiography.

The development of a new aneurysm or progression of an existing one will be assessed in patients who underwent repeat coronary angiography. Aneurysm progression is diagnosed as an increase in size demonstrated by at least two orthogonal angiographic views.

Statistical analysis

A standard descriptive statistic will be used in the analysis. Depending on the normal distribution, continuous data will be compared with the t-test or the Mann–Whitney test. Categorical variables will be compared with the χ^2 test. A logistic regression analysis will assess determinants of CAAE occurrence and progression. The Kaplan–Meier method will present the event rates at follow-up. Moreover, a Cox proportional regression model will be used to determine the influence of clinical and angiographic variables on clinical outcomes. The observation period will include the time from the CAAE diagnosis to the end of the study (censored observation). All statistical analyses will be conducted with PQStat Software (PQStat v.1.8.0.476, Poland).

EXPECTED BENEFITS AND DISCUSSION

Data obtained from the CARED-POL Registry will enable the selection of morphological risk factors for the unfavorable course of CAAE, including the development and progression of giant aneurysms, aneurysm clotting with vessel occlusion, and thromboembolic complications. Independent predictors of CAAE progression and complications in long-term follow-up will be determined using artificial intelligence algorithms. In turn, comparing the safety and effectiveness of available CAAE treatment methods in individual patient subgroups will allow individualization of treatment, including anticoagulant therapy. The analyses will be performed for the overall study population and in subgroups of patients with giant CAAEs, isolated CAAEs of the left main coronary artery, a positive family history of CAAEs, other associated coronary artery anomalies, and aneurysms in other locations [15].

Current data on the prevalence and predictors of CAAE development, as well as population characteristics and risk factors for complications, are limited. So far, the largest CAAE registry focused on the clinical and angiographic characteristics of the CAAE population is the Coronary Artery Aneurysm Registry (CAAR) (NCT02563626), which ultimately included 1565 patients, mainly from Spanish and Italian centers [2]. The established incidence of CAAE in the CAAR Registry was estimated at 0.35%. The worse prognosis in this group of patients compared to those without CAAE has been confirmed, including the incidence of thromboembolic complications of the aneurysm, requiring proper anticoagulant therapy [2]. It is noteworthy

that recently a Jordanian Coronary Artery Ectasia Registry (JoCAER) has been initiated with objectives similar to the CAAR Registry (NCT05213429).

Article information

Conflict of interest: None declared.

Funding: None.

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Aggressive lipid-lowering treatment in Managed Care after Acute Myocardial Infarction (MC-AMI) patients: Results better but still not satisfactory. A single-center prospective analysis

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DOI: 10.33963/v.kp.98143

Received:
September 26, 2023

Accepted:
November 6, 2023

Early publication date:
November 29, 2023

INTRODUCTION

Managed Care in Acute Myocardial Infarction (MC-AMI) is a program aimed at comprehensive, scheduled, and supervised care for patients with AMI to improve their long-term prognosis [1]. The high risk of cardiovascular complications within the first months after MI is attributable to several factors including incomplete revascularization, insufficient utilization of implantable devices, poor access to cardiac rehabilitation, and inadequate control of cardiovascular risk factors due to lack of scheduled outpatient cardiology care [2, 3]. Despite ESC recommendations for secondary cardiovascular disease prevention, the real-world data show that there is still much to do with regard to post-MI care and coordination of all the key elements of post-MI care [4, 5]. The novelty of the MC-AMI approach is execution of all the guideline-recommended therapeutic interventions, which are normally available within the healthcare system, but hardly followed accurately.

It has already been demonstrated that participation in MC-AMI improves short-term [6] and long-term prognosis [7–9]. However, contribution of particular MC-AMI components in the final effect is still being evaluated.

A reduction of low-density lipoprotein cholesterol (LDL-C) is a crucial intervention in both primary and secondary prevention of cardiovascular events [10]. The 2021 ESC guidelines recommend a stepwise approach in patients with established atherosclerotic cardiovascular disease with an LDL-C goal of <70 mg/dl in the first and <55 mg/dl in the second step [11].

This prospective study aimed to assess the effect of scheduled, 2-step, aggressive lipid-lowering therapy in patients after myocardial infarction participating in MC-AMI.

METHODS

This was a prospective analysis from a single, high-volume, tertiary cardiology care center (Upper Silesian Medical Center, Medical University of Silesia in Katowice, Poland). The study group consisted of 160 consecutive subjects diagnosed with AMI from January to June 2023 who were qualified for ambulatory cardiac rehabilitation in our center and consented to participate in MC-AMI. A detailed description of the MC-AMI program is available in our previous reports [6–9].

Lipid profiles, including total cholesterol, LDL-C, high-density lipoprotein cholesterol, and triglycerides were assessed during MI hospitalization. In all patients, high-intensity statin (atorvastatin 40–80 mg, rosuvastatin 20–40 mg) was introduced at index hospitalization unless contraindicated or the LDL goal was already reached. During the 6-week cardiac rehabilitation program, patients received additional dietary and lifestyle modification counseling. The lipid profiles were reassessed at 6 and 12 weeks with respective interventions (continuation, intensification, or de-escalation of therapy).

The study protocol was approved by the Ethics Committee of the Medical University of Silesia in Katowice.

Baseline characteristics

Age (years) median (Q1-Q3)	65.5 (57-71)
Sex (Female) n (%)	39 (24.4%)
History of CHD n (%)	67 (41.9%)
Hypertension n (%)	121 (75.6%)
Diabetes n (%)	39 (24.4%)
Hiperlipidaemia n (%)	79 (49.4%)
CKD (GFR<60ml/min/1.73) n (%)	8 (5%)
GFR (ml/min/1.73) median (Q1-Q3)	86 (71-95)
Current smoker n (%)	69 (43.1%)
History of MI n (%)	50 (31.3%)
History of PCI n (%)	49 (30.6%)
History of CABG n (%)	13 (8.1%)
LVEF (%) median (Q1-Q3)	50 (40-55)

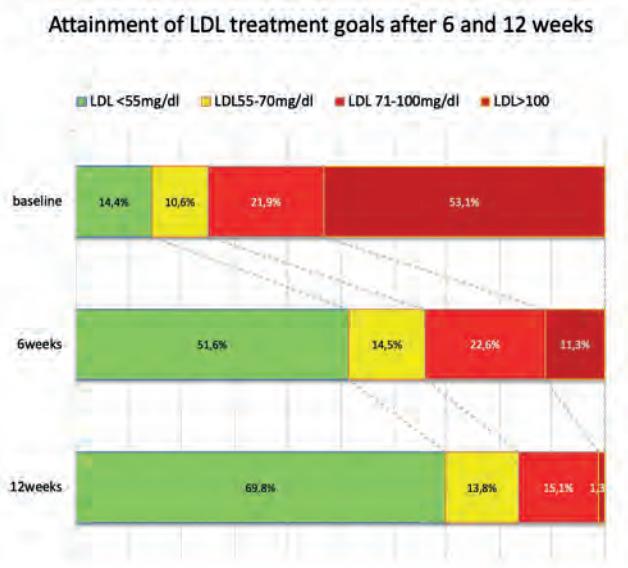

Figure 1. Baseline characteristics and attainment of LDL-C goals in 12-week observation. Baseline characteristics (left panel) and attainment of LDL-C goals at 6 and 12 weeks after myocardial infarction (right panel)
Values expressed as median (Q1–Q3) or n (%)

Abbreviations: CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHD, coronary heart disease; CKD, chronic kidney disease; LDL, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention

Statistical analysis

Statistical analysis was performed with Statistica (StatSoft, Poland). Quantitative variables were specified as medians and interquartile ranges, whereas qualitative parameters were expressed as numbers and percentages. We used the Shapiro–Wilk test to check if continuous variables followed a normal distribution. The Friedman test along with the Nemenyi *post-hoc* test were used to compare dependent variables of non-normal distribution. Cochran's Q test was used for testing differences between frequencies.

A *P*-value of less than 0.05 was regarded as statistically significant.

RESULTS AND DISCUSSION

The baseline characteristics of the studied groups are shown in Figure 1.

Patients were treated with atorvastatin (n = 85; 53%) and rosuvastatin (n = 75; 47%). High-intensity statin was introduced at the baseline in 89% of patients, and 32 patients (20%) received ezetimibe at index hospitalization.

Median baseline LDL-C was 102 mg/dl (68–135 mg/dl). It was reduced to 55 mg/dl (41–80 mg/dl) after 6 weeks and remained at 54 mg/dl (41–62 mg/dl) at 12 weeks (P <0.001). At 6 weeks the statin therapy was intensified in 32% of subjects, continued in 61%, and deescalated in 7%. Ezetimibe was introduced in further 30 patients (38.8% of all subjects starting week 6).

At 12 weeks, almost 70% of subjects reached the LDL-C <55 mg/dl goal with only 2 patients (1.3%) not reaching the LDL-C goal <100 mg/dl. In 87% the therapy was continued, in 4% — further intensification was required, and in 9% the treatment was de-escalated (Figure 1).

High-density lipoprotein cholesterol remained similar over the observation time. Triglyceride levels improved from 117 mg/dl (88.5–165.5 mg/dl) baseline to 93 mg/dl (82–120 mg/dl) at 12 weeks, P <0.001.

The results in this prospective study show much better LDL-C control in post-AMI patients when the intervention and the goals are clearly defined, and the emphasis is put on executing the recommendations. Surprisingly, despite similar baseline LDL-C levels and similar characteristics of the study group, the effects of reaching LDL-C goals in our prospective study were much better than in the recent MC-AMI multicenter retrospective analysis, where only 20% of subjects attained LDL-C <55 mg/dl goal [12]. Similar data come from the POLASPIRE study [13] and the DA VINCI study [14]. Although our study was performed in a selected population of AMI patients (a higher proportion of more motivated patients willing to participate in the ambulatory cardiac rehabilitation program), our results show that better LDL-C control in secondary prevention is feasible. On the other hand, the results point out that despite all the efforts made and with the use of available treatment options, there are still 30% of patients who do not reach the LDL-C goal. This fact highlights the need for broader availability and applicability of PCSK9 inhibitors in secondary prevention, which currently are available only if LDL-C remains >100 mg/dl. In our cohort, this would only apply to 1.3% of patients leaving 29% without further options.

Article information

Conflict of interest: None declared.

Funding: None.

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Optimal hospital discharge time after cardiac implantable electronic device implantation: A retrospective study from a tertiary electrotherapy center

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DOI: 10.33963/v.kp.97210

Received:
May 11, 2023

Accepted:
August 28, 2023

Early publication date:
September 15, 2023

INTRODUCTION

Despite many publications on early complications of cardiac implantable electronic device (CIED) implantations, there are no specific recommendations on the suggested discharge time after such procedures. This retrospective pilot observation aimed to evaluate the occurrence of early complications following CIED implantations, which could inform optimal post-procedural patient management and timing of discharge.

METHODS

This retrospective study included patients who underwent a cardiac implantable electronic device (CIED) implantation procedure, with at least one lead implanted, between January 1, 2021 and December 31, 2021. Explantation procedures were also included if they were immediately followed by a reimplantation. Patients who underwent only explantation and those who had pulse generator replacement were excluded from the study. All CIED implantations were performed in the Department of Cardiology and Electrotherapy, Medical University of Gdańsk. The standard policy in our center was to discharge patients two days after the lead implantation, with a routine chest X-ray on the first day after the procedure. After discharge from the hospital, patients were then routinely invited for the first check-up approximately 3 months after CIED implantation. In exceptional situations (patients after lead reposition due to dislodgment, pocket hematoma not eligible for intervention, suboptimal lead parameters), patients were asked to report to the clinic on the 7th day after the procedure to remove the sutures and to check CIED parameters. The demographic data, the type of procedure, comorbidities, laboratory test results, and pharmacological treatment were obtained from patients' electronic medical records available in the hospital's database and then precisely analyzed. Data on frequently occurring comorbidities (chronic heart failure [CHF], atrial fibrillation, hypertension, coronary artery disease [CAD], type 2 diabetes mellitus, stroke or transient ischemic attack, chronic kidney disease, and active cancer) were extracted from the discharge summary at the time of the implantation procedure. Detection of a complication related to CIED implantation within the first 30 days after the procedure was qualified as the endpoint.

Statistical analysis

For all comparisons and calculations, a *P*-value of less than 0.05 was assumed as statistically significant. Numerical variables were expressed as means (SD) if normally distributed or as medians (interquartile range [IQR]). In the case of continuous variables, normal distribution was tested using the one-sample Kolmogorov–Smirnov test. Categorical data were expressed as numbers and percentages. Numerical variables were compared using the independent-sample parametric (unpaired Student t) or nonparametric (Mann–Whitney U) tests. Categorical variables were compared using the χ^2 test or Fisher's exact test when appropriate. Correlations between selected quantitative variables were assessed using the Spearman rank correlation test. The

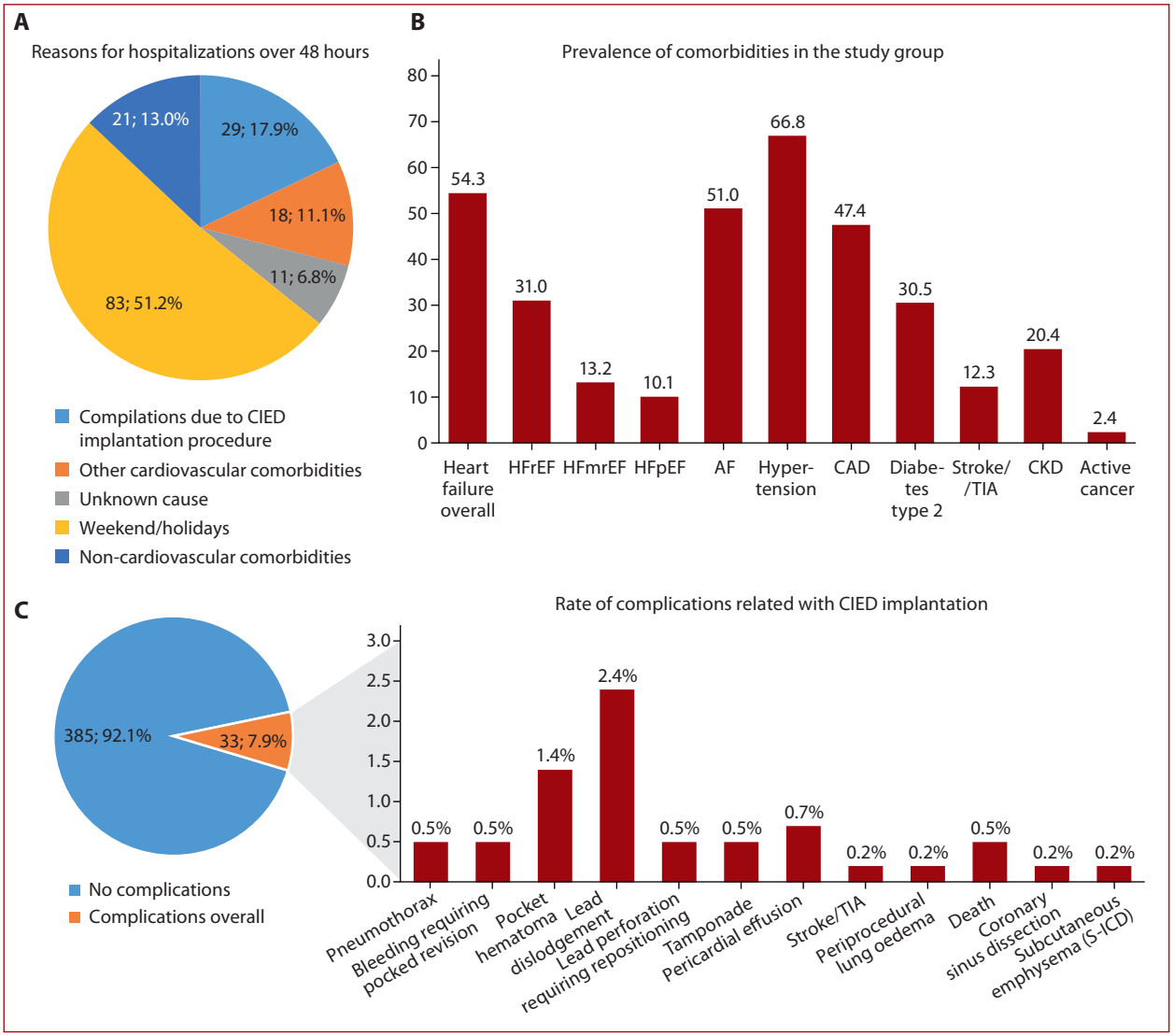

Figure 1. A. Reasons for hospitalizations beyond 48 hours. **B.** Prevalence of comorbidities in the study group. **B.** Rate of complications related to CIED implantation

Abbreviations: AF, atrial fibrillation; CIED, cardiac implantable electronic devices; CAD, coronary artery disease; CKD, chronic kidney disease; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; S-ICD, subcutaneous implantable cardioverter-defibrillator; TIA, transient ischemic attack

ultimate analysis to determine risk factors of complications after CIED procedures was based on logistic regression. The multivariable analysis included variables that had yielded statistical significance defined as a *P*-value of 0.1 or lower, in the univariate analysis. The data were analyzed using Statistica 13 software. The study was approved by the bioethics committee (no. NKBBN/644/2022).

RESULTS AND DISCUSSION

Four hundred sixteen CIED procedures were included in the study, of which 325 (78.1%) were *de novo* CIED implantation procedures. The majority of the study group were men (n = 261, 62.7%) at a mean (SD) age of 70 (14) years. The most common comorbidities in the study group were hypertension, CHF, and CAD (Figure 1B). The median (IQR) hospitalization time was 5 (3–8) days. The median (IQR) time from procedure to hospital discharge was 2 (2–3) days. In 162 cases (38.9%), the time to discharge after the procedure was >2 days. It should be emphasized that 51.2% of these prolonged stays occurred due to weekends/holidays following the lead implantation procedure, and in another 11.1% of cases no clear medical reason explaining prolonged hospitalization could be identified (Figure 1A). The time to discharge was found to increase with higher levels of B-type natriuretic peptide ($P = 0.01$; $r = 0.14$) and lower left ventricular ejection fraction ($P = 0.02$; $r = –0.12$). The descriptive characteristics of the study group are presented in the Supplementary material, *Table S1*.

Complications related to CIED implantation were found in 33 patients (7.9%), with lead dislodgment being the most prevalent (n = 10). Most complications (84.8%) were detected within the first 24 hours after the procedure, and 91.0% were found within the first 48 hours. Complications that occurred beyond 24 hours were pocket hematoma

(n = 3), perforation requiring lead reimplantation — found on the 24th day after the procedure (n = 1), and ischemic stroke observed on the second day after the procedure (n = 1). There was one case of death on the 3rd day after the procedure due to aspiration at the time of the procedure and the resulting complicated aspiration pneumonia (Figure 1C).

Patients who experienced CIED-related complications were more likely to have been previously diagnosed with CHF ($P = 0.03$) and CAD ($P = 0.02$). Patients with complications observed later than 24 hours after procedures were characterized by a significantly higher median (IQR) age-adjusted Charlson comorbidity index (7 [6–8] vs. 5 [3–6] points, $P = 0.03$) and were significantly more often treated with vitamin K antagonists (VKA) (2 ([15.4%] vs. 3 [11.5%]; $P = 0.04$). A univariate analysis proved that CAD (odds ratio [OR], 2.38; 95% CI, 1.12–5.04; $P = 0.02$) and CHF (OR, 2.41; 95% CI, 1.09–5.33; $P = 0.03$) were associated with a higher risk of complications, whereas regarding C-reactive protein concentration, a tendency toward a higher risk of complications was observed (OR, 0.96; 95% CI, 0.016–0.99; $P = 0.09$). Multivariable analysis identified CAD as the only independent predictor of the subsequent complications (OR, 2.26; 95% CI, 1.06–4.79; $P = 0.03$).

Based on the literature data, it is known that most very early complications following CIED procedures occur within the first 6 hours after the procedure, which makes discharge from the hospital on the day of the procedure safe and preferred by patients [1–3]. Some authors go a step further, proposing discharge after transvenous lead extraction performed for non-infectious reasons on the same day [4]. In contrast, Ohlow et al. [5] state that 100% of potentially life-threatening acute complications occur during the first 72 hours. These data are consistent with those obtained in our study, where, excluding a case of perforation requiring lead replacement detected only 24 days after the procedure, 100% of the complications were found within the first 72 hours after the procedure. Other authors also emphasize that lead dislodgements occur during the first few days of implantation but are not limited to the first 24 hours [6]. However, the E-MOTION trial confirmed that early mobilization at 3 hours following CIED procedures is safe and feasible compared with standard immobilization and is not associated with increased risk of periprocedural complications or the 24-month lead dislodgment rate [7]. Significant differences in the duration of hospitalization of patients after CIED implantation are observed not only between individual centers but also between countries — the median length of stay after pacemaker implantation in Japan and in the US was 8 (7–11) and 1 (1–3) days, respectively [8]. Finally, it seems that the decision on early discharge following CIED procedures should still be individualized, and extended stay should apply to patients with pacemaker dependency, especially after lead implantation/extraction or pocket revision, patients with increased risk of bleeding or thrombosis/thromboembolism, patients with hemodynamic instability, patients with comorbidities requiring continued observation and other risk factors for complications [6]. Based on the data in our study, patients with multiple comorbidities, patients treated with VKA, and those with CAD require longer observation.

