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Polish Heart Journal

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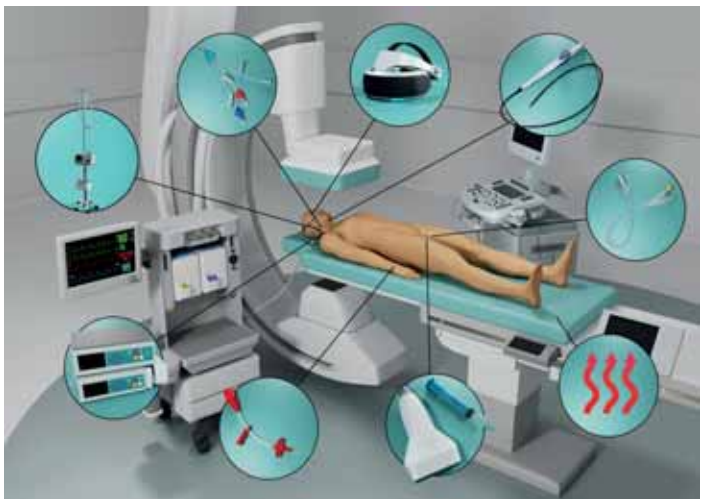

Hybrid room setup for transcatheter edge-to-edge repair, see p. 779

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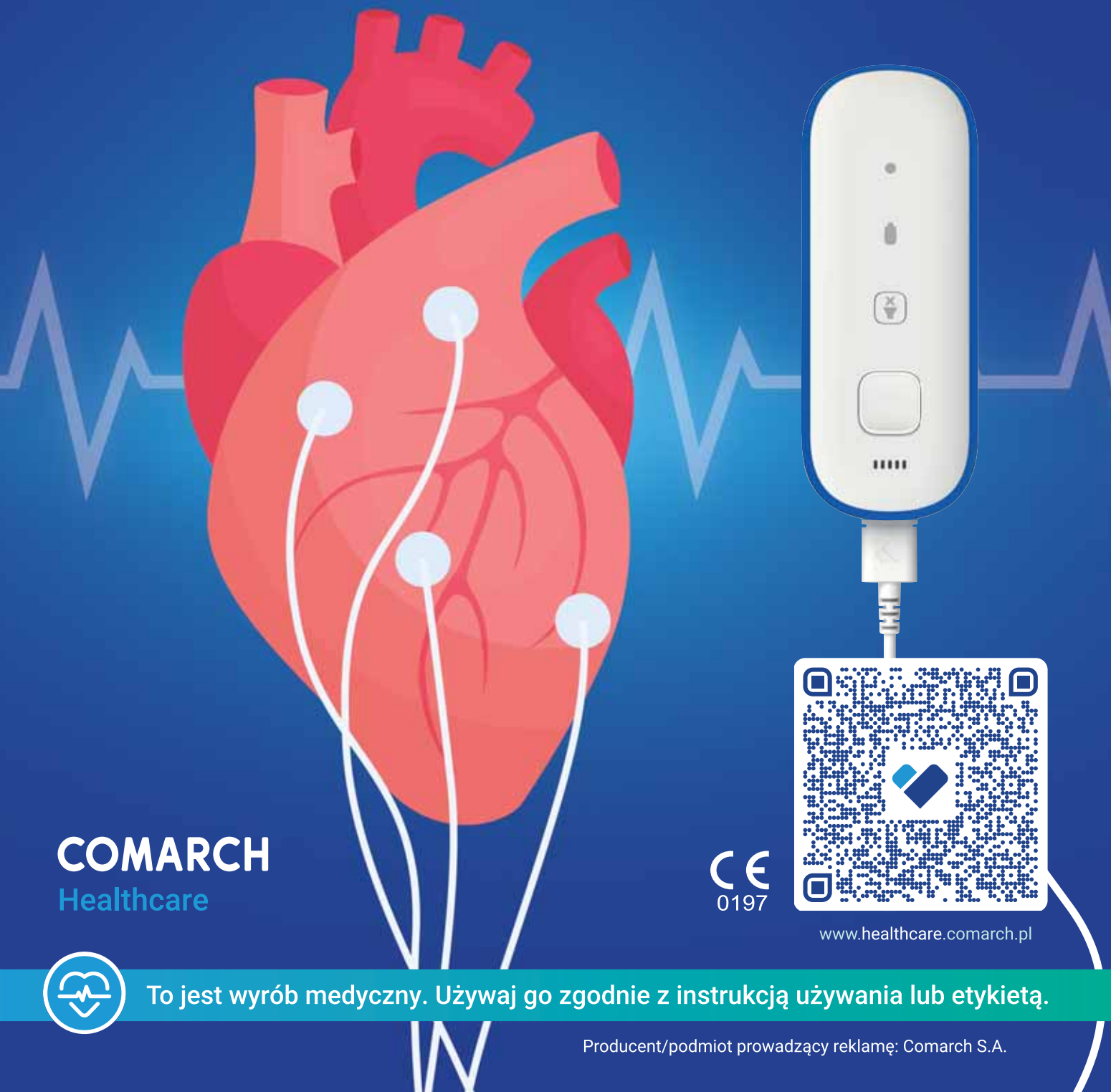

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KARDIOLOGIA POLSKA
Polish Heart Journal

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LETTER TO THE EDITOR

EXPERT OPINION

The 2022 Impact Factor of 3.3: We are the best Polish cardiology journal

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On June 28, 2023, Clarivate Analytics announced an update of the most well-known metric in scholarly publishing, the journal Impact Factor (IF) for more than 21 000 journals, as part of the Web of Science Journal Citation Reports®. This day is always a much-anticipated event for all academic publishers and editors since the two-year IF remains the most important metric of a journal's standing in sciences. This year, for the first time, the journal IF is presented with one decimal place, instead of 3, which was the tradition since its first release in 1975.

The latest IF of *Kardiologia Polska* (*Kardiol Pol*, *Polish Heart Journal*) is **3.3**. Our previous IF was slightly higher and amounted to 3.7. Reasons for this decrease are multiple starting from the fluctuations in citation counts of COVID-19 papers, a transient increase in the number of original articles up to 8 per issue in 2021, and finally, everyday