The financial aspect is also significant. The strategy of early discharge on the first day after the procedure with no exceptions for weekends or holidays could potentially save 150 euros per patient/day. Moreover, such an approach would allow shorter waiting times for patients awaiting elective CIED implantation.

In connection with the obtained results, an echocardiogram aimed at assessing the pericardium is performed in patients after CIED implantation to detect fluid in the pericardium before discharge from the hospital.

CONCLUSIONS

The complication rate after CIED procedures is low but not negligible, with complications occurring mainly on the first day after the procedure. Considering the growing costs of hospitalization and prolonged waiting time for elective electrotherapy procedures, it seems safe and justified to discharge selected patients without risk factors for subsequent complications on the first day after CIED implantation. Early follow-up appointments at the hospital outpatient center and remote monitoring could facilitate detection of rare delayed complications, such as pocket hematomas or lead dislodgment/heart perforation.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: None declared.

Funding: None.

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New-onset acute heart failure: Clinical profile and one-year outcomes. Observations from the OP-AHF Registry

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DOI: 10.33963/v.kp.98444

Received:
July 6, 2023

Accepted:
December 7, 2023

Early publication date:
December 21, 2023

INTRODUCTION

Acute heart failure (AHF) can either be a first-time occurrence, referred to as new-onset (NO-AHF) or a deterioration of pre-existing heart failure (HF), known as acutely decompensated HF (ADHF) [1, 2]. AHF is responsible for the majority of unplanned hospital admissions among patients admitted to the Cardiology Department at the University Hospital in Opole [3]. Although they share certain characteristics, the two types of AHF differ in their pathophysiology, causes, and disease progression [2, 4]. NO-AHF is often caused by a sudden event or underlying cardiovascular disease that may have been asymptomatic. In contrast, ADHF is a pre-existing heart condition that worsens due to factors such as inflammation, arrhythmia, ischemia, non-optimal medical treatment, or lack of patients' adherence to prescribed therapy [2].

The purpose of the study was to compare the clinical characteristics of patients with NO-AHF and ADHF and evaluate 12-month prognosis in both groups.

METHODS

As part of the prospective Opole Registry of Acute Heart Failure (OP-AHF), data from 122 patients hospitalized in the Intensive Cardiac Care Unit between May 2019 and January 2021 were prospectively recorded. The inclusion criteria were hospitalization for AHF and the use of at least one of the following: intravenous diuretics, pressor amines, and/or mechanical circulatory support. The only exclusion criterion was lack of patient consent.

From the analyzed population, two groups were selected: patients with a history of HF admitted to the hospital due to worsening heart failure (66 [54%]) — ADHF, and patients without underlying chronic heart failure, admitted because of the first episode of AHF (56 [46%]) — NO-AHF. Of these 122 patients, 25 had acute coronary syndrome (ACS) diagnosed as the cause of AHF and were excluded from further analyses. Finally, the NO-AHF group comprised 39 and the ADHF group 58 patients. The registry data covered the in-hospital period and 12-month follow-up after discharge available for all patients. All information about deaths was obtained from hospital reports or, in the case of deaths outside the hospital, from the patients' families by telephone contact. The study was conducted in accordance with the Declaration of Helsinki and accepted by the Ethics Committee of the University of Opole.

Statistical analysis

Categorical variables were presented as percentages while continuous variables as mean values with standard deviation or medians with interquartile ranges based on data distribution and compared using the chi-square test with Yates's correction when necessary, and Student's t-test (for independent or dependent groups as appropriate) or Mann-Whitney U-test, respectively. Unadjusted and adjusted event-free survival was presented using Kaplan-Meier survival curves. Adjusted survival was calculated using the inverse probability weight method. Inverse probability weighting relies on building a logistic regression model to estimate the probability of exposure for a particular person and using the predicted probability as a weight in subsequent analyses. A *P*-value of less than 0.05 was considered significant.

All presented statistical analyses were performed using R software v.4.2.2 (the R Foundation for Statistical Computing, Vienna, Austria).

RESULTS AND DISCUSSION

After excluding ACS patients, there were 39 (40%) NO-AHF patients and 58 (60%) ADHF patients. Detailed characteristics of the analyzed groups are presented in Supplementary material, *Table S1*. Both groups were dominated by men; however, NO-AHF patients were younger. ADHF patients had statistically more often coexisting hypertension, chronic kidney disease, atrial fibrillation, and hypercholesterolemia, as well as past myocardial infarction and pre-hospitalization coronary revascularization or surgical intervention (CABG), which is similar to results shown in several meta-analyses [5, 6]. The dominant causes of AHF in NO-AHF patients were inflammation (28%), valvular diseases (15%), and tachyarrhythmia (13%), while in ADHF patients these were: coronary heart disease (41%), valvular diseases (21%), dilated cardiomyopathy (8.6%), and inflammation (8.6%). Studies have shown that about 13% of patients admitted to the emergency department with myocardial infarction develop AHF [7]. HF progression is largely related to excessive fluid accumulation caused by many factors [8]. Median hospitalization was similar in both groups (14 vs. 19 days; $P = 0.13$).

Shortness of breath occurred with a similar frequency in both groups on admission. Increasing edema appeared comparably in both groups (56% NO-AHF vs. 53% ADHF; $P = 0.77$), whereas chest pain occurred in 38% ADHF vs. 25% NO-AHF patients ($P = 0.21$) — both results were statistically irrelevant. Pulmonary edema was remarkably more often diagnosed in NO-AHF patients compared to ADHF (31% vs. 10%; $P = 0.01$).

In laboratory tests, NO-AHF patients were characterized by statistically important lower concentrations of creatinine and higher hemoglobin levels compared to ADHF patients. Among the selected echocardiographic parameters, mean left ventricular ejection fraction (LVEF) was similar in both groups (33% NO-AHF vs. 32.5% ADHF).

Catecholamines were used more often in the ADHF group, indicating a tendency toward their increased utilization in this patient population (13% NO-AHF vs. 28% ADHF; $P = 0.08$). The same is true for levosimendan (10% vs. 28%; $P = 0.04$). According to the European Society of Cardiology guidelines, levosimendan, as an alternative to dobutamine, can be mainly used in AHF (recommendation class IIb) [1]. However, taking into account its mechanisms of action [9], ongoing clinical trials assess the efficacy and safety of repetitive use of levosimendan in ambulatory patients with chronic HF with reduced ejection fraction [10].

Another option to support the cardiovascular system when pharmacological therapy has failed is mechanical circulatory support (MCS). According to the expert opinion of the Association of Intensive Cardiac Care and the Association of Cardiovascular Interventions of the Polish Cardiac Society, MCS can be used as a bridge to a decision, bridge to recovery, bridge to transplant, or sometimes as a destination therapy [11]. In the analyzed group, the intra-aortic balloon pump (IABP) was not frequently used in either group (3%). On discharge, New York Heart Association class II predominated in both groups (95% NO-AHF and 57% ADHF; $P < 0.001$). We did not observe any differences between the two groups depending on the type of medications that the patients used shortly before and after discharge; however, such differences have been described in several studies [13, 14].

After adjusting for age and sex, 12-month survival was significantly better in NO-AHF than ADHF (Figure 1A). NO-AHF patients were younger and less burdened with comorbidities compared to ADHF patients with a history of heart failure before the episode. This seems to have had an impact on better prognosis in the NO-AHF group. Prior diagnosis of HF was reported as an independent predictor of 5-year mortality [12]. Our study showed that NO-AHF patients have better both in-hospital and 12-month prognosis from the moment of admission to the hospital (Supplementary material, *Table S1*, and *Figure S3*) while outcomes from the day of discharge (Supplementary material, *Figures S1*, and *S2*) as well as when ACS patients were included (Supplementary material, *Figure S4*) were similar after adjustment for age and sex. Furthermore, in NO-AHF patients discharged from the hospital and surviving one year after the AHF episode, LVEF improved significantly (33% increased to 50.2%), while no such effect was observed in ADHF patients (32.5% raised to 37.2%) (Figure 1B).

AHF is a varied condition that needs complex treatment including all new available methods from pharmacotherapy to MCS [15]. NO-AHF seems to have better outcomes, however, our research was carried out with a limited number of AHF patients. Improvement of LVEF after discharge in NO-AHF patients could be at least in part responsible for their better prognosis.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Acknowledgments: This work was supported by the Institute of Medical Sciences, University of Opole (grant number: INM-2021-P-2020-029).

Conflict of interest: None declared.

Funding: None.

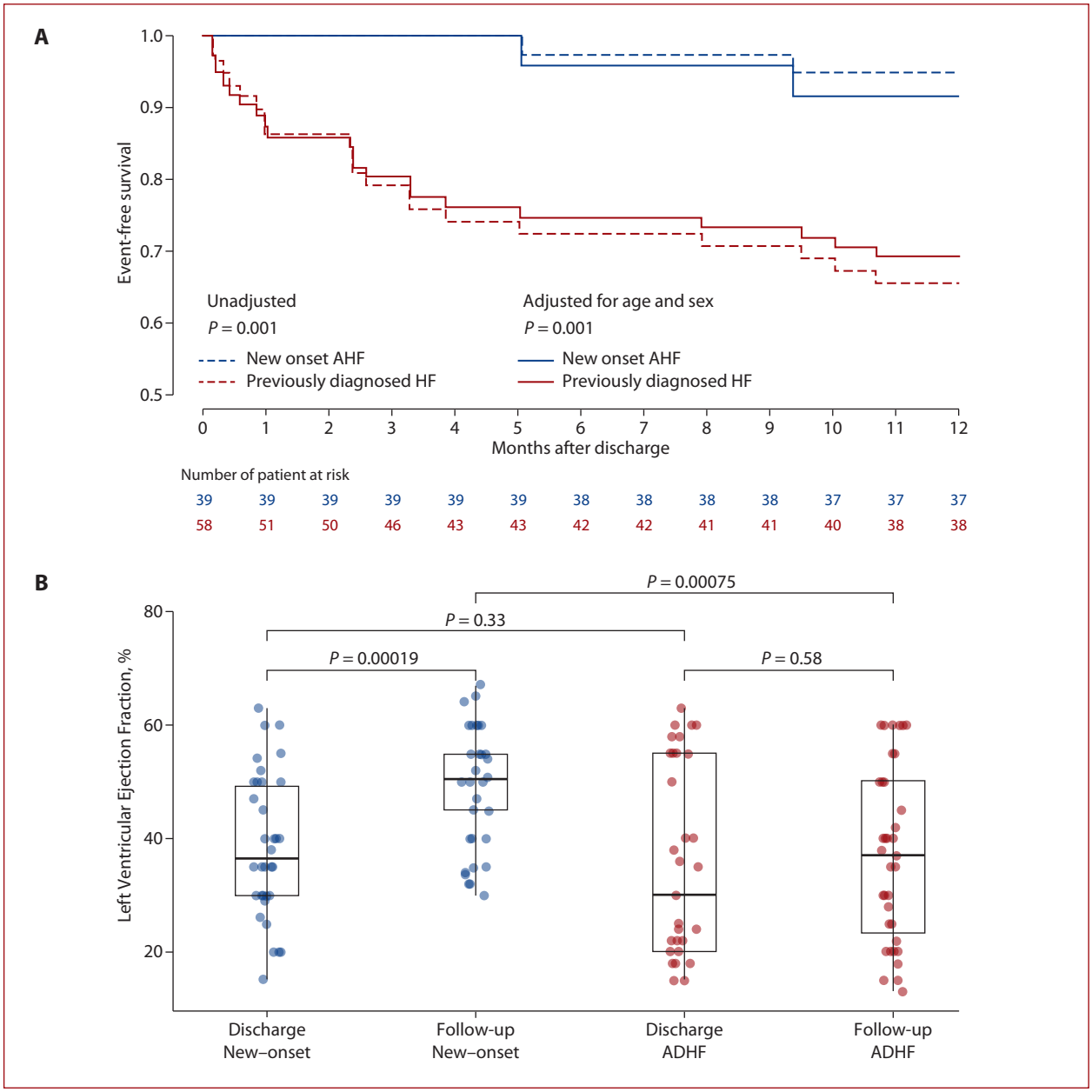

Figure 1. A. 12-month survival of patients with NO-AHF and ADHF (in-hospital deaths included). **B.** Boxplot presenting LVEF differences between discharge day and 12-month follow-up in NO-AHF and ADHF patients

Abbreviations: ADHF, acutely decompensated heart failure; LVEF, left ventricular ejection fraction; NO-AHF, new-onset acute heart failure

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Genetic background assessment with whole exome sequencing in a giant coronary artery ectasia: A pilot study

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DOI: 10.33963/v.kp.97684

Received:
June 6, 2023

Accepted:
October 1, 2023

Early publication date:
October 16, 2023

INTRODUCTION

Coronary artery aneurysm and ectasia (CAAE) is defined as a dilation of the coronary artery by at least 1.5 times compared to the adjacent reference segment. The reported incidence of CAAE is 0.3%–5.3% of patients undergoing coronary angiography and 1.4% of post-mortem examinations [1, 2]. Giant CAAE is a rare phenomenon characterized by a dilation of a coronary artery exceeding 2 cm, and it was found only in 0.02% of patients undergoing coronary angiography [1, 3]. The most common etiology of CAAE is atherosclerosis, followed by Kawasaki disease, infectious septic emboli, connective tissue disease, and arteritis. Iatrogenic causes are less common [4].

There are few genetic reports on potential loci associated with CAAE [1]. A meta-analysis of genome-wide association studies performed in European and Japanese populations of children with Kawasaki disease has identified *ITPKC*, *FCGR2A*, *CASP3,* and *FAM167A* genomic regions to be associated with susceptibility to CAAE [5]. Furthermore, the 9p21 variant has been linked with coexistence of coronary artery disease, cerebral artery aneurysms, and aortic aneurysms, mainly due to suspected potential adverse vascular remodeling [6]. Nevertheless, the direct association of specific genetic variants with CAAE formation, especially with those giant, has not been confirmed [1].

Therefore, we present our pilot data on applying whole exome sequencing (WES) in a patient with extreme giant coronary artery ectasia (CAE) and positive family history.

METHODS

Proband characteristic

A 70-year-old male, with previously diagnosed giant right CAE and multiple cardiovascular risk factors, was admitted for assessment before planned thoracic surgery due to a tumor in the right lung apex. On admission, the patient reported physical activity limitation, with exertional fatigue and paroxysmal palpitations. His history was also remarkable for common iliac artery aneurysm, abdominal aortic stent graft implantation due to aortic aneurysm, and bilateral adrenal adenomas with subclinical Cushing syndrome, treated with right adrenalectomy. His family history included an aortic aneurysm in his father, hemorrhagic stroke in his paternal grandfather, and fatal congenital heart disease in his child.

The CAE diagnosis has been established seven years before the present admission. At that time, coronary angiography revealed a partly thrombosed diffuse ectasia along the right coronary artery with a maximum diameter of 15 mm in the proximal segment and in the proximal left anterior descending and proximal to the mid-left circumflex arteries (Figure 1A, B). Since coronary lesions were not suitable for any interventions, the Heart Team recommended optimal medical treatment. During follow-up, significant progression to 60 × 61 mm, 70 × 64 mm, and finally to 86 × 60 mm was observed on subsequent coronary computed tomography angiographies (CCTA) (Figure 1C, D). In serial transthoracic and transesophageal examinations, the com-

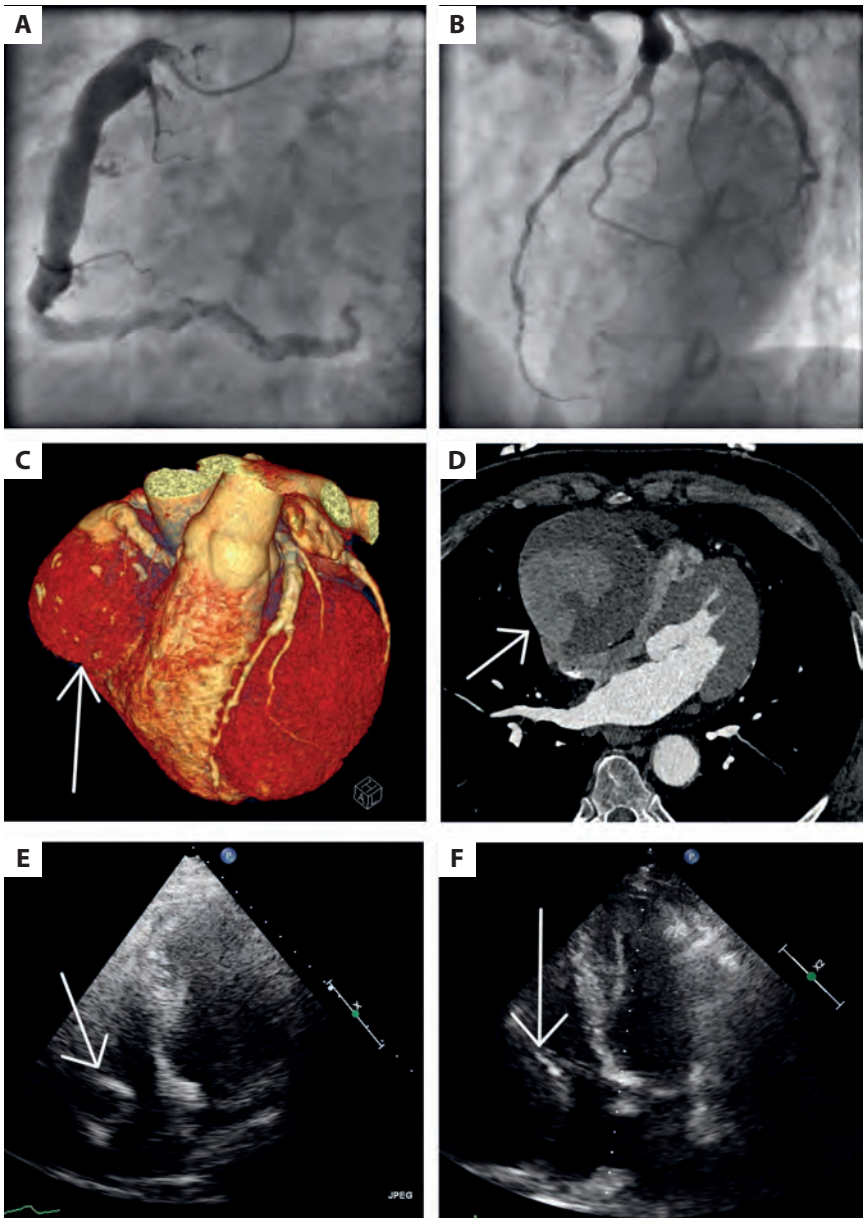

Figure 1. Diagnostic images of the coronary artery ectasia (CAE). **A, B.** The right CAE and disseminated ectasias in other vessels on initial coronary angiography. **C.** Digital reconstruction of the giant right CAE (arrow) based on computed tomography angiography performed immediately after diagnosis. **D.** Significant progression of the diameter of the giant right CAE to 86 × 60 mm (arrow) on the last computed tomography. **E, F.** The modeling of the right heart chambers by the giant ectasia (arrow) on echocardiography performed two years earlier and recently

pression of the right atrium, right ventricle, and tricuspid annulus have been visualized (Figure 1E, F).

Due to the suspicion of a genetic background for the giant CAE, the patient was referred for WES. The targeted genetic tests and CCTA were also offered to three proband's daughters. The study protocol complied with the Declaration of Helsinki and was approved by the Jagiellonian University Medical College Ethics Committee (Consent No. 1072.6120.49.2022). It was registered at ClinicalTrials.gov (NCT06001957). Written informed consent to participate in this study was provided by the proband and his relatives.

Whole exome sequencing analysis

DNA from proband was obtained from peripheral blood and extracted using standard protocols. Library preparation for the WES was performed on proband's DNA sample with Twist Human Core Exome spiked-in with Twist mtDNA Panel, Twist RefSeq Panel, and Custom Panel covering variants located in noncoding regions that have been linked to clinical phenotypes according to the ClinVar database (Twist Bioscience, San Francisco, CA, US). The enriched library was paired-end sequenced (2 x100 bp) on NovaSeq 6000 (Illumina, San Diego, CA, US) to obtain 116 001 610 reads resulting in a mean depth of 129.8x (99.5% of target bases were covered at a minimum of 20×, whereas 99.7% had coverage of min. 10×). Bioinformatic analysis of the raw WES data and variants prioritization were performed as previously described [7–9]. Reads were aligned to the hg38 reference genome sequence and visualized by Integrative Genomic Viewer.

RESULTS AND DISCUSSION

The comprehensive analysis of the WES data showed neither single nucleotide variants (SNV) nor copy number variants (CNV) that could explain the occurrence of giant CAE in the proband. Genes associated with the development of CAAE in Kawasaki disease [5] as well as potentially associated with the pathogenesis of CAAE (*ATG7*, *MMP-2*, *MMP-9*, *GRIN3A*, *TIMP2*, *TIMP3*, *ACE*) were analyzed in detail. CCTA screening of the patient's daughters showed the absence of CAAE. Considering all obtained results, genetic testing of the proband's daughters was abandoned.

To the best of our knowledge, the presented case is the second largest CAAE reported in Poland and one of the biggest described worldwide [10, 11]. Moreover, it is also one of the first reports on WES applications in CAAE [12]. The patient selected for genetic analyses was also initially characterized as having a high risk of genetic background. He had advanced CAE with dynamic progression but without significant stenoses in the coronary arteries. Moreover, his aneurysms were identified in different vascular territories. He had no history of any diseases that are a confirmed etiological factor for CAAE nor previous cardiac interventions. In addition, his family history was strongly positive towards aneurysmal lesions. Nevertheless, as has been pointed out, the WES analysis did not reveal any 62,69 pathogenic or potentially pathogenic variants.

Our pilot study has important limitations. The applied WES-based SNV/CNV analysis has limited sensitivity and specificity. Potentially, other methods, such as whole genome sequencing (WGS), optical genome mapping (OGM), high-resolution array comparative genomic hybridization (aCGH), or multiplex ligation-dependent probe amplification (MLPA) could lead to the identification of pathogenic variants. Considering the mentioned above limitations, further research on WES/WGS and its broader use in CAAE on larger groups of patients is warranted to identify novel pathogenic variants in different CAAE phenotypes [13, 14].

So far, there are no CAAE-specific clinical guidelines. Furthermore, modern calculators and scales for assessing the complexity of coronary artery disease omit the CAAE presence despite their indisputable negative impact on outcomes, which arises from specific complications, such as thrombosis, distal embolism, rupture, or vasospasm [2, 15]. The results of further WES/WGS studies could provide more insights into the pathogenesis of CAAE and bring substantial benefits for the patients, such as better risk stratification, personalized management, additional monitoring, or familial screening.

Article information

Conflict of interest: None declared.

Funding: This work was supported by Jagiellonian University Medical College Students' Scientific Society Grant (NZ4-2021/2022 to AM).

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Incidence and prevalence of cardiomyopathies in Poland and outcomes for patients in the years 2016–2020

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DOI: 10.33963/v.kp.98357

Received:
November 11, 2023

Accepted:
November 9, 2023

Early publication date:
January 11, 2024

INTRODUCTION

Regardless of the increasing number of novel screening and diagnostic methods, the diagnostic process in cardiomyopathies (CMs) remains poor [1, 2]. This results in differences between theoretical and real-life data on CM incidence and prevalence [3]. Despite the discrepancies, the data indicate an increasing importance of CMs in the incidence and prevalence of illnesses and deaths [4]. Based on current estimations of hypertrophic CM (HCM) prevalence of 1:200 [1], HCM may affect 180 000 patients in Poland. We are aware of differences between the numbers of estimated and diagnosed patients in our country; however, the scale of the problem has not been evaluated yet. In this article, we aimed to investigate the registered annual incidence and prevalence CM rates, as well as outcomes for patients with a clinical diagnosis of CMs in Poland in the period 2016–2020.

METHODS

This population-based cross-sectional study was conducted using the Polish National Health Fund (NFZ, *Narodowy Fundusz Zdrowia*) database. The database was queried using International Classification of Diseases and Related Health Problems, 10th Revision (ICD10) codes I42, I42.0, I42.1, I42.2, I42.3, I42.4, I42.5, I42.6, I42.7, I42.8 or I42.9 [5] to identify CM patients from January 1, 2016 to December 31, 2020. The analysis was performed separately in the whole CM population and in specific CM types defined as dilated CM (DCM) — I42.0, HCM — I42.1 or I42.2, and others (remaining codes). The above-mentioned ICD-10 codes were derived from patient hospitalization records at any time during the course of the disease. Exclusion criteria involved ICD codes consistent with ischemic heart disease: I24, I25, I21, I20. The analysis comprised information on the initial diagnosis of CM with a potential transfer to another department or hospital, other hospital admissions, and data from outpatient visits.

Statistical analysis

The registered incidence was defined as the number of new patients per year who, for the first time, appeared in the NFZ database with the applicable ICD-10 codes. The registered prevalence was defined as a number of patients, who appeared at least once in the NFZ database with the mentioned earlier ICD codes and who were alive by December 31 of the index year. The number of deaths was estimated based on data from 2016–2020 obtained from the public healthcare system and the Ministry of Digitization. Epidemiological indicators for voivodeships were standardized by age, sex, and place of residence for the Polish population, based on the Central Statistical Office data. Statistical significance for the comparison of survival curves for the analyzed variable was verified using the

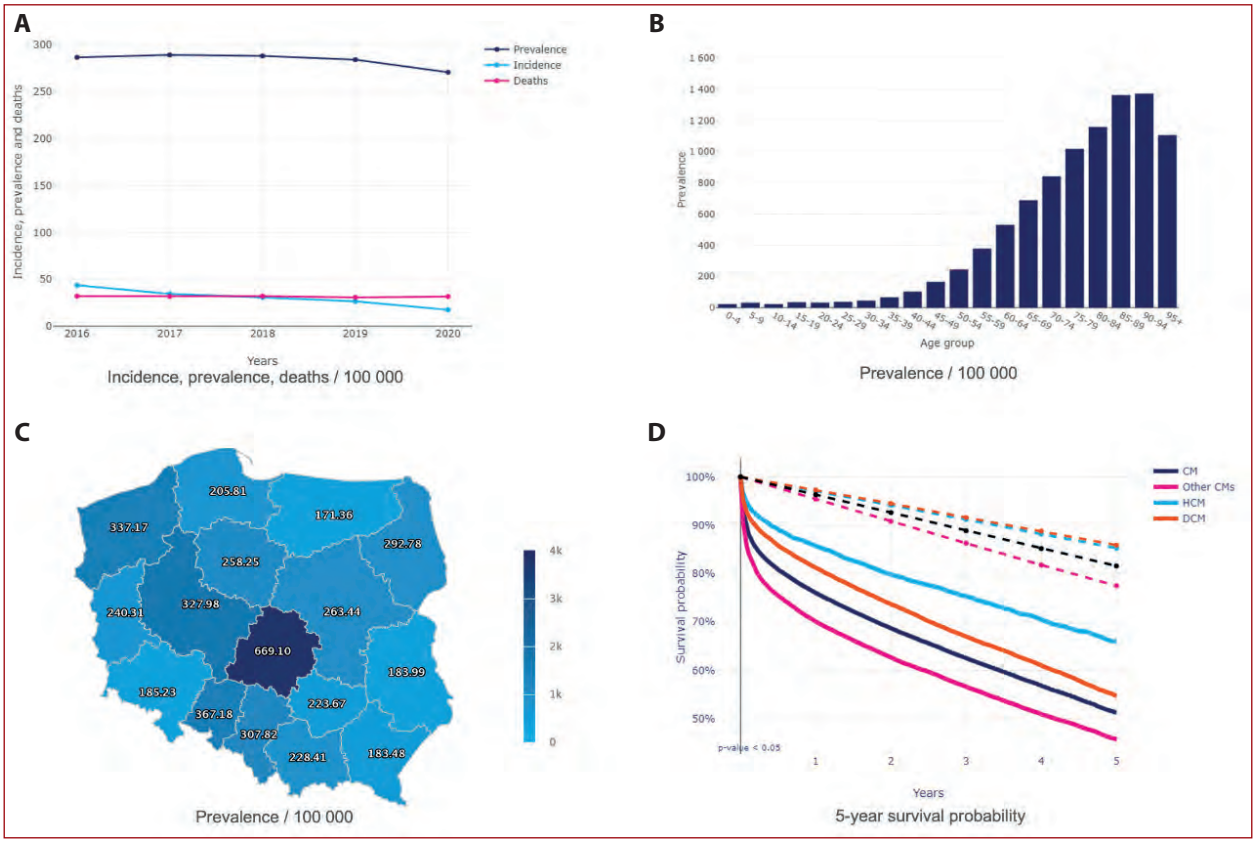

Figure 1. A. Registered annual prevalence, incidence, and number of deaths from cardiomyopathies (CMs) in Poland in the period 2016–2020 — data per 100 000 inhabitants. **B.** Registered prevalence of CMs in Poland in 2019 according to the age — data per 100 000 inhabitants. **C.** Registered prevalence, of CMs in Poland in 2019 according to the voivodeship — data per 100 000 inhabitants. **D.** The 5-year estimated survival rate in the analyzed types of the registered CM population: hypertrophic CM, dilated CM, and others (*P*-value for the difference between estimated survival curves for individual cardiomyopathies; dotted lines: population matched by the age and sex)

Mantel-Haenszel test (log-rank) for the Kaplan–Meier survival estimator.

RESULTS AND DISCUSSION

In 2016, the annual incidence of CM was 16801 (43.72/100 000, 0.044%; 64% males [M]), and in 2020 it decreased reaching 6729 (17.59/100 000, 0.018%; M: 67%) CM patients.

The annual prevalence of CM in the period 2016–2020 was between 110146 (285.59/100 000, 0.286%) in 2016 and 103638 (270.84/100 000, 0.271%) in 2020 (Figure 1A).

The following data were registered for CM subtypes:

- DCM — the annual incidence of DCM in 2016: 6307 (16.31/100000, 0.016%; M: 82%); in 2020: 2898 (7.57/100 000, 0.008%; M: 81%); the annual prevalence of DCM in 2016: 46010 (119.71/100 000, 0.119%); in 2020: 43595 (109.05/100 000, 0.109%),
- HCM — the annual incidence of HCM in 2016: 1494 (3.89/100000, 0.004%; M: 55%); in 2020: 782 (2.04/100 000, 0.002%; M: 58%); the annual prevalence of HCM in 2016: 13271 (34.53/100 000, 0.034%); in 2020: 14094 (36.83/100 000, 0.036%).

The total number of annual deaths was comparable between the years (2016 — 12360, 32.16/100 000, 0.032%; 2020 — 12141, 31.73/100 000, 0.032%) — in 2020 the number of deaths exceeded the annual incidence of CM diagnosis (Figure 1A).

The following data were registered for CM subtypes:

- DCM — annual mortality in 2016: 4770 (12.41/100 000, 0.012%); in 2020: 4948 (12.64/100000, 0.013%);
- HCM — annual mortality in 2016: 824 (2.14/100 000, 0.002%); in 2020: 1000 (2.61/100 000, 0.003%).

The registered annual prevalence of CMs in 2019 according to the age and voivodeships is presented in Figure 1B–C. The 5-year survival rate was significantly lower in the CM population (51%) as compared to the population matched in terms of age and sex (82%). The 5-year survival rate was low and differed between CM subtypes: HCM (66%), DCM (55%), and others (46%; *P* <0.01) (Figure 1D).

The presented study is the first population-based cross-sectional analysis summarizing data on the registered prevalence and incidence of CMs in Poland in the period of 2016–2020. In 2016 the registered annual incidence of CMs was 43.72/100 000, and it decreased in 2020 reaching 17.59/100 000 as a result of the COVID-19 pandemic. The annual prevalence of CMs and the number of annual deaths remained at a constant level over the analyzed period; in 2020 the number of deaths exceeded the annual incidence of CM diagnosis. The analysis of the 5-year survival rate showed significantly reduced life expectancy in the whole

CM population and in the subgroups with DCM and HCM. Indices were comparable to the data from analogous registries from other countries [6–10], yet lower than the standard data on the epidemiology of CMs reported in the literature [1].

In our analysis, the registered prevalence of CMs in 2016 was 285.59/100 000 (0.286%; 1:350). Taking into consideration the number of inhabitants, it corresponds to approximately 120 thousand people who were registered in the NFZ system with the ICD code indicating CM. This value differs from the literature data [1] and confirms that CMs are underdiagnosed in Poland.

Additionally, in 2020, the registered incidence of CMs was 2.5 times lower than in 2016, which resulted from restrictions related to the COVID-19 pandemic.

Notably, 64%–67% of the CM population were men, which is consistent with the results of other published epidemiological data [6, 7]. Current results indicate that the registered incidence and prevalence of DCM was higher than HCM in line with a similar British analysis [6] and data from ESC guidelines (DCM: 0.036%–0.400% vs. HCM 0.2%) [1]. In our analysis, the registered prevalence of DCM and HCM was 0.119% and 0.034%, respectively. Data on the HCM epidemiology in the American population based on the Health Core Integrated Research Database (period: 2013–2019) show that HCM's prevalence was 52/100 000 (0.052%) [9]. According to the British data analyzing the period from 2000 to 2018, the recorded prevalence of HCM in 2018 was 3.5/10000 (0.035%) [6], which is comparable to our findings. Similar data were also published by Korean authors showing an HCM prevalence of 0.016% in 2010 and 0.031% in 2016 [7]. In the German population in 2015, the HCM prevalence was 0.07% with an average age of 63 (SD 17) years and 65% of patients were male [8], which shows a similar demographic profile as in our population. Similar to our finding, the registered prevalence of HCM increased with age [7–9]. Our analysis also demonstrated advanced age at CM diagnosis, local differences in the registered epidemiology, and impaired prognosis for CM patients.

Limitations of our study involve data extraction from a large healthcare provider registry based on ICD-10 codes. The ICD-10 classification does not allow for identification of restrictive and arrhythmogenic right ventricular CM. Some cases of CM may have been coded as heart failure leading to overall CM underreporting. Data from 2020 were included in the analysis, but they should be interpreted with caution due to the COVID-19 pandemic.

Conclusions

The study delivers novel data on the registered annual incidence and prevalence of CMs in Poland as well as outcomes for Polish CM patients. The registered annual incidence and prevalence of CMs, together with their unfavorable clinical outcomes, warrant an urgent need for improvement of CM screening and diagnostic processes in Poland.

Article information

Conflict of interest: None declared.

Funding: None.

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Acute purulent pericarditis complicated by cardiac tamponade in a patient with human immunodeficiency virus

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DOI: 10.33963/v.kp.96608

Received:
June 7, 2023

Accepted:
July 21, 2023

Early publication date:
September 15, 2023

A 42-year-old male with a positive history of drug abuse was admitted to the cardiology department on account of signs and symptoms of cardiogenic shock and echocardiographic features of life-threatening myocardial tamponade (Figure 1A). The patient denied any chronic conditions. The patient was urgently subjected to percutaneous pericardiocentesis performed through the infrasternal angle at the local catheterization laboratory (Figure 1B), allowing for slow drainage of 700 ml of dense turbid effusion via a pig-tail catheter (Figure 1C). Computed tomography of the chest did not show significant inflammatory abnormalities within the lung parenchyma, while the normal location of the pericardial drain and significant deposits of fluid in the pericardial and pleural cavities were confirmed (Figure 1D). Microbiological analysis of the purulent effusion (Figure 1C) indicated growth of *Haemophilus influenzae*, and subsequent serologic tests excluded tuberculosis infection but confirmed the presence of human immunodeficiency virus (HIV). The patient finally admitted having undergone an incomplete antiretroviral therapy for acquired immunodeficiency syndrome.

From the onset of in-hospital stay, the patient received complex antibiotic therapy comprising intravenous ceftriaxone in combination with ciprofloxacin for 14 days, which was consistent with subsequent antibiogram, leading to a gradual decrease in inflammatory parameters. During the in-hospital stay, several episodes of atrial fibrillation were reported, which led to the decision to perform pharmacological cardioversion with amiodarone. As a result of the applied treatment, the patient's general condition improved, and he received further cardiac follow-up on an outpatient basis.

Recommendations included a diuretic and colchicine, proton pump inhibitor, thromboprophylaxis, antiarrhythmic treatment for one month, and resumption of retroviral therapy. Given the symptoms of gastritis, non-steroidal anti-inflammatory drugs were discontinued. The follow-up visit at 1 month showed mild features of pericardial constriction on transthoracic echocardiography with a small amount of fluid behind the right ventricle and no pleural effusion while the patient remained asymptomatic. The prognosis of pericarditis strictly depends on the cause of infection. Untreated bacterial pericarditis is associated with a high mortality rate, while cardiac tamponade and constrictive pericarditis are commonly observed complications [1, 2]. Diagnosis of purulent pericarditis is extremely rare and should also be considered in the context of HIV.

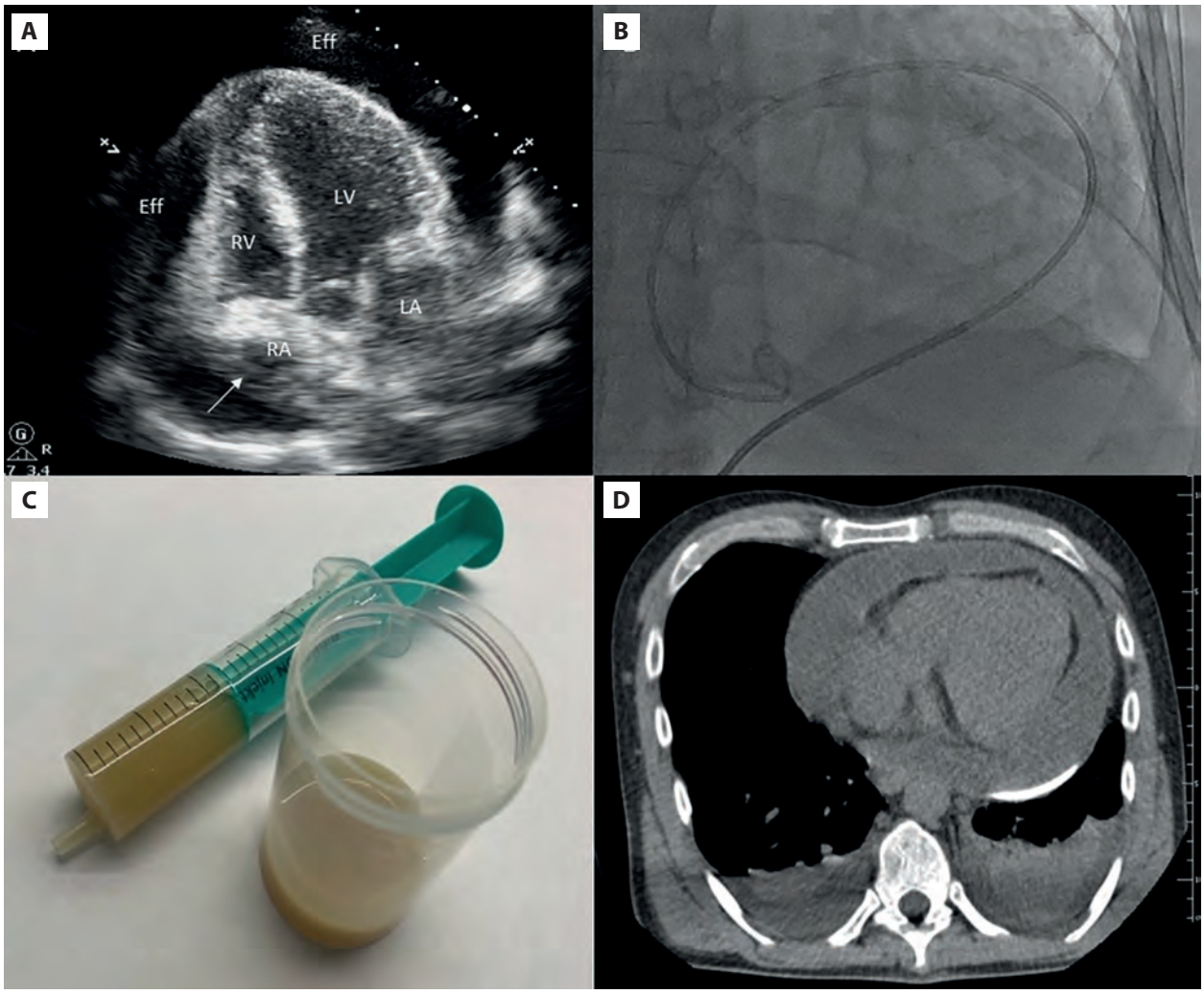

Figure 1. Diagnostics and treatment of cardiac tamponade in the course of bacterial pericarditis in a patient with the human immunodeficiency virus. **A.** Transthoracic echocardiography; pericardial effusion of 28 mm with echocardiographic signs of cardiac tamponade (arrow: compression of the right atrium by effusion). **B.** Fluoroscopy with a pig-tail catheter introduced to the pericardial cavity via the infrasternal angle. **C.** Creamy effusion drained from the pericardial cavity. **D.** Computed tomography of the chest with signs of residual pericardial and bilateral pleural effusion and no overt pathological lesions within the lung parenchyma and mediastinum

Abbreviations: Eff, effusion; RV, right ventricle; RA, right atrium; LV, left ventricle; LA, left atrium

Article information

Conflict of interest: None declared.

Funding: None.

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Left main coronary artery perforation with rescue stentgraft implantation, complicated by circumflex artery occlusion promptly treated with intentional stentgraft puncture

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DOI: 10.33963/v.kp.97957

Received:
August 8, 2023

Accepted:
October 24, 2023

Early publication date:
October 26, 2023

Coronary artery perforation (CAP) is an infrequent, yet life-threatening, complication of percutaneous coronary interventions (PCIs). The incidence of CAP is estimated at 0.4%–0.7% of all PCIs, with a 7%–17% mortality rate [1, 2].

CAP can be rated according to its location and severity using the Ellis classification [3]. Perforations are more frequent in female and older patients and depend on coronary anatomy, use of oversized balloons or stents, atheroablative devices, hydrophilic guidewires, and postdilatation with high pressure. The risk of CAP increases with procedure complexity up to 2.9% in chronic total oclussion interventions [4]. Prompt recognition and adequate treatment of CAP are crucial [5].

We report a case of an uncommon treatment approach that allowed to maintain flow in both left anterior descendent (LAD) and circumflex (Cx) arteries after perforation of the left main (LM) coronary artery. A 75-year-old female after previous LAD PCI, with bare metal stent implantation in 2013 was admitted to the Department of Cardiology for acceleration of angina symptoms. We performed coronary angiography and diagnosed multi-vessel disease — critical stenosis of the? obtuse marginal artery (OM) and significant stenosis of the proximal LAD. Since the patient refused

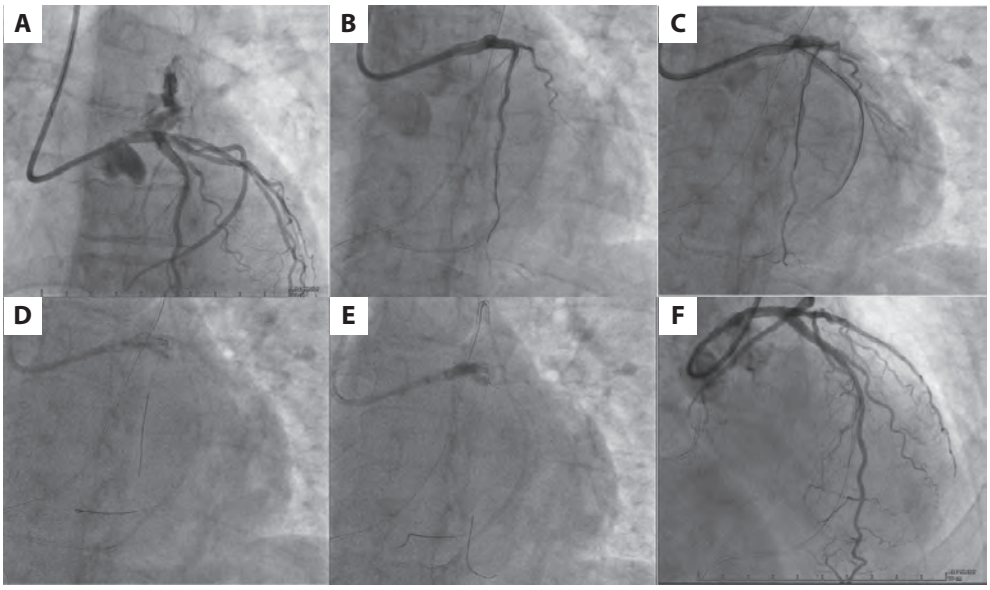

Figure 1. A. Left main coronary artery perforation. **B.** Sealed site of bleeding and closure of the circumflex artery (Cx) after stentgraft implantation. **C.** Insertion the wire through the stentgraft into the Cx. **D.** Inflations of progressively increasing sizes of balloons in the Cx ostium. **E.** "Kissing balloons" technique in the bifurcation of the left main coronary artery. **F.** Final result

bypass surgery, we performed uneventful OM PCI with drug-eluting stent (DES) implantation. The next day, the patient reported chest pain, with no apparent ECG changes, yet we decided to perform control coronarography that revealed a? patent stented OM, so, considering the symptoms, we targeted the LM bifurcation. After predilatation, a DES (Promus PREMIER 3.5 × 20 mm) was implanted from the LM into the Cx. Afterward, during implantation of the second DES (Ultimaster 4.0 × 38 mm) from the LM to the LAD, CAP occurred, resulting in tamponade. Despite immediate pericardiocentesis (yielding 150 ml of blood) and prompt stentgraft (Papirus 3.5 × 20 mm) implantation, cardiac arrest in the pulseless electrical activity mechanism occurred with the return of spontaneous rhythm after resuscitation. The next contrast injection revealed a sealed bleeding site and closure of the Cx at the same time. We attempted to open the Cx. After a few trials with hydrophilic wires, stentgraft membrane, and struts we went through the stentgraft with chronic total oclussion dedicated wire (Confianza PRO). Afterward, a lumen in the stengraft membrane was created with inflations of progressively increasing sizes of balloons (from 1.2 × 15 mm to a noncompliant 3.0 × 15 mm balloon). Next, the "kissing balloon" technique was performed (with a noncompliant 3.5 × 20 mm balloon in the Cx and a noncompliant 4.0 × 12 mm balloon in the LAD). Finally, the proximal optimization technique (POT) was performed with a noncompliant balloon 4.5 × 12 mm, resulting in TIMI 3 flow, with no dissection and no pericardial bleeding.

In the following days, the patient remained stable on mechanical ventilation and catecholamines, with left ventricular ejection fraction of 45% and no pericardial effusion. The troponin level decreased after the initial peak of 8333 ng/l. However, despite proper anticoagulation with enoxaparin, on the 15th day post-intervention, the patient suffered a severe fatal ischemic stroke.

The presented infrequent example of optimizing the effect of bifurcation PCI procedures demonstrates an approach to managing possible treatment complications. We should keep in mind, however, the increased risk of stroke in post-PCI patients.

Article information

Conflict of interest: None declared.

Funding: None.

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Acute single leaflet detachment following implantation of a PASCAL PRECISION P-10 device and its management

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DOI: 10.33963/v.kp.97153

Received:
July 27, 2023

Accepted:
August 28, 2023

Early publication date:
September 15, 2023

Single leaflet detachment (SLD) is a well-known complication of transcatheter edge-to-edge repair (TEER) and occurs in up to 5% of procedures [1, 2]. Usually SLD results in mitral regurgitation (MR) recurrence and clinical symptoms worsening. Percutaneous SLD management might be difficult or even impossible, and surgical treatment may be required. We present a patient with acute SLD of PASCAL PRECISION P-10 (Edwards LifeSciences, Irvine, CA, US) that was successfully managed with implantation of two adjacent PASCAL PRECISION ACE devices.

A 73-year-old male with heart failure (New York Heart Association [NYHA] class III) and severe functional MR (effective regurgitant orifice [ERO], 0.5 cm^2) (Figure 1A, B) due to ischemic etiology was scheduled for a TEER procedure with the PASCAL system. Direct measurement of left atrial pressure (LAP) confirmed significant MR (Figure 1C). A PASCAL P-10 device was implanted in the A2/P2 region. The leaflet optimization technique was used both for the posterior and anterior leaflets to ensure the optimal length of insertion. Nevertheless, despite careful echocardiographic guidance before device release, acute SLD had occurred and led to an immediate recurrence of severe MR. The Pascal P-10 device remained attached to the anterior leaflet only (Figure 1G). Two Pascal ACE devices were then implanted medially and laterally to stabilize the position of the P-10 device (Figure 1H). To avoid a significant mitral gradient, the ACE devices were positioned as close as possible to the initially implanted P-10. The final echocardiographic result was acceptable (Figure 1F) with less than moderate MR, mean mitral gradient (MGM) of 4.2 mm Hg, and full stabilization of the P-10 implant. The

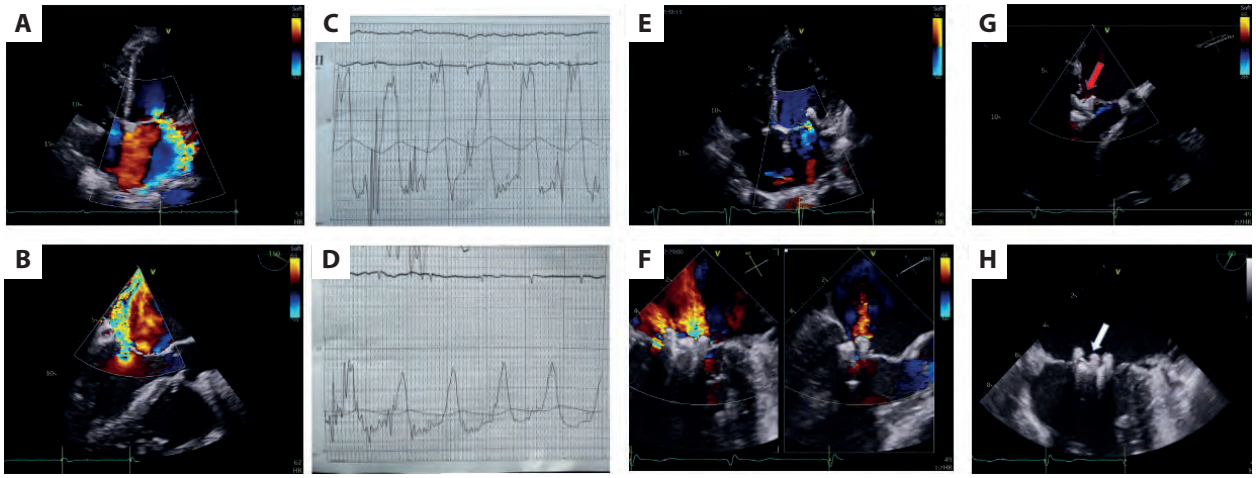

Figure 1. Echocardiographic and hemodynamic evaluation before, during, and after the transcatheter edge-to-edge repair (TEER) procedure. **A.** Transthoracic echocardiography with significant functional mitral regurgitation (MR). **B.** Transesophageal echocardiography with significant functional MR. **C.** Left atrial pressure before the TEER procedure. **D.** Left atrial pressure after the TEER procedure. **E.** Transthoracic echocardiography at 30-day follow-up. **F.** Immediate intraprocedural echocardiographic result after implantation of two Pascal ACE devices medially and laterally to P-10 with single leaflet detachment. **G.** Single leaflet detachment of the Pascal P-10 device (red arrow points at the gap between P-10 and the posterior leaflet). **H.** Transesophageal appearance of Pascal P-10 stabilized by two Pascal ACE devices (white arrow points at the P-10 device)

hemodynamic response reflected by changes in LAP additionally confirmed the good result of the TEER procedure (Figure 1D). The post-procedural period was uneventful. Follow-up transthoracic echocardiography revealed good and stable results with less than moderate MR and an MGM of 5 mm Hg. The patient was discharged home two days after TEER. At 30-day follow-up, the patient's condition improved to NYHA class I. Echocardiography confirmed the good and stable TEER results. (Figure 1E). The clinical and echocardiographic improvement was also reflected by a decrease in NT-proBNP level from 8874 before TEER to 2111 at 30-day follow-up.

The current report is the first description of SLD in a patient treated with a new-generation device – the PASCAL PRECISION system. The upgraded instrument is considered to provide more precise, predictable, and stable device positioning, which is believed to result in the reduction of the potential risk of clip detachment in comparison with previously implanted systems. In the described case, SLD occurred despite accurate "clocking" and optimal deployment, and its mechanism remains unclear. Nevertheless, we documented that full stabilization of the largest available TEER device (P-10) in the case of SLD occurrence is possible with the use of two additional smaller devices and may result in a satisfactory MR reduction (without creating a significant MGM) and satisfactory clinical outcomes.

Article information

Conflict of interest: None declared.

Funding: None.

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Slow flow in ectatic dilated coronary arteries as the cause of sudden cardiac arrest during diagnostic coronary angiography

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DOI: 10.33963/v.kp.97726

Received:
July 11, 2023

Accepted:
October 5, 2023

Early publication date:
October 19, 2023

Coronary artery ectasia (CAE) is the widening of a coronary artery segment by at least 1.5 times compared to the adjacent segment. CAE is often accompanied by slow vascular flow while CAE with coexisting atherosclerosis is associated with adverse cardiovascular events [1].

A 75-year-old female patient with a history of hypertension and hyperlipidemia, atypical angina pain for about a year, and a clinically and electrocardiographically positive stress test was admitted to the Department for coronary angiography. On admission, the patient remained stable, her blood pressure was 138/82 mm Hg, and ECG showed a sinus rhythm of 63 beats per minute, intermediate axis. The patient underwent echocardiography, which showed normal valve function, mildly impaired diastolic function, and normal left ventricular systolic function with ejection fraction of 60%. The patient underwent coronary angiography (Figure 1A–C), which showed a dilated left main coronary artery, left anterior descending artery, and circumflex artery with adjacent atherosclerotic lesions, slowed flow, and contrast backlog (Figure 1A, B). During the left coronary artery catheterization, the patient developed sudden cardiac arrest in ventricular fibrillation, which was successfully defibrillated. The patient was qualified for further conservative treatment of coronary artery disease. Twenty-four-hour Holter ECG monitoring was performed, in which no complex forms of arrhythmia were observed. Trimetazidine was added to the existing pharmacological treatment of coronary artery disease (acetylsalicylic acid, cilazapril, amlodipine, bisoprolol, and rosuvastatin). The patient was discharged.

Coronary artery ectasias are vascular anomalies involving segmental vasodilatation with impaired coronary flow. The flow may be slowed and turbulent, which promotes thrombus formation and coronary artery spasm.

Slowed coronary flow in dilated vessels contributes to clinical symptoms, mainly exercise and resting angina pain. In addition, life-threatening arrhythmias and sudden cardiac arrest can occur in patients with slow flow [1, 2]. Coronary ectasia is found in 0.3%–4.9% of coronary angiography studies, and most cases are detected incidentally [3].

Coronarography is the main test used to diagnose ectasia. However, delayed contrast filling, segmental retrograde flow, and contrast stasis in dilated vessel segments make the study difficult to perform. A strong and prolonged injection of contrast is often necessary, increasing the risk of complications during the study. Our patient had coronary artery ectasias and slowed coronary flow during coronary angiography. In addition, the administration of contrast induced sudden cardiac arrest through ventricular fibrillation. Malignant ventricular arrhythmias are very rare during diagnostic coronary angiography (<0.5%), and contrast agent is considered to be their most common cause.

The presented patient was treated with an antianginal drug, trimetazidine, due to the reported retrosternal pain. In CAE, nitrates are contraindicated because they may exacerbate clinical symptoms. However, trimetazidine, which increases exercise tolerance in these patients, is recommended and safe [4].

In previous studies, the prognosis of CAE patients with varies, but the accompanying

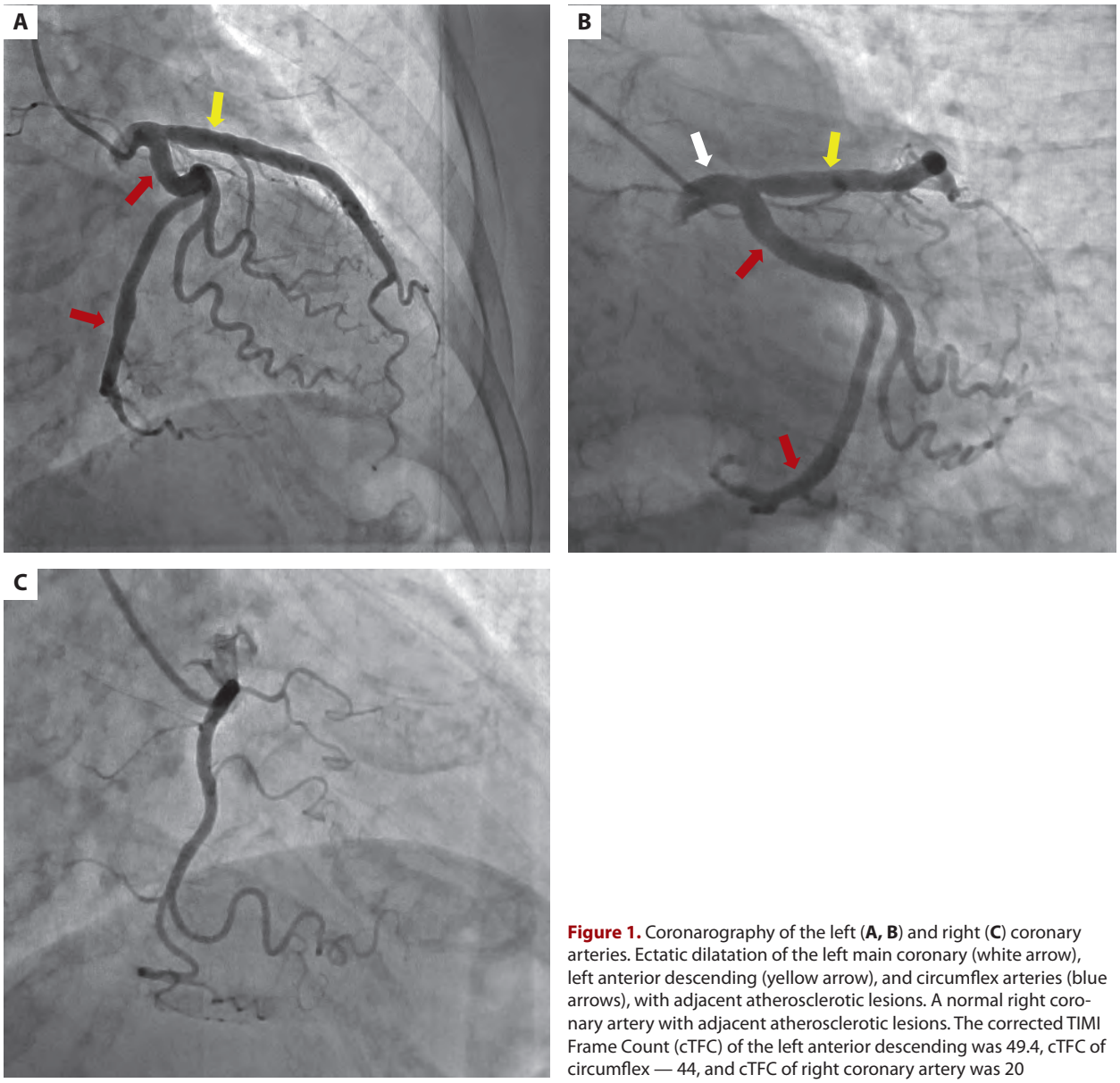

Figure 1. Coronarography of the left (**A, B**) and right (**C**) coronary arteries. Ectatic dilatation of the left main coronary (white arrow), left anterior descending (yellow arrow), and circumflex arteries (blue arrows), with adjacent atherosclerotic lesions. A normal right coronary artery with adjacent atherosclerotic lesions. The corrected TIMI Frame Count (cTFC) of the left anterior descending was 49.4, cTFC of circumflex — 44, and cTFC of right coronary artery was 20

slowed coronary flow causes angina complaints, which accounts for more frequent hospital admissions of patients and increases mortality in follow-up over several years [2]. The diagnosis and prognosis of these patients are further worsened by the coexistence of coronary atherosclerosis, so patients with coronary ectasias require special long-term follow-up [2, 5].

Article information

Conflict of interest: None declared.

Funding: None.

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Inferior ST-segment elevation myocardial infarction and intramyocardial dissecting hematoma following blunt chest trauma

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DOI: 10.33963/v.kp.97754

Received:
September 19, 2023

Accepted:
October 8, 2023

Early publication date:
October 24, 2023

A blunt chest trauma is a rare etiology of non-atherosclerotic acute coronary syndrome (ACS), needing early diagnosis and treatment [1]. Trauma-related ACS mechanisms include intimal tear, subintimal hemorrhage, intra-luminal thrombosis, and spasm [2]. We present a case of inferior ST-segment elevation myocardial infarction (STEMI) caused by the crushing of the right coronary artery (RCA) following blunt chest trauma that was successfully treated with percutaneous coronary intervention.

A 69-year-old female patient was referred to the emergency department for polytrauma from a traffic collision. Total-body computed tomography scanning revealed lung contusion, left-sided hemopneumothorax, sternal fracture, Th12 vertebral fracture, craniofacial disjunction, and upper extremities fractures. The highest priority was craniofacial disjunction, and the patient was admitted to the Department of Maxillofacial Surgery. After *circa* 48 hours, the patient reported typical angina at rest. ECG displayed inferior ST-segment elevation. A coronary angiogram revealed acute occlusion in the proximal/mid RCA. After reopening the artery with a wire, we observed linear dissection in mid-RCA and a parallel artery, acute marginal branch (AM), filling retrogradely from the collateral circulation from the posterolateral artery. At the site of the cardiac contusion, we observed myocardial blush along the AM with contrast jet extravasation suggesting it had been crashed. Initial RCA pre-dilation with a balloon was followed by the drug-eluting stent implantation with TIMI 3 flow grade. An attempt to find the orifice of the crashed AM failed (Figure 1A–C; Supplementary material, *Video S1–S3*). We observed a resolution of angina and progression of high-sensitive cardiac troponin T typical for STEMI. Dual antiplatelet therapy was initiated. Transthoracic echocardiography (TTE) revealed basal and mid inferolateral hypokinesia and a pulsatile dissection flap, delineating a 34 × 12 mm neocavity of intramyocardial dissecting hematoma (IDH), left ventricular ejection fraction (LVEF) of 55%, and partially organized hemopericardium that had not been observed on focus cardiac ultrasound on admission (Figure 1D; Supplementary material, *Video S4*). Cardiac computed tomography angiography (CCTA) demonstrated a total occlusion of the AM at the site of IDH and showed no evidence of communication between IDH and the pericardium or the left ventricle (Figure 1E; Supplementary material, *Figure S1*). Analysis of CCTA performed before the accident confirmed high RCA bifurcation and non-obstructive lesions in the coronary arteries (Figure 1F). Follow-up TTE performed 2 weeks later showed partial resorption of IDH with preserved LVEF (Supplementary material, *Figure S2* and *Video S5*), so we continued conservative treatment. TTE performed 5 months later showed basal and mid inferolateral akinesia with LVEF of 52% and without IDH; TTE remained comparable at 1-year follow-up.

The management of trauma-related ACS is not standardized. Reported cases were treated with dual antiplatelet therapy, thrombolytic therapy, balloon angioplasty, stent angioplasty, or coronary artery bypass grafting [2, 3]. Prognosis worsens if IDH occurs [4]. An approach to IDH depends on the patient's stability, IDH localization, and communication

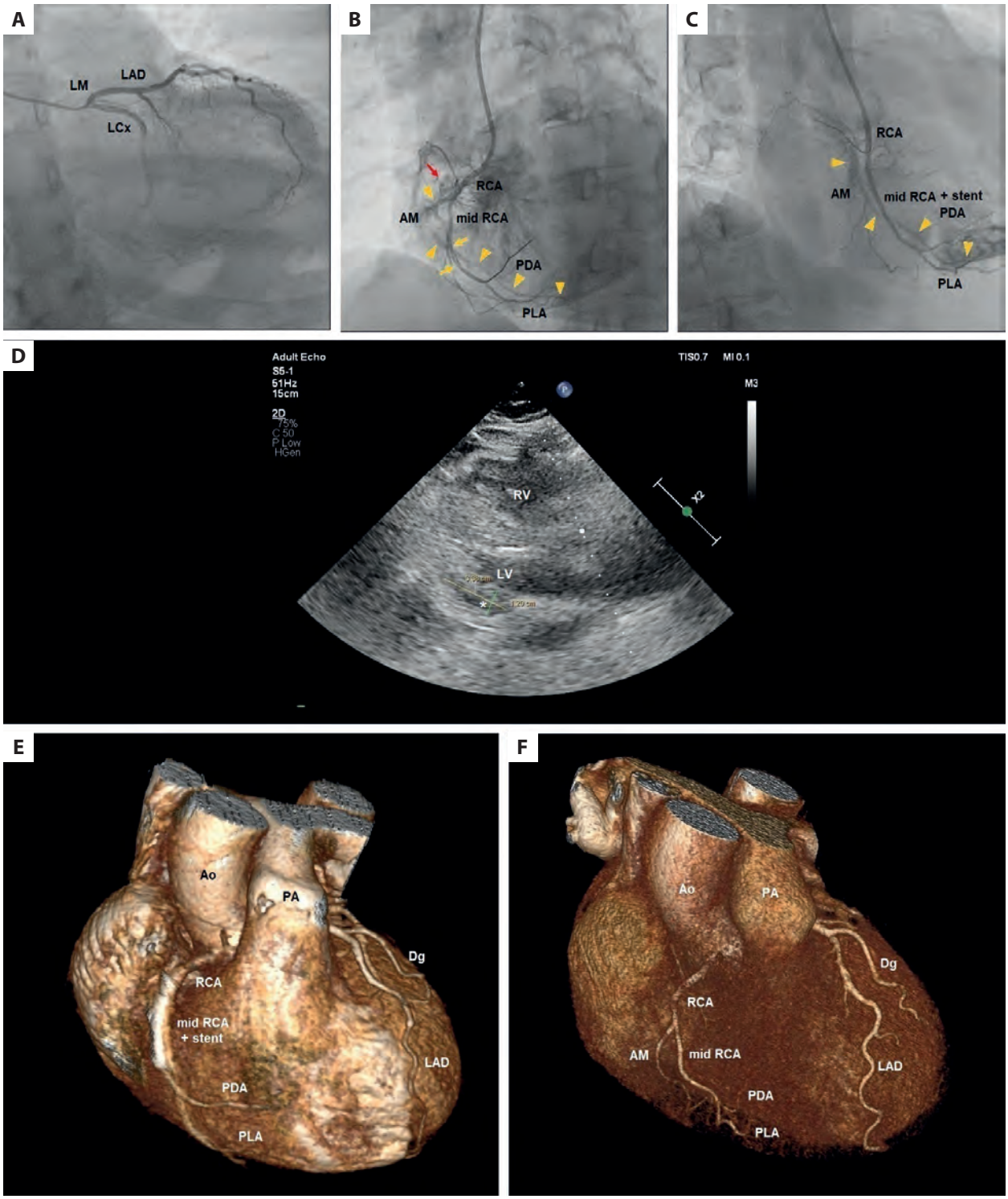

Figure 1. A–C. Invasive coronary angiography and percutaneous coronary intervention. **A.** Non-obstructive lesions in the left main coronary, left anterior descending, and left circumflex arteries. **B.** A lesion in the right coronary artery bifurcated into the mid-right coronary artery, and a crashed acute marginal branch (arrowheads) filled retrogradely from the collateral circulation from the posterolateral artery. Coronary angiogram before angioplasty showed dissection in the mid-right coronary artery (yellow arrows) and blush along the acute marginal branch with contrast jet extravasation (red arrow). **C.** The crashed acute marginal branch (arrowheads) was inaccessible with a guide wire. **D.** Transthoracic echocardiography, parasternal long axis showing intramyocardial dissecting hematoma (asterisk) 3 days after percutaneous coronary intervention, dimeters: 34 × 12 mm. **E.** 3D VR cardiac computed tomography angiography (64 thick) performed 3 days after percutaneous coronary intervention confirmed total occlusion of the crashed artery. **F.** 3D VR cardiac computed tomography angiography (128 thick) performed 1 year before the accident demonstrated high bifurcation of the right coronary artery into the mid-right coronary artery and the acute marginal branch with non-obstructive lesions

Abbreviations: AM, acute marginal branch; Ao, aorta; Dg, diagonal branch; IDH, intramyocardial dissecting hematoma; PA, pulmonary artery; PDA, posterior descending artery; PLA, posterolateral artery; LAD, left anterior descending artery; LCx, left circumflex artery; LM, left main artery; LV, left ventricle; RCA, right coronary artery; RV, right ventricle; VR, volume rendering

with IDH [4]. In our case, we decided to treat trauma-related ACS with primary percutaneous coronary intervention and IDH conservatively in the case of patient's stability, no presence of communication between IDH and the cavities, and gradual resorption of IDH with favorable short- and long-term outcomes.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: None declared.

Funding: None.

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A rare case of intravascular leiomyomatosis from the ovarian vein to the right atrium in an asymptomatic woman

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DOI: 10.33963/v.kp.98714

Received:
November 3, 2023

Accepted:
December 28, 2023

Early publication date:
January 2, 2024

Intravascular leiomyomatosis (IVL) is a rare benign condition characterized by non-tissue-invasive intravascular proliferation of smooth muscle cells originating from uterine venous wall or uterine leiomyoma, affecting premenopausal women, typically with a history of uterine leiomyoma or gynecological surgery [1]. The vascular spread is usually *via* iliac or ovarian veins [2], occasionally extending into the inferior vena cava and right heart chambers (intracardial leiomyomatosis).

Symptoms, if present, are usually non-specific and arise from vascular or intracardiac obstruction, potentially leading to cardiac failure. The treatment of choice is total surgical resection, including hysterectomy [3]. However, the therapeutic plan depends on the patient's clinical status, her desire to preserve fertility, and the size and extent of the lesion. Alternative treatment options are hormonotherapy or observation. The recurrence rate is about 16.6%–30% [4], therefore, long-term follow-up is recommended.

This condition was first described by Birch-Hirschfeld in 1896. The incidence of this disease is 0.25% to 0.40% of patients with uterine fibroma [3]. Full IVL pathogenesis remains unclear. Until now, more than 300 cases have been described in the literature.

In this report, we present a case of an asymptomatic 64-year-old woman who was referred to our hospital for further investigation of a mass in the right heart atrium and the inferior vena cava on echocardiography. She had no relevant medical history, and other examinations were negative, apart from the intravascular mass. These included gynecological examination with ultrasound, with no fibroids found. There was no history of gynecological surgery. The differential diagnosis of the mass included thrombus, leiomyosarcoma, soft-tissue sarcoma, lymphoma, tumor thrombosis, and metastasis.

Contrast-enhanced computed tomography (CT) demonstrated intravascular tortuous enhancing non-invasive mass extending from the right ovarian vein through the inferior vena cava to the right atrium (Figure 1A). 18F-FDG positron emission tomography/CT demonstrated low glucose metabolism of the intravascular mass (Figure 1B–C). Both examinations made IVL the most likely diagnosis, the sole confounder was the absence of fibroids or gynecologic surgery. Examinations also ruled out other complications such as organ ischemia.

The multidisciplinary team suggested surgical treatment. The patient consented and underwent a one-stage extensive surgery performed by an experienced cardiovascular surgery team. We administered extracorporeal circulation, deep hypothermia 28°, aortic cross-clamp (for 28 minutes, cardioplegia custodiol 1000 ml), and 8-minute circulatory arrest. During that time, the tumor was extracted in one piece through a radial incision in the right atrium. The inferior vena cava was inspected, and the right ovarian vein was extirpated (Figure 1D). With a partial clamp on the right atrium, we started cardiopulmonary bypass and rewarming, and we sutured the right atrium. No periprocedural complications were reported, and the patient made an excellent postoperative recovery.

Histopathology showed (Figure 1E–F) epitheloid cells with abundant stromal hyalinization immunoreactive for both α-actin and estrogen receptors, consistent with the

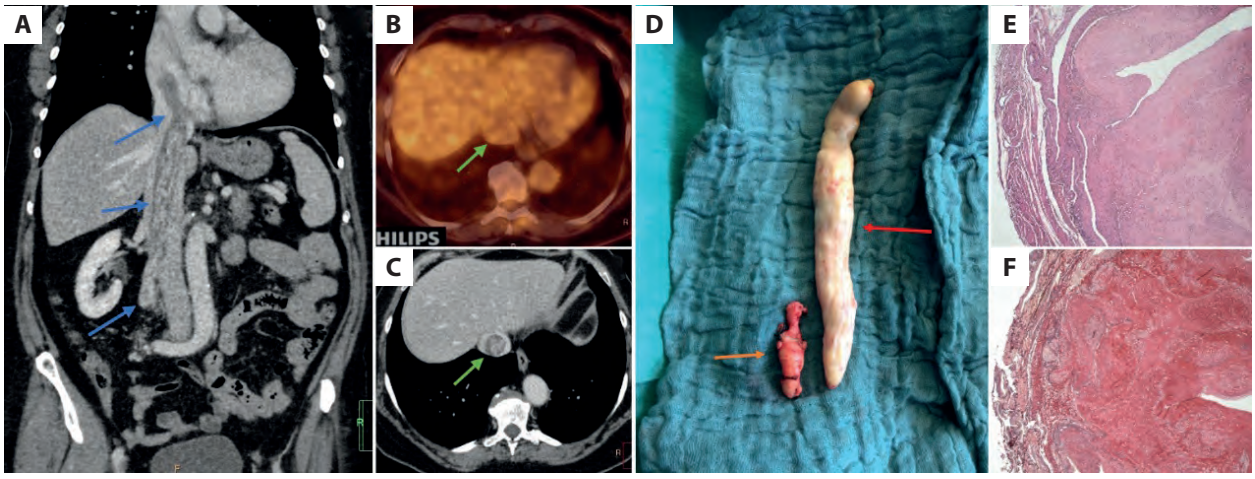

Figure 1. A. Computed tomography (CT) oblique coronal reformat demonstrating enhancing mass extending from the right ovarian vein, through the inferior vena cava to the right atrium (blue arrows). **B, C.** Comparison of an axial slice of contrast-enhanced CT (**B**) and fused positron emission tomography/CT (**C**) demonstrating low glucose metabolism of the intravascular mass (green arrows). **D.** Surgical specimen of the tumor extracted from the inferior vena cava (red arrow) and the extirpated right ovarian vein with tumor (orange arrow). **E, F.** Histopathologic specimen of leiomyoma consisted of epitheloid cells with abundant stromal hyalinization and edema obturating the lumen of the ovarian vein. Hematoxylin and eosin stain (**E**). Verhoeff-Van Gieson stain (**F**)

diagnosis of intravascular leiomyomatosis. Adjuvant hormonal therapy was not indicated since complete surgical resection was achieved [5].

Although the guidelines suggest bilateral salpingo-oophorectomy and hysterectomy to prevent recurrence, the patient preferred regular follow-up without any additional surgery. Subsequently, an expert gynecological ultrasound discovered one small uterine fibroid (9 mm in size). Follow-up examinations (cardiac magnetic resonance, CT, and pelvic ultrasound) showed no signs of local recurrence, and the patient remains asymptomatic.

Article information

Conflict of interest: None declared.

Funding: None.

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Insidious infective endocarditis: Should we use positron emission tomography more often?

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DOI: 10.33963/v.kp.96588

Received:
May 20, 2023

Accepted:
July 18, 2023

Early publication date:
September 18, 2023

The diagnosis of infective endocarditis on a prosthetic valve (PVE) remains a challenge even for an experienced team. Effective diagnosis of the disease is particularly important due to the high percentage of in-hospital mortality (~17%) [1]. In addition to symptoms that may have a heterogeneous clinical manifestation, blood cultures, and echocardiography play a key role in baseline diagnostic workup. In some cases, making a diagnosis requires a more sophisticated diagnostic approach.

A 35-year-old man with a history of aortic valve replacement with the Edwards Magna 23 mm bioprosthesis due to regurgitation in the course of infective endocarditis (IE) three years earlier, was admitted to the hospital for a periodic fever up to 38.5°C appearing in the evenings over the past 1.5 months. The patient had been hospitalized one month earlier in another cardiology department, where negative blood cultures were obtained, and transthoracic (TTE) and transesophageal echocardiography (TEE) showed no echocardiographic evidence of PVE. IE was excluded based on that, and the patient was discharged home.

Currently, on admission patient was in stable condition and denied any symptoms. Physical examination revealed low-grade fever and a loud systolic murmur over the whole heart, radiating to the carotid arteries. Laboratory tests demonstrated elevated inflammatory markers (C-reactive protein 69 mg/dl, white blood cell count 11 × 10^3/μl), normocytic anemia (hemoglobin 11.5 g/dl), and slightly elevated levels of fibrinogen (484 mg/dl), D-dimer concentration (586 ng/ml) and N-terminal pro-B- type natriuretic peptide (163 pg/ml). Chest X-ray showed no consolidations. Again, TTE and TEE showed no echocardiographic evidence of IE. Due to the fever of unknown origin, it was decided to perform [^{18}F]fluorodeoxyglucose positron emission tomography ([^{18}F]FDG PET)], which showed a moderately increased uptake of [^{18}F]FDG in the area of the aortic valve, with the maximum standard uptake value (SUVmax) = 3.4, most likely due to inflammation [2]. Furthermore, a positive blood culture with *Streptococcus mitans* and a positive urine culture with *Enterococcus faecalis* were obtained. Urinalysis was negative for urinary tract infection. This led to the diagnosis of PVE.

According to current guidelines, PVE patients should receive intravenous antibiotic treatment for 6 weeks [3]. In our case, antibiotic therapy with intravenous ceftriaxone (2 g once a day) for 28 days and gentamicin (240 mg once a day) for 21 days was applied, resulting in clinical improvement, resolution of fever, normalization of inflammatory markers, and negative blood cultures. After 28 days, it was decided to switch the patient to an oral antibiotic treatment with amoxicillin (1 g three times a day) for 14 days. The patient was discharged home in good condition with the recommendation to discontinue amoxicillin after 14 days [4]. During follow-up visits at 1 and 6 months, no signs, symptoms, laboratory, or echocardiographic findings (in TTE) of IE were found; there was no evidence of bioprosthesis degeneration.

The purpose of reporting this case is to underline clinical utility of [^{18}F]FDG PET in the management of patients with suspected PVE. [^{18}F]FDG PET has high sensitivity (86%) and specificity (84%) for IE diagnosis [5]. We were able to show the clinical course of IE

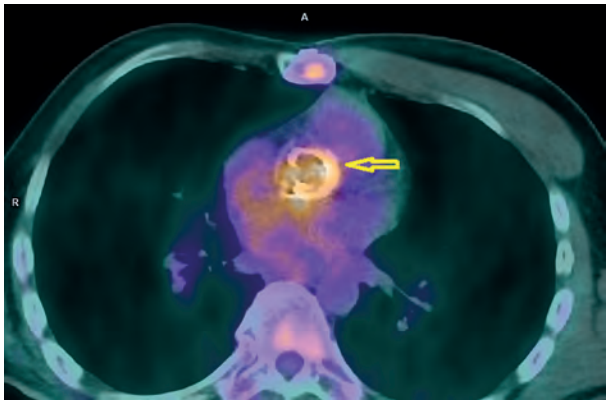

Figure 1. Fusion images of PET/CT performed to diagnose infective endocarditis. Images were acquired with a Biograph 64 PET/CT scanner (Siemens Medical Solutions, Inc.) 60 minutes after injection of 330 mBq [^{18}F]FDG. Presented image shows a transversal, fused PET/CT image, corrected for attenuation. Yellow arrow shows increased radiotracer uptake in the aortic annulus consistent with infection. The semiquantitative PET/CT analysis was performed using the SYNGOVIA application. Standardized uptake value (SUVmax) for valve area was 3.4; reference (myocardial blood pool [MBP] was 2.1, liver SUVmax 2.9)

treated partially with oral antibiotics following the results of a randomized trial in a selected group of IE subjects, which showed that replacing intravenous antibiotics with oral treatment was safe and shortened the patient's hospital stay [4].

Article information

Conflict of interest: None declared.

Funding: None.

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The effect of comprehensive management of heart failure in an adult with a systemic right ventricle

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DOI: 10.33963/v.kp.98305

Received:
October 16, 2023

Accepted:
November 23, 2023

Early publication date:
January 3, 2024

Patients with a systemic right ventricle (SRV) represent a significant proportion of adults with congenital heart defects (CHD) [1]. Over time, most of them show various degrees of heart failure (HF) symptoms [1–5]. The lack of clear guidelines based on hard evidence and the increasing number of adult CHD patients make treatment of SRV failure one of today's greatest challenges.

We present a case of a 40-year-old woman with corrected congenital transposition of great arteries, double-outlet right ventricle, ventricular septal defect, and dextrocardia, after surgical closure of septal defect at the age of five. She was admitted for symptoms of HF in New York Heart Association (NYHC) class III — exertional dyspnea and multiple episodes of presyncope. From her pediatric care period to her current admission, she had been under the care of a regional cardiology center, without any pharmacotherapy.

Transthoracic echocardiography (TTE) revealed a significantly enlarged SRV with poor systolic function (11 mm tricuspid annular plane systolic excursion [TAPSE] and 6.4 cm/s when the longitudinal velocity of the tricuspid annulus [S'] was evaluated by tissue Doppler), moderate/severe systemic and moderate mitral valves regurgitations (Figure 1A). SRV ejection fraction in cardiac magnetic resonance imaging was 18%. The N-terminal pro B-type natriuretic peptide was 5856 pg/ml. The initial maximal oxygen consumption (VO_2max) was 16.6 ml/min/kg. However, an exercise test was complicated by a significant drop in blood pressure and prodromal symptoms of syncope in recovery. Holter electrocardiography showed significant ventricular arrhythmia with 14 episodes of nonsustained ventricular tachycardia (nsVT), right bundle branch block, QRS widening up to 200 ms, and first-degree AV block (Figure 1B). The patient received pharmacotherapy recommended in classical HF: sotalol 2 × 40 mg, dapagliflozin 10 mg, sacubitril/valsartan 24/26 mg, spironolactone 25 mg.

Moreover, she was qualified for urgent cardiac resynchronization therapy (CRT-D) implantation with computed tomography (CT) guidance (Figure 1C). The chest X-ray in Figure 1D shows the final position of the leads. After 4 months, CRT-D control revealed high latency with approximately 300 msec between the pacing peak and the left ventricular (LV) response. After exclusion of electrode dislocation, optimization of CRT-D system settings was performed with transthoracic echocardiography assistance from the M3-SVC vector biventricular pacing (LV to SRV) with LV preexcitation of 80 ms. Sotalol was changed to bisoprolol (2.5 mg).

At follow-up after 12 months, the patient reported significant improvement in exercise tolerance and NYHA class II symptoms. VO_2max increased to 22.3 ml/kg/min, without any worrisome effort-related symptoms. The echocardiographic picture of SRV was stable with ejection fraction estimated at around 20% (2D SRV volume quantification and visual assessment by a very experienced echocardiography specialist in a modified SRV-focused view), improved TAPSE (12 mm), and S' (7.5 cm/s), moderate/severe systemic atrioventricular valve regurgitation (Figure 1E). However, the N-terminal pro B-type natriuretic peptide level decreased to 3832 pg/ml. On Holter electrocardiography, the average heart rate was 64/min with stimulation of 97% with

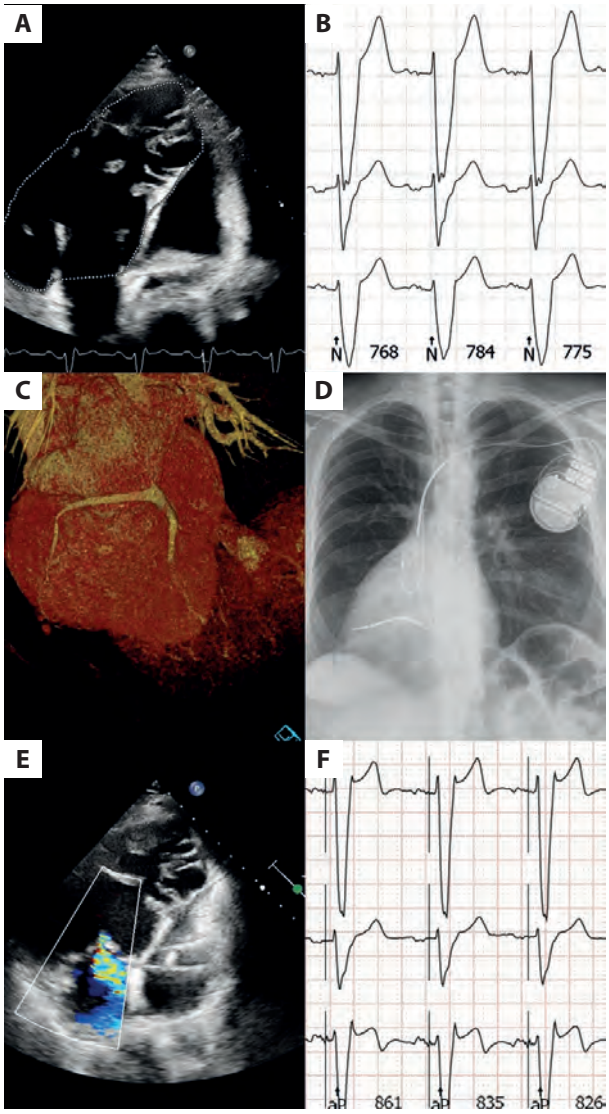

Figure 1. A. Apical four-chamber view on initial echocardiography. Enlarged systemic right ventricle (SRV). **B.** Image from Holter electrocardiography (ECG) recording before treatment. **C.** 3D reconstruction from computed tomography angiography performed before the procedure of cardiac resynchronization therapy (CRT-D) device implantation, with coronary sinus imaging. **D.** Chest X-ray after implantation of CRT-D showing the final position of the leads. **E.** Apical four-chamber view on echocardiography conducted after comprehensive treatment. The stable picture of SRV with ejection fraction estimated at around 20% and moderate/severe systemic atrioventricular valve regurgitation. **F.** Holter ECG monitoring recording after successful CRT-D implantation with apparent shortening of QRS complexes

1845 ectopic ventricular beats but without nonsustained ventricular tachycardia episodes (Figure 1F). Due to the tendency to hypotension, the doses of the drugs were not escalated.

Our case confirms the efficacy and safety of comprehensive management of SRV failure. However, this subject is still debatable [1–5]. A recent study based on the German National Register for Congenital Heart Disease revealed that in the SRV population cardiovascular drug polypharmacy was rare (4.5%), and 38.5% of patients did not take any medication [5]. The impact of comprehensive management including sacubitril/valsartan and flozins in SRV failure treatment should be further investigated.

Article information

Conflict of interest: None declared.

Funding: None.

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Aortic root aneurysm in a patient with Marfan syndrome and D-transposition of the great arteries

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DOI: 10.33963/v.kp. 97719

Received:
September 9, 2023

Accepted:
October 1, 2023

Early publication date:
October 16, 2023

We present a case of a 13-year-old boy with Marfan syndrome and an aortic root aneurysm. In medical history, the child was diagnosed at birth with D-transposition of the great arteries (D-TGA) and operated on with arterial switch operation (ASO) with the Le Compte maneuver. The diagnosis of Marfan syndrome was established at the age of 3 years. Follow-up transthoracic echocardiography (TTE) showed a progressive life-threatening aortic root aneurysm requiring cardiac surgery. On cardiac evaluation, the patient was in good condition. Vital signs showed a regular heart rate of 70/min, blood pressure of 110/70 mm Hg, and normal oxygen saturation (SaO_2) >95%. The Marfan phenotype was found on physical examination with a tall and slender silhouette (body weight 53 kg, height 1.8 m, bovine serum albumin [BSA], 1.72 m^2), scoliosis, pectus deformity, arachnodactyly and nearsightedness.

Transthoracic echocardiography (TTE) and magnetic resonance imaging showed left ventricular dilation (end-diastolic diameter 60 mm, z score +2.4, end-systolic diameter 43 mm, z score +3.0), decreased contractility (ejection fraction [EF], 55%), significant aortic annulus dilatation (37 mm, z score +6.9), aortic root aneurysm (51 mm, z score +6.3 measured from inner edge to inner edge at the widest diameter in diastole) and severe aortic valvar regurgitation (Figure 1A–C; Supplementary material, *Video S1–S3*). The patient was qualified for the Bentall procedure in cross-clamp circulation. The pulmonary trunk was in front of the aorta following the Le Compte maneuver and required resection to get access to the aneurysm. Aortic root replacement was performed with a mechanical prosthetic valve (29 mm SJM masters HP series Valved Graft) followed by coronary arteries re-implantation. Finally, a 22-mm valved prosthesis was implanted at the position of the pulmonary trunk with an additional 16 mm prosthesis into the pulmonary confluence creating a letter "T". Hemostasis was a severe problem, and the patient required blood, fresh frozen plasma, and platelets transfusions as well as a TachoSil Fibrin Sealant Patch. The postoperative period was complicated by low cardiac output and poor myocardial contractility. Therefore, mechanical circulatory support was established with extracorporeal membrane oxygenation (ECMO) via the femoral vein and aortic arch cannulas. The patient was unstable despite multidrug therapy with adrenaline, dopamine, milrinone, and levosimendan infusions.

Coronary angiography revealed features of distal embolization of the right coronary artery (Figure 1D; Supplementary material, *Video S4–S6*). Pleural and pericardial bleeding required chest revision, with ECMO cessation and a simultaneous Nuss procedure, with titanium steel bar implantation correcting chest deformity. Right heart catheterization was performed and a 12 mm × 39 mm BeGraft balloon expandable covered stent (Bentley InnoMed, Hechingen, Germany) with low foreshortening and high radial force was deployed into the stenotic right pulmonary artery. The stent was redilated with a 16 mm Tyshak balloon catheter, with simultaneous left pulmonary artery angioplasty (Figure 1E; Supplementary material, *Video S7–S9*). Within

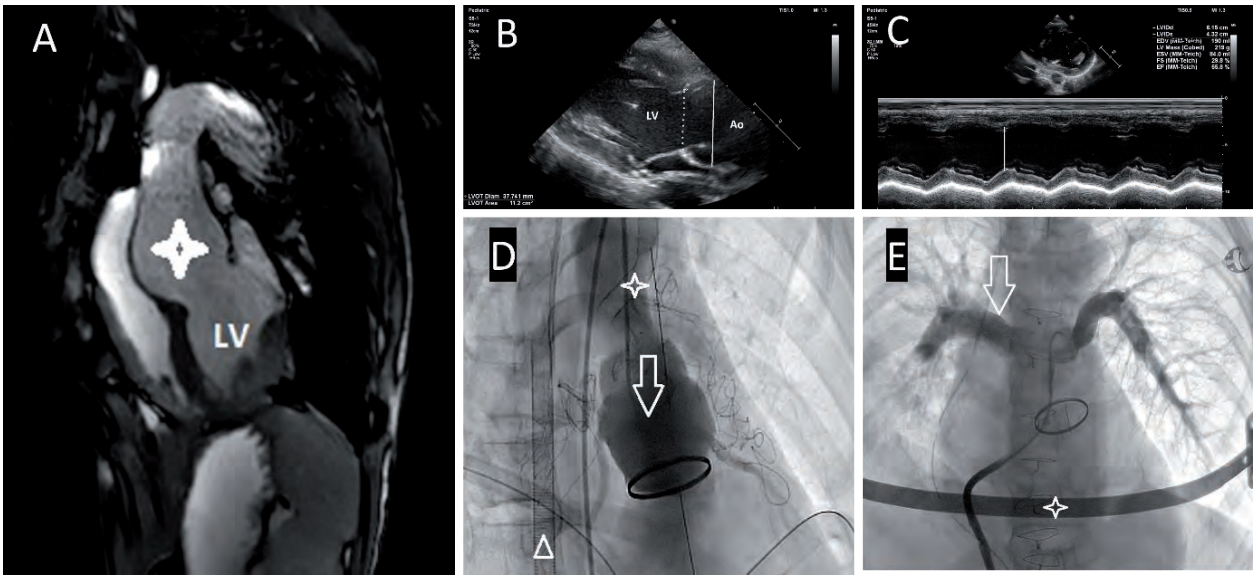

Figure 1. A. MRI. Lateral view showing dilated left ventricle and aortic root aneurysm (white star). **B.** TTE. Parasternal long axis view. Dilated aortic valve 37 mm (dotted line) and aortic root aneurysm 51 mm (white line). **C.** TTE. M-mode in parasternal long axis view of the left ventricle showing dilated end-diastolic and end-systolic (white line) diameter with decreased ejection fraction of 55%. **D.** Aortography in RAO 30° projection. Extracorporeal circulation with aortic (white star) and venous (white triangle) cannulas. Aortic prosthesis (white arrow) with artificial aortic valve (black eclipse). **E.** Pulmonary trunk angiography in cranial view (38°) showing right pulmonary artery with a covered stent (white arrow) and left pulmonary artery following balloon angioplasty. A steel bar (white star) implanted during Nuss procedure due to chest deformity

Abbreviations: MRI, magnetic resonance imaging; RAO, right anterior oblique; TTE, transthoracic echocardiography

two weeks TTE showed improvement with left ventricular ejection fraction (EF, 42%) and right ventricular fractional area change (40%). Chronic respiratory failure required a temporary tracheotomy. The patient was discharged home in good condition with multidrug therapy (warfarin, angiotensin-converting-enzyme inhibitor, and verospiron).

Conclusion: Patients with congenital heart defects require lifelong follow-up and reoperation of significant residual or newly emerging lesions, especially with coexisting Marfan syndrome, which predisposes to progressive aortic root dilation requiring an extensive range of operations with high risk of postoperative complications [1–5].

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: None declared.

Funding: None.

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An unusual long-term follow-up of a patient with a left ventricular pseudoaneurysm after myocardial infarction

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DOI: 10.33963/v.kp.97727

Received:
July 10, 2023

Accepted:
October 5, 2023

Early publication date:
October 19, 2023

Left ventricular free wall rupture can be complicated by cardiac tamponade or pseudoaneurysm. The latter complication manifests clinically with heart failure and thromboembolic complications, but 10% to 48% of patients remain asymptomatic [1, 2].

A thin wall and reduced stress tolerance increase the risk of pseudoaneurysm rupture, which occurs in 30% to 45% of cases [3]. The gold standard treatment is cardiac surgery [1]. In rare cases, pseudoaneurysms are treated conservatively or with percutaneous repair [4].

A 75-year-old woman was admitted for inferolateral myocardial infarction. We performed *ad hoc* circumflex artery angioplasty that was complicated by coronary artery perforation. Surgical relief of cardiac tamponade was performed, and the perforation was successfully sealed using a TachoSil patch. The patient developed paroxysmal atrial fibrillation, which was treated with rivaroxaban.

At 8 weeks, the patient had a consultation with the Heart Team due to a pseudoaneurysm in the inferolateral left ventricular wall, as shown on computed tomography (CT) (Figure 1A). She was considered ineligible either for surgical or percutaneous aneurysm closure. Discontinuation of anticoagulant treatment was recommended. Follow-up CT (Figure 1B) at 5 months showed significant thrombosis of the aneurysm. During the subsequent year, ambulatory treatment with rivaroxaban was introduced. Control CT (Figure 1C) revealed partial recanalization of the aneurysm. Following the previous percutaneous closure of the left atrial appendage using the Watchman device, and 8 weeks after the procedure, anticoagulant treatment was discontinued. This led to the formation of a device-related thrombus, as shown on echocardiography (Figure 1D) at 12 weeks. Ten months after the initiation of rivaroxaban, the device-related thrombus resolved and partial recanalization of the pseudoaneurysm was achieved, as evidenced by magnetic resonance imaging. Anticoagulant treatment was again discontinued, but imaging studies 2 months later showed a free-floating thrombus originating from the aneurysm cavity as well as multiple occlusions in the arteries of the right lower limb. Unfractionated heparin was administered, followed by rivaroxaban, resulting in complete thrombus resolution after 7 days of treatment. CT at 3 months revealed the lack of an organized thrombus. The size of the pseudoaneurysm remained stable over the 3-year follow-up. The Heart Team decided on the continuation of rivaroxaban.

Despite cardiac surgery recommendation for our patient [5], we opted for a watchful waiting approach, mainly because of the high perioperative risk (sternotomy 2 months earlier) and good general clinical condition [2]. The decision on anticoagulant treatment remained challenging. On one hand, anticoagulation was necessary due to atrial fibrillation. On the other hand, it could compromise wall thickness by reducing the thrombus content of the aneurysm. Data on anticoagulant treatment in patients with pseudoaneurysms are scant. In our patient rivaroxaban led to partial recanalization of the pseudoaneurysm. However, discontinuation of anticoagulant treatment resulted in the formation of a device-related thrombus following Watchman device placement as well as a free-floating thrombus arising from the thrombosed aneurysm. Based on the risk-benefit assessment,

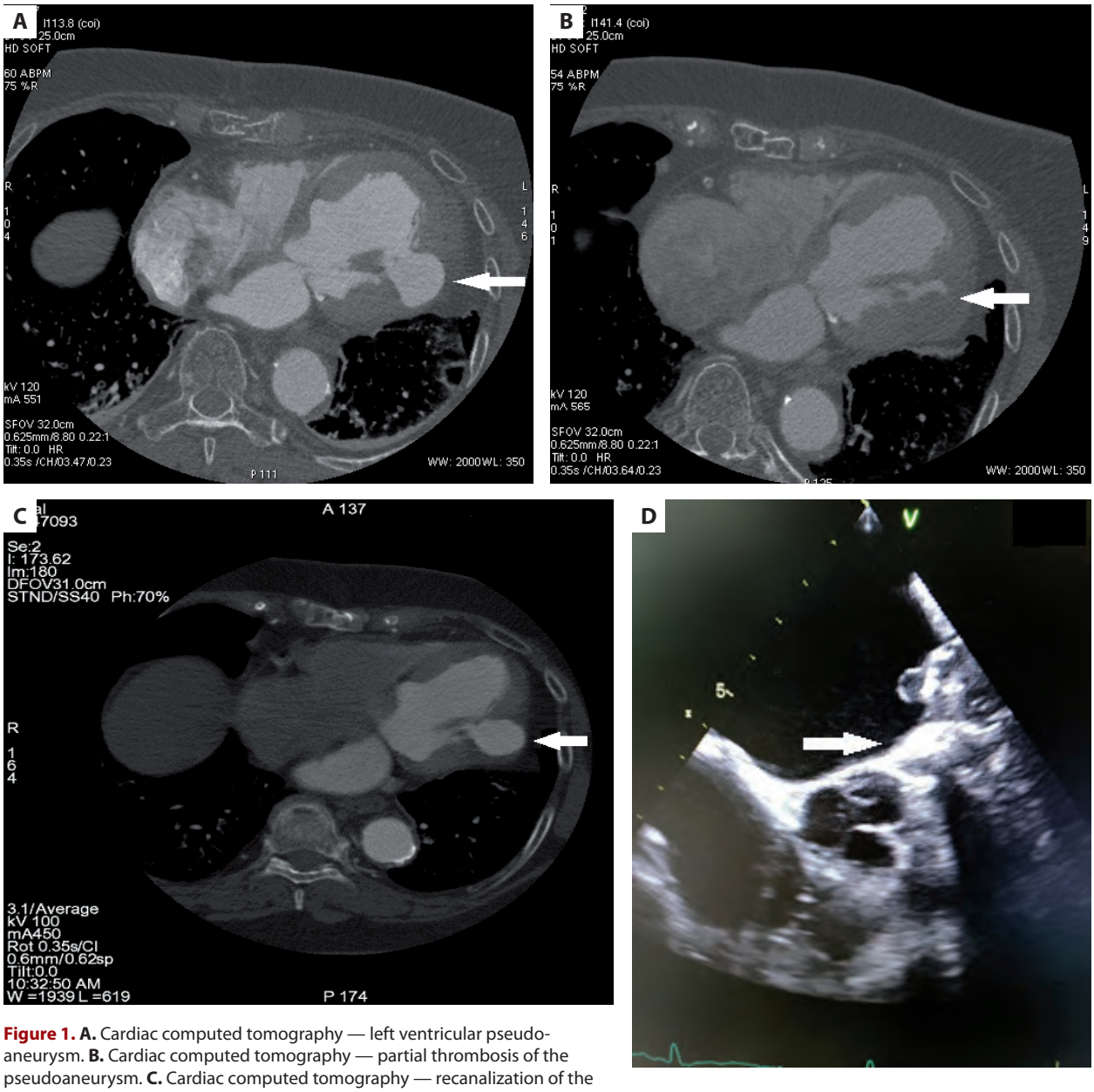

Figure 1. A. Cardiac computed tomography — left ventricular pseudoaneurysm. **B.** Cardiac computed tomography — partial thrombosis of the pseudoaneurysm. **C.** Cardiac computed tomography — recanalization of the pseudoaneurysm. **D.** Transesophageal echocardiography. The arrow indicates a thrombus adherent to the occluding device

the final decision was made to continue anticoagulation with rivaroxaban. During the 4 years of follow-up, the patient remained in good clinical condition.

Article information

Conflict of interest: None declared.

Funding: None.

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Current practice of care for adolescent and adult patients after Fontan surgery in Poland: Heart transplantation

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DOI: 10.33963/v.kp.98383

Received:
November 29, 2023

Accepted:
November 30, 2023

Early publication date:
December 1, 2023

We have read with great interest the article "Current practice of care for adolescent and adult patients after Fontan surgery in Poland" by Ewa Warchoł-Celińska et al. [1] along with the connected Editorial article by Clift et al. [2]. It is very good to know that an attempt to unify the care of the patients after Fontan surgery has been made in our country. The number of included patients was quite large — 398, taking into consideration that only 6 cardiological centers from Poland participated in the survey. In the records of the Pediatric Outpatient Clinic (not including the Adult Outpatient Clinic) of the Silesian Center of Cardiology Diseases in Zabrze (Poland), there have been 262 patients with single ventricles registered from 2008, and 30 of them had Fontan operation. In the latter group, over time, a significant number of complication occurs, including impairment of ventricular function and heart failure, regurgitation of the atrioventricular valves, protein-losing enteropathy, hepatic failure, progressive cyanosis, thromboembolic complications, development of vascular fistulas in the lung, arrhythmias, etc. Currently, the ultimate treatment for failed Fontan circulation is cardiac transplantation, which is a very complex procedure per se, with very promising results when successful [3]. Clift et al. [2] stated that all specialized centers treating patients after Fontan operation should have a relationship with a cardiac transplant center to be able to assess patients for possible cardiac transplantation. In our Center, to date, 8 such procedures have been performed by dr Szymon Pawlak (publication in preparation).

Article information

Conflict of interest: None declared.

Funding: None.

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Current practice of care for adolescent and adult patients after Fontan surgery in Poland: Heart transplantation. Author's reply

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DOI: 10.33963/v.phj.98873

Received:
January 6, 2024

Accepted:
January 6, 2024

Early publication date:
January 10, 2024

Thank you for your interest in our article "Current practice of care for adolescent and adult patients after Fontan surgery in Poland" [1]. Indeed, we believe that a formalized surveillance approach for Fontan patients is crucial to providing optimal care for those patients. This approach should aim at preventing Fontan circulation failure and extending patient survival. We appreciate the positive evaluation of our efforts [2].

We would like to emphasize that our study aimed to evaluate the current practice of care for Fontan patients in Poland using a multicenter survey, and we did not assess the clinical data of Fontan patients or their treatment. We obviously agree that in failing Fontan patients, heart transplantation is both the ultimate, but very complex, procedure with promising results when successful.

We follow, with great appreciation, progress in the field of heart transplantation in failing Fontan patients in Poland, which in adults often has to be performed with simultaneous liver transplantation. We would like to congratulate the team from the Silesian Center for Heart Diseases for their pioneering efforts and for performing an impressive number of heart transplantations in this extremely challenging group of patients. We agree with the authors of the letter that an experienced transplant center should be an essential element in the network of coordinated care for patients after Fontan surgery.

Article information

Conflict of interest: None declared.

Funding: None.

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Sudden cardiac arrest in the setting of coronary artery ectasia: Mechanistic and clinical perspectives

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DOI: 10.33963/v.kp.98414

Received:
November 7, 2023

Accepted:
December 4, 2023

Early publication date:
December 5, 2023

Coronary artery ectasia (CAE) has been defined as diffuse dilatation of a particular coronary segment presenting with a diameter >1.5 times the diameter of the reference coronary segment [1–4]. In this context, focal coronary dilatation is called a "coronary aneurysm" that involves less than one-third the length of the coronary artery [2–4]. Pathogenetically, these entities might be attributable to a variety of factors including atherosclerosis, vasculitis (such as Kawasaki disease, etc.), and iatrogenic causes, etc. [1–4]. As expected, prognosis largely depends on the underlying etiology and anatomical features [1–4]. The recent report by Zalewska-Adamiec et al. [1] has described a case of CAE involving the whole left coronary system (widely termed as type-1 CAE [2, 4]) complicated by aborted sudden cardiac arrest (SCA) during coronary angiography [1]. Accordingly, we would like to highlight some mechanistic and clinical implications of SCA in the setting of CAE (and coronary aneurysms):

In the out-of-hospital setting, SCA in patients with CAE or coronary aneurysms might have particular aspects:

- First, SCA in these patients might be caused by exercise-induced myocardial ischemia possibly as a consequence of substantial flow stagnation at the macrovascular level [1, 2, 4]. This seems consistent with the positive exercise testing in the patient despite her non-obstructive coronary anatomy [1].
- Second, severe coronary microvascular dysfunction (associated with diffuse endothelial dysfunction [2–4]) might primarily account for or contribute to exercise-induced myocardial ischemia and might also be associated with coronary flow stagnation in these patients [4]. Did the authors plan further tests for potential microvascular dysfunction including positron emission tomography, etc.?
- Third, these patients might also be prone to coronary vasospasm [1, 2, 4], and might unexpectedly incur SCA at rest. Therefore, well-known strategies for the management of vasospastic angina (VSA) (including avoidance of potential VSA triggers (high dose acetylsalicylic acid, non-selective beta-blockers, etc.) along with initiation or up-titration of calcium channel blockers) should also be implemented [4]. We wonder about the doses of prescribed agents and the typical history of VSA in the patient [1].
- Fourth, evolution of acute coronary syndromes (ACSs) due to distal coronary embolism (manifesting as myocardial infarction with non-obstructive coronary arteries) is also quite likely and accounts for SCA in some cases as well [2–4]. Therefore, long-term antiplatelet therapy and/or anticoagulation have been used in these patients largely based on the size of the ectatic or aneurysmatic segments that might change drastically in time [3, 4]. Moderate or giant aneurysms (with diameters of >2 and >4 times the diameter of the reference segment, respectively) usually require long-term anticoagulation (particularly for the secondary prevention of coronary thromboembolism) [3]. Did the patient have an overt history of ACS?
- Fifth, CAEs and coronary aneurysms (particularly the giant ones) may also be complicated by mechanical complications including rupture and fistula formation that might present with a non-arrhythmic SCA and require urgent surgery [3, 4].

- Finally, persistent giant dilatations, rapid expansion, intractable anginal symptoms, recurrent ACSs (despite optimal therapy), and co-existing stenotic lesions may warrant elective percutaneous or surgical intervention [3, 4] to prevent possible SCA. Regardless of the management strategies, aborted SCA in the out-of-hospital setting should warrant implantable-cardioverter defibrillator implantation in these patients. We also wonder about the schedule of surveillance (Holter monitoring, frequency of coronary imaging on follow-up, etc.).

Importantly, these patients may also have a significant proclivity for arrhythmic SCA in the setting of coronary angiography and coronary interventions due to a variety of specific triggers [1]. One such trigger might be catheter-induced coronary spasm (a phenomenon well known to be more frequent in patients with vasospastic angina). Therefore, excessive manipulation of engaged coronary catheters and also other tools (guidewires, etc.) should be avoided in these patients. Notably, intermittent intracoronary nitrate injection might be a potential strategy for the prevention of coronary vasospasm during coronary interventions (though long-term use of nitrates is discouraged in these patients [1, 4]). Another SCA trigger in this context might be excessive and forceful injection of contrast agents (for better visualization) that might potentially lead to contrast-induced arrhythmogenesis [1] and also possible fragmentation and embolism of a pre-existing coronary thrombus. Consequently, prolonged (but not forceful) injection of contrast agents during cineangiography seems more prudent. Therefore, we wonder about the pattern and magnitude of cardiac troponin elevation (if any) that might have suggested coronary embolism [1].

In conclusion, SCA in patients with CAE might be considered a multi-faceted phenomenon mostly associated with a variety of ischemic triggers [1–4]. Therefore, strategies aiming to mitigate such ischemic triggers (both in interventional and out-of-hospital settings) are necessary for SCA prevention in these patients.

Article information

Conflict of interest: None declared.

Funding: None.

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Sudden cardiac arrest in the setting of coronary artery ectasia: Mechanistic and clinical perspectives. Author's reply

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DOI: 10.33963/v.kp.98718

Received:
December 23, 2023

Accepted:
December 27, 2023

Early publication date:
December 28, 2023

We would like to thank Yalta et al. [1] for their interest in our report on sudden cardiac arrest (SCA) during diagnostic coronary angiography in a patient with coronary artery ectasias (CAE) [2].

We believe that coronary artery ectasias constitute a very important clinical problem, both diagnostic and therapeutic, therefore, the occurrence of such a serious complication as SCA in our patient with CAE motivated us to describe this case. Unfortunately, the limited number of words in the clinical vignette prevents a thorough discussion of all clinical aspects. Therefore, we are especially grateful for all the valuable comments of Yalta et al., to which we can respond here.

Yalta et al. presented possible causes of SCA in patients with CAE in clinical implications:

- Myocardial ischemia due to slowed flow at the macrovascular level. We consider this aspect to be the most likely cause of the angina pain reported by our patient.
- Severe dysfunction of coronary microcirculation responsible for myocardial ischemia. We cannot rule out microcirculation disorders in our patient, but currently, we are not planning additional tests, such as positron emission tomography. Further diagnosis of the causes of ischemia in the patient depends on the further clinical course.
- Possible vasospastic component requiring appropriate pharmacological treatment [3]. In our patient, we did not find a typical history of vasospastic angina. The patient received typical pharmacological treatment (acetylsalicylic acid 75 mg/day, cilazapril 5 mg/day, amlodipine 5 mg/day, bisoprolol 3.75 mg/day, and rosuvastatin 10 mg/day). Trimetazidine 2 × 35 mg/day was added to the treatment.
- Occurrence of acute coronary syndromes as a result of peripheral embolism of the distal sections of coronary arteries. Our patient has not had any acute coronary syndrome to date.
- Mechanical complications of ectatically dilated arteries (rupture, fistulas).
- Percutaneous and cardiac surgical interventions in patients with advanced coronary artery ectasias resistant to pharmacological treatment. Qualifying these patients for interventional treatment is extremely difficult and requires joint decision-making within the Heart Team and often additional hemodynamic tests, e.g. fractionated flow reserve [4].

Analyzing all possible SCA mechanisms in our patient, we considered slow flow of the injected contrast agent in the ectatically dilated left coronary artery to be the most likely cause. We referred our patient for further outpatient cardiological care with the recommendation for regular electrocardiography monitoring using the Holter method. However, the in-depth diagnostics (positron emission tomography, imaging of the coronary arteries) depend on the patient's clinical condition.

To sum up, the presented case and demonstrated clinical implications related to coronary artery ectasias indicate the need for special cardiological care for these patients, taking into account various diagnostic tests and therapeutic methods. However, maintaining registries and long-term observational studies of CAE patients would allow for the development of recommendations for the management of these patients in long-term care.

Article information

Conflict of interest: None declared.

Funding: None.

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Identification and therapy for patients with heart failure with preserved ejection fraction: An expert opinion of the Heart Failure Association of the Polish Cardiac Society

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DOI: 10.33963/v.phj.98878

Received:
January 2, 2024

Accepted:
January 2, 2024

Early publication date:
January 10, 2024

ABSTRACT

Diagnosis of heart failure with preserved ejection fraction (HFpEF) may be challenging owing to the heterogeneous clinical presentation and comorbidities in this population of patients, along with the limited availability of standard diagnostic tools, including natriuretic peptide tests and functional testing. This expert opinion summarizes the current state of knowledge on the identification and therapy for patients with HFpEF based on recent European and American recommendations. This expert opinion aims to aid clinicians in HFpEF management.

Key words: heart failure, heart failure with preserved ejection fraction

Heart failure (HF) with preserved ejection fraction (HFpEF) is diagnosed in patients with HF and an ejection fraction of 50% or higher. This HF phenotype accounts for at least 50% of HF cases, and the HFpEF population is growing due to aging and the increasing prevalence of risk factors for HF [1]. Of all the HF types, HFpEF is associated with the most heterogeneous clinical presentation and the highest comorbidity burden. Therefore, symptoms often overlap (e.g., dyspnea in patients with concomitant chronic obstructive pulmonary disease), further complicating the HFpEF diagnosis [2, 3]. Importantly, even in the presence of medical conditions with overlapping symptoms, patients should be tested for HF. Moreover, according to the most recent 2023 expert consensus of the American College of Cardiology (ACC), diagnosis of HFpEF should account for medical entities, both cardiac and noncardiac, that can mimic HFpEF (so-called HFpEF mimics) [4]:

Cardiac disease mimics:
- infiltrative cardiomyopathy,
- hypertrophic cardiomyopathy,
- valvular disease,
- pericardial disease,
- high-output heart failure;

Noncardiac disease mimics:
- kidney disease,
- liver disease,
- chronic venous insufficiency.

All this may constitute a challenge in the identification of HFpEF patients in daily clinical practice. Thus, this expert opinion aimed to aid clinicians in the diagnosis of HFpEF.

According to the universal definition proposed in 2021, HF is a clinical syndrome with symptoms and/or signs that are caused by structural and/or functional cardiac abnormality, as confirmed by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion [5]. Pulmonary or systemic congestion may be

Table 1. Signs and symptoms of heart failure [2]

Symptoms	
Typical	Breathlessness Orthopnea Paroxysmal nocturnal dyspnea Reduced exercise tolerance Fatigue, tiredness Prolonged recovery after exercise Ankle swelling
Less typical	Nocturnal cough Wheezing Bloated feeling Loss of appetite Confusion (especially in the elderly) Depression Palpitation Dizziness Syncope Bendopnea
Signs	
More specific	Elevated jugular venous pressure Hepatojugular reflux Third heart sound (ventricular gallop) Laterally displaced apical impulse
Less specific	Unintentional weight gain >2 kg/week Weight loss Cachexia Cardiac murmur Peripheral edema (ankle, sacral, scrotal) Pulmonary rales Pleural effusion Tachycardia Tachypnea (>16/min) Irregular pulse Narrow pulse pressure Hepatomegaly Ascites Oliguria Cheyne-Stokes respiration Cold extremities

confirmed by chest X-ray, echocardiography, or hemodynamic measurement (right heart catheterization). The signs and symptoms of HF are summarized in Table 1. The most common manifestations of HFpEF are dyspnea and edema.

For each patient with dyspnea, reduced exercise tolerance, weakness, and easy fatigue, HF suspicion should be raised, and a stepwise diagnostic process should be used to avoid misdiagnosis (Figure 1) [2, 4, 6].

The first step is to establish the probability of HF based on clinical data. The patient should be assessed for the presence of risk factors as well as signs and symptoms of HF. Patients with the following risk factors have a high probability of HFpEF: older age, hypertension, atrial fibrillation (AF), diabetes, chronic kidney disease, previous cardiotoxic cancer treatment, or obesity.

Signs and symptoms of HF are nonspecific and may be present also in other entities. Examples of medical conditions that should be considered in differential diagnosis include coronary artery disease, lung disease, and anemia.

The second step in the diagnosis of HFpEF involves beside physical examination testing (Figure 1). The following tests are recommended in all patients with suspicion of HF (class of recommendation I) [2]:

1) measurement of B-type natriuretic peptide (BNP) levels or N-terminal pro B-type natriuretic peptide (NT-proBNP);
2) routine laboratory testing: complete blood count, urea, creatinine, electrolytes, fasting glucose, glycated hemoglobin HbA1c, iron tests (ferritin, transferrin saturation), lipid levels, thyroid function;
3) chest X-ray (absence of abnormalities does not exclude HF); and
4) resting electrocardiogram (ECG).

ECG in patients with suspicion of HF may reveal AF, abnormal Q waves, signs of left ventricular (LV) hypertrophy, and prolonged QRS complex. ECG sensitivity in HFpEF is lower than that in HF with reduced ejection fraction. Normal ECG findings are reported in 35% to 45% of HFpEF patients [7].

Natriuretic peptides are an important component of the universal definition of HF and the second step in the diagnostic algorithm. Natriuretic peptide levels below the recommended cutoff point (<35 pg/ml for BNP and <125 pg/ml for NT-proBNP) have a high negative predictive value (95%–99%). This means that a patient with dyspnea and an NT-proBNP level below 125 pg/ml has a low risk of HF and should be examined for other causes of dyspnea if there are no other data to indicate a high clinical probability of HF [2–4, 6]. When interpreting the results of natriuretic peptide tests, it is important to consider other conditions that are associated with elevated levels (such as older age, chronic kidney disease, AF) as well as reduced levels of natriuretic peptides, such as obesity or current use of HF medications (Table 2A).

For accurate interpretation of natriuretic peptide measurements, it is important to know the patient's heart rhythm because AF patients have 3- to 3.5-fold higher natriuretic peptide levels, and the cutoff value for HF is 365 pg/ml or higher for NT-proBNP and 105 pg/ml or higher for BNP [2, 8]. Importantly, even up to 25% of patients with invasively confirmed HFpEF may have NT-proBNP levels of less than 125 pg/ml [8].

In line with the universal definition of HF, elevated natriuretic peptide levels constitute an important component of HF diagnosis, and the higher the levels of these markers, the higher the clinical probability of HF.

Natriuretic peptide measurements should always be interpreted together with clinical and echocardiographic data

Echocardiographic examination is the third step in the diagnostic algorithm. It is important not only for assessment of ejection fraction but also for assessment of structural and/or functional abnormalities, whose presence is required for the diagnosis of HFpEF in line with the European Society of Cardiology (ESC) guidelines [2–4].

When interpreting echocardiographic findings, clinicians should look beyond ejection fraction alone. In HFpEF patients, other abnormalities should be considered, including LV hypertrophy, left atrial enlargement, abnormal mitral inflow pattern (which indicates LV diastolic dysfunction and elevated LV filling pressure), and tricuspid regurgitation in-

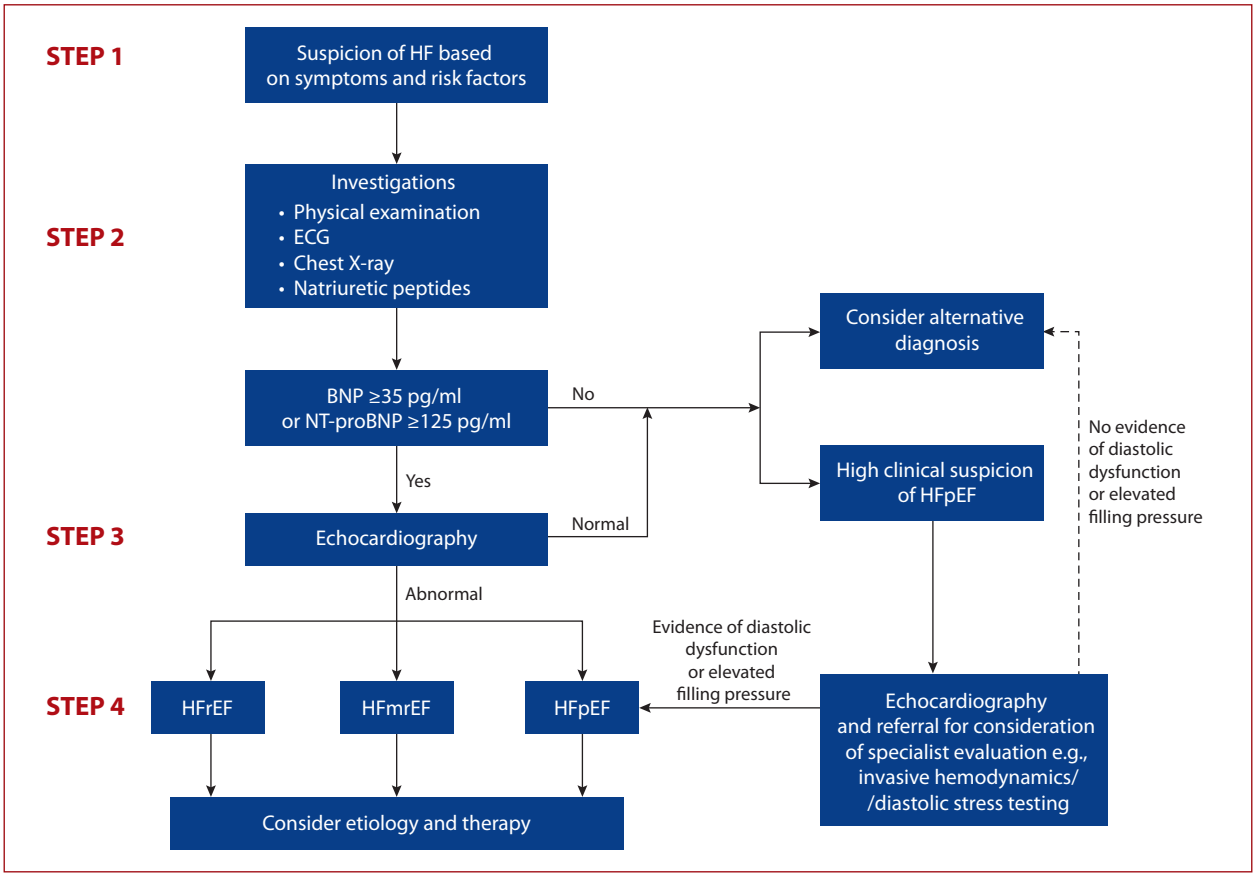

Figure 1. Algorithm for the diagnosis of heart failure [2, 4, 6]

Abbreviations: BNP, brain natriuretic peptide; ECG, electrocardiography; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide

Table 2. Practical principles for the use and interpretation of natriuretic peptides

A. Causes of elevated and reduced natriuretic peptide concentration (modified from McDonagh et al. [2])

Selected causes of elevated natriuretic peptide levels		Reduced natriuretic peptide levels
Cardiac	Noncardiac	
Heart failure	Advanced age	Obesity (by 50%)
Acute coronary syndrome	Anemia	Dehydration
Cardiomyopathy, including hypertrophic cardiomyopathy	Kidney disease	Hypovolemia
Valvular heart disease, congenital heart disease	Liver disease (e.g., cirrhosis with ascites)	Previous heart failure treatment
Pericardial disease	Chronic obstructive pulmonary disease	Cardiac tamponade
Atrial fibrillation	Severe pneumonia, sepsis	
Myocarditis	Ischemic stroke	
Cardiac surgery	Subarachnoid hemorrhage	
Cardioversion, ICD shock	Paraneoplastic syndrome	
Cardiotoxicity, including cancer treatment	Severe burns	
Pulmonary hypertension	Severe metabolic and hormone abnormalities (e.g., thyrotoxicosis, diabetic ketoacidosis)	

Abbreviations: ICD, implantable cardioverter-defibrillator

B. Rule-out cutoff values for natriuretic peptide levels in acute and chronic heart failure according to the body mass index [13]

Heart failure	Natriuretic peptide	BMI	Cut-off points (ng/l)
Acute	BNP	All	<100
		If BMI <25 kg/m^2	<170
		If BMI 25–35 kg/m^2	<110
		If BMI ≥35 kg/m^2	<54
	NT-proBNP	–	<300
Chronic	BNP	–	<35
	NT-proBNP	–	<125

Abbreviations: BMI, body mass index; other — Figure 1

Table 3. Echocardiographic abnormalities in heart failure with preserved ejection fraction [2, 4]

Parameter	Threshold	Comment
LV mass index	≥95 g/m² (women) ≥115 g/m² (men)	The absence of LV hypertrophy does not exclude the diagnosis of HFpEF
Relative wall thickness	>0.42	
Left atrial volume index	>34 ml/m² (sinus rhythm) >40 ml/m² (atrial fibrillation)	Left atrial enlargement reflects chronically elevated LV filling pressure (in the absence of atrial fibrillation or valve disease)
E/e'	>9 at rest	Sensitivity, 78%; specificity, 59% for the presence of HFpEF confirmed by invasive exercise testing
Tricuspid regurgitation velocity	>2.8 m/s at rest	Sensitivity, 54%; specificity, 85% for the presence of HFpEF confirmed by invasive exercise testing
Pulmonary artery systolic pressure, estimated	>35 mm Hg	

Abbreviations: LV, left ventricular; other — Figure 1

Table 4. The H_2FPEF score for the diagnosis of heart failure with preserved ejection fraction [2, 8]

	Clinical variable	Values	Points
H_2	**H**eavy	BMI >30 kg/m²	2
	Hypertensive	≥2 antihypertensive drugs	1
F	Atrial **F**ibrillation	Paroxysmal or persistent	3
P	**P**ulmonary hypertension	PASP >35 mm Hg	1
E	**E**lderly	Age >60 years	1
F	**F**illing pressure	E/e' >9	1

Abbreviations: E/e', ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity; PASP, pulmonary artery systolic pressure; other — see Table 2

dicating elevated right ventricular systolic pressure, which in the absence of pulmonary stenosis, suggests elevated pulmonary artery pressure.

The 2021 ESC guidelines [2] and the 2019 consensus recommendation of the Heart Failure Association of the ESC [8] indicate the echocardiographic parameters that provide objective evidence of structural and/or functional abnormalities specific to HFpEF (Table 3) and propose diagnostic workup including minor and major echocardiographic criteria in the HFA-PEFF score [8]. The algorithm for echocardiographic evaluation of left ventricular filling pressure in HFpEF is well described in the expert consensus document of the European Association of Cardiovascular Imaging [9]. However, in clinical practice, it is possible that echocardiographic assessment will not include all these parameters. In such cases, it is recommended to examine the parameters that are used in clinical trials of HFpEF: 1) LV wall thickening at ≥12 mm; 2) left atrial enlargement, increased left atrial volume, and/or increased left atrial volume index; and 3) signs of diastolic dysfunction or elevated filling pressure (formerly referred to in the literature as impaired relaxation, pseudonormal mitral inflow pattern, or restrictive mitral inflow pattern). The higher the number of abnormalities on echocardiography, the greater the probability of HFpEF.

Patients with normal echocardiographic findings and/or low natriuretic peptide levels (NT-proBNP <125 pg/ml, BNP <35 pg/ml), but with a high clinical probability of HFpEF, should be referred to a specialist center for extensive diagnostic workup with functional or invasive hemodynamic testing (right heart catheterization) (Figure 1) [6]. The diagnosis of HFpEF is established based on the presence of signs of diastolic dysfunction or elevated LV filling pressure; however, this kind of testing is not widely available. These signs are

1) in diastolic stress testing: stress echocardiography with average E/e' ≥15; tricuspid regurgitation velocity >3.4 m/s or invasive testing with pulmonary capillary wedge pressure >25 mm Hg at peak exercise, or
2) right heart catheterization at rest: pulmonary capillary wedge pressure >15 mm Hg [6].

In the absence of these findings, the patient should be examined for other causes of the presenting symptoms [6].

The HFA experts emphasized that the use of the clinical scoring system H_2FPEF and the HFA-PEFF diagnostic algorithm can aid in diagnosis of suspected HFpEF. Both algorithms are based on the assessment of the likelihood that HFpEF is the underlying cause of the patient's dyspnea.

In patients with dyspnea and no signs of fluid overload, use of the H_2FPEF score is recommended to establish the diagnosis of HFpEF. The H_2FPEF score is a simple diagnostic tool that includes 4 clinical and 2 echocardiographic variables (Table 4), each assigned several points [10]. A total score of 6 points or higher indicates a high probability of HFpEF (>90%). The H_2FPEF algorithm can be used when natriuretic peptide testing or echocardiography is not available. For example, a patient with obesity (body mass index 31 kg/m²), hypertension, treated with 2 antihypertensive drugs, and a history of paroxysmal AF obtains a total H_2FPEF score of 6 points (probability of HFpEF = 90%). If this patient was older than 60 years, then the H_2FPEF score would be 7 points, and the probability of HFpEF would reach 95%.

In contrast, the HFA-PEFF diagnostic algorithm, is less well validated and performs worse than the H_2FpEF score in terms of HFpEF diagnostics in the outpatient setting. In our

Table 5. Multimodality imaging and etiology approach in HFpEF [9]

Etiology	Echo	Coronary angiography (CT or invasive)	CT	CMR	SPECT	DPD (bone and cardiac)	PET	Right catheterization at rest/exercise
Arterial hypertension	+++	+		+				
CAD	+++	+++		+++	+++		+++	
HCM	+++			++				
Cardiac amyloidosis	+++			++		+++	+	
Cardiac sarcoidosis	++			+++			+++	
Storage disease e.g. Fabry	+++			+++				
Constrictive pericarditis	+++		+++	+++				+++
Non-cardiac PH	+++		++					+++

Abbreviations: CAD, coronary artery disease; CMR, cardiovascular magnetic resonance imaging; CT, computed tomography; DPD, 99mTc with 3,3-diphosphono-1,2-propanodicarboxilic acid bone and cardiac scintigraphy, planar scintigraphy; HCM, hypertrophic cardiomyopathy; PET, positron emission tomography, useful for assessing cardiac sarcoidosis; PH, pulmonary hypertension; SPECT, single photon emission computed tomography

opinion, it is challenging to use this diagnostic algorithm in the Polish healthcare system because of the limited access to functional/invasive testing [4, 8, 11].

Once HFpEF diagnosis is confirmed, the fourth step is to determine the etiology of HF using advanced imaging (advanced echocardiography, cardiac magnetic resonance, DPD single-photon emission computed scintigraphy, cardiac computed tomography coronary angiography, or positron emission tomography). Table 5 presents the multimodality imaging and etiology approach in HFpEF [9].

Previous hospitalization is important for the identification of an HFpEF patient if:

- that hospitalization was for reduced exercise tolerance, peripheral edema, and/or pulmonary congestion, and fluid overload was confirmed by imaging tests;
- the patient received intravenous drugs (diuretics, vasodilators, and/or positive inotropic agents). The diagnosis is further confirmed by elevated natriuretic peptide levels and echocardiographic abnormalities described above if the tests were done during hospitalization. A positive response to standard HF treatment such as loop diuretics also increases the probability of HFpEF.

The most important clinical scenarios associated with the risk of HFpEF are described below.

OBESITY

Obesity is one of the strongest risk factors for HFpEF. Overweight or obesity was reported in 80% of patients with HFpEF [12]. Diagnosis of HFpEF in patients with obesity remains challenging. Clinical symptoms such as shortness of breath or fatigue are observed in patients with obesity with and without HFpEF. On the other hand, HFpEF patients often do not present with typical HF symptoms such as neck vein distension, third heart sound, displaced apex beat, or ankle edema. Moreover, chest X-ray and transthoracic echocardiography, the cornerstones of HF diagnostics, provide poorer-quality images in obese patients as compared to lean individuals. Furthermore, it was reported that diagnosis of acute congestive HF may be missed in 1 of every 5 patients with a body mass index of more than 35 kg/m^2 when using the standard cutoff point of 100 pg/ml for BNP [13]. The link between obesity and low natriuretic peptide levels is well-known and constitutes an important problem in clinical practice. Therefore, to improve the accuracy of HFpEF diagnosis in obese patients, new cutoff values were proposed for acute HF (Table 2B) [13]. However, the BNP and NT-proBNP cutoff points for identifying chronic HF in obese patients remained the same as in the general HF population.

ATRIAL FIBRILLATION

Atrial fibrillation is a common comorbidity in patients with any HF phenotype. It is estimated that AF is present in about 50% of HFpEF patients [2, 4, 8]. On the one hand, it may lead to HF (it is a major risk factor for HF, especially HFpEF). On the other hand, HF is a common cause of AF.

Diagnosis of HF in AF patients constitutes a considerable challenge because of the nonspecific symptoms (like in HF). The most common symptoms related to AF are fatigue/tiredness, dyspnea on exertion, and, less commonly, palpitations.

Atrial fibrillation alone causes elevated levels of natriuretic peptides. Therefore, it is recommended that clinicians use higher thresholds for BNP and NT-proBNP to establish HF diagnosis in AF patients than those used for sinus rhythm, as mentioned above. According to the 2021 ESC guidelines on HF management, the threshold for HFpEF diagnosis in AF patients is >365 pg/ml for NT-proBNP (>105 pg/ml for BNP), as compared to 125 pg/ml in those with sinus rhythm [2]. Atrial fibrillation, especially in cases with a rapid ventricular rate, may lead to tachycardia-induced cardiomyopathy. In some patients, it may initially be fully asymptomatic. We recommend that AF patients should be routinely assessed for HF and those with HF should be routinely assessed for AF.

It is important to note that in the H_2FPEF scoring system for HFpEF diagnosis, the presence of AF scores 3 points. It seems that the H_2FPEF score should be recommended for use in daily clinical practice also in those patients who have limited access to natriuretic peptide testing.

CARDIAC AMYLOIDOSIS

In the 2023 ACC consensus, cardiac amyloidosis is listed as one of HF mimics [4]. Although in some patients, cardiac amyloidosis leads to the development of HF symptoms, its treatment is different. Cardiac amyloidosis is typically a type of restrictive cardiomyopathy, which is caused by extracellular accumulation of amyloid deposits. The two most common types of amyloidosis include immunoglobulin light chain (AL) amyloidosis, characterized by the deposition of abnormal light chains, and transthyretin (TTR) amyloidosis, which is caused by the deposition of amyloid fibrils composed of the TTR protein.

Recent advances in research have vastly improved the accuracy of noninvasive diagnostic evaluation for TTR amyloidosis based on scintigraphy. As a result, TTR amyloidosis is increasingly commonly diagnosed, especially in older patients [13]. However, TTR amyloidosis is still underdiagnosed in a large proportion of HF patients, particularly those with HFpEF. The most common symptoms that indicate amyloidosis [14] are left ventricular hypertrophy ≥12 mm and ≥1 of the following:

- HF in patients aged ≥65 years,
- elevated NT-proBNP levels (disproportionately to the degree of HF),
- aortic stenosis in patients aged ≥65 years,
- low or normal blood pressure in patients with previous hypertension,
- autonomic or sensory neuropathy,
- peripheral polyneuropathy,
- proteinuria,
- bilateral carpal tunnel syndrome,
- biceps tendon rupture,
- subendocardial late gadolinium enhancement or increased extracellular volume,
- reduced longitudinal strain with the apical sparing pattern on echocardiography,
- reduced QRS voltage to the degree of LV thickness,
- pseudo-infarct ECG pattern,
- atrioventricular conduction disorders on ECG
- family history.

OLD AGE AND HFpEF

The percentage of patients at older age has been increasing due to a global increase in longevity. HFpEF is common in the elderly population. The incidence of HF gradually increases with age, reaching about 20% in patients older than 75 years. Therefore, some authors describe HF as a geriatric syndrome associated with poorer prognosis, longer residual disability, and the presence of common age-related comorbidities. The typical causes of HFpEF at older age or comorbidities in elderly patients with HFpEF include hypertension, obesity, diabetes, AF, coronary artery disease, obstructive sleep apnea, and chronic kidney disease [15].

In daily clinical practice, it may be difficult to differentiate between physiological aging and the presence of HFpEF in elderly patients. Cardiac abnormalities associated with aging and differences between the physiological symptoms of aging and symptoms of HFpEF are summarized in Table 6.

Table 6. Age-related cardiac changes and differences between the symptoms of physiological aging and heart failure with preserved ejection fraction

Age-related cardiac changes	
Left ventricle	Left ventricular hypertrophy, preserved or impaired diastolic function
Right ventricle	Preserved ejection fraction, diastolic dysfunction, changes in the geometry of the right ventricular outflow tract
Atria	Atrial enlargement, mechanical dysfunction, atrial fibrillation
Systolic function	Reduced maximal cardiac output, reduced cardiac output reserve
Coronary arteries	Endothelial dysfunction, atherosclerosis
Chronotropic activity	Reduced maximal heart rate, increased chronotropic response to beta-adrenergic receptor stimulation
Cardiac muscle	Cardiac fibrosis due to chronic neurohumoral activation
Peripheral arteries	Vascular stiffness, endothelial dysfunction, hypertension, vasodilatation, aneurysms, pulmonary hypertension
Aging heart	**HFpEF**
Symptoms	
Mild Subjective fatigue Reduced exercise tolerance Low mood	Significant Objective evidence of reduced exercise tolerance Dyspnea on exertion/at rest Peripheral edema
Comorbidities	
Less common Typically, obesity	Common Chronic kidney disease, chronic obstructive pulmonary disease, anemia
Cardiac comorbidities	
Less common Typically, hypertension	Common Typically, atrial fibrillation Atherosclerosis
Echocardiography	
Physiological changes associated with aging: • Mild atrial enlargement • Low LV volume • Reduced LV mass • Mild LV hypertrophy • Age-related diastolic function	Pathological cardiac remodeling Significant atrial enlargement Increased LV volume Increased LV mass Increased LV filling pressure Signs of diastolic dysfunction
Natriuretic peptides	
Normal or slightly elevated	Significantly elevated

Abbreviations: see Table 3

The aging process and the above comorbidities may induce chronic systemic inflammation, leading to myocardial remodeling and HFpEF [16]. Owing to the specific characteristics of the elderly age group and the presence of various comorbidities with overlapping symptoms, HF is often underdiagnosed in these patients [17].

SEX-RELATED DIFFERENCES IN THE DIAGNOSIS OF HFpEF

Compared with men, women with HFpEF have more severe dyspnea and more often have a reduced quality of life [18].

Table 7. Recommendation for the treatment of patients with symptomatic heart failure with preserved ejection fraction [2, 22]

Recommendation	Class	Level
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended to reduce the risk of heart failure hospitalization, or cardiovascular death	I	A
Diuretics are recommended for patients with fluid retention to alleviate symptoms and signs	I	C
Treatment for etiology, cardiovascular, and non-cardiovascular comorbidities is recommended	I	C

Physical examination is usually similar in men and women with HFpEF; however, diagnostic tests may reveal some sex-related differences. For example, women with HFpEF more often have more severe LV concentric remodeling on echocardiography, which is associated with greater impairment of LV relaxation and higher diastolic stiffness, as compared with men [19]. Due to a more concentric remodeling, women typically have a smaller LV diameter and thus higher ejection fraction than men. This may lead to underestimation of impaired LV systolic function in women. It is important to note that patients with HFpEF are typically women at an older age who report reduced quality of life and present with numerous comorbidities such as hypertension, AF, obesity, chronic kidney disease, and type 2 diabetes.

THERAPY OF HFpEF

Taking into account the results of two trials, EMPEROR-Preserved [20] and DELIVER [21], the 2023 ESC guidelines have recommended using sodium-glucose co-transporter 2 (SGLT2) inhibitors (empagliflozin and dapagliflozin) in symptomatic patients with HFpEF to reduce the risk of HF hospitalization or cardiovascular death (class I, level A) [22]. The positive clinical effect of SGLT2 inhibitors on the quality of life is seen after a short time from the initiation of therapy [20–23]. There are also the 2023 ESC recommendations concerning patients with HFpEF for using diuretics in fluid retention and treatment for etiology, cardiovascular, and non-cardiovascular comorbidities at class I level [22]. Pharmacotherapy of HFpEF depending on the congestion, etiology, and comorbidities was also described in the 2021 ESC guidelines [2] and emphasized in the Expert Opinion of the Heart Failure Association of the Polish Cardiac Society [24, 25] and in the statement of three European associations related to different HFpEF phenotypes [26]. Table 7 presents the recommendation for therapy in HFpEF.

Finally, after the positive results of the STEP-HFpEF trial [27], it seems that a new therapeutic approach proposed by Verma et al. for patients with HFpEF and obesity will be the next change — SGLT2 inhibitors to reduce clinical events and SGLT2 inhibitors with glucagon-like peptide-1 receptor agonist (semaglutide) to improve symptoms, physical limitations, and exercise function [28].

In summary, the diagnosis of HFpEF is complex, and already at early stages of the diagnostic workup, it is necessary to establish if the patient has any cardiac or noncardiac disease that may lead to symptom overlap, affect the levels of natriuretic peptides, or mimic HFpEF. Nevertheless, to identify patients with suspected HFpEF in the outpatient setting and to establish definitive diagnosis, it is necessary to follow the diagnostic algorithm presented in this expert opinion. After identification of HFpEF, the etiology and therapy should be established.

Article information

Conflict of interest: ML received lecture and consulting fees from Boehringer Ingelheim, AstraZeneca, and Roche Diagnostics and was involved in clinical trials sponsored by Boehringer Ingelheim, Novo Nordisk, and Pfizer. AP received lecture and consulting fees from Boehringer Ingelheim, lecture fees from AstraZeneca and Roche Diagnostics. ESM received lecture fees and consulting fees from Boehringer Ingelheim and Pfizer, and lecture fees from AstraZeneca. JN received lecture and consulting fees from Boehringer Ingelheim and lecture fees from AstraZeneca and Roche Diagnostics. PR received lecture fees from Boehringer Ingelheim and Pfizer.

Funding: None.

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nadciśnienie tętnicze praktycznie

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arterial hypertension

nadciśnienie tętnicze
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Łódź, 10–11 maja 2024 roku

Przewodniczący Komitetu Organizacyjnego:

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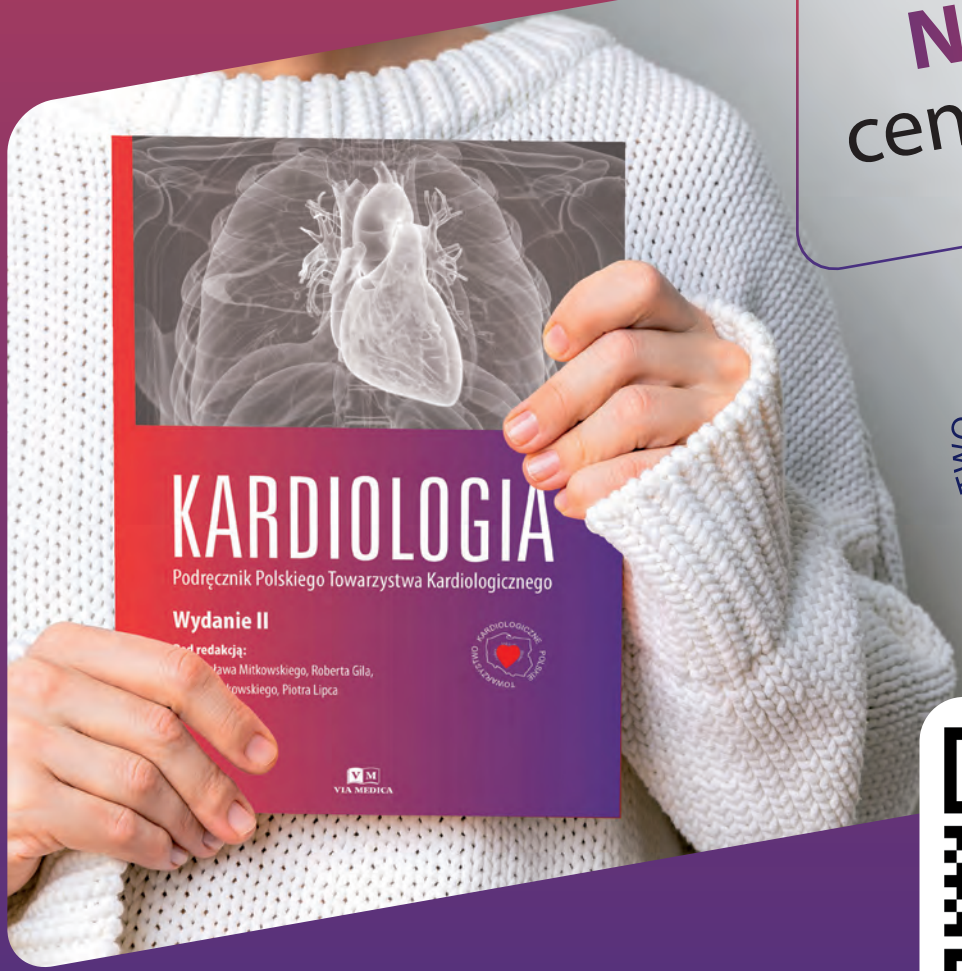

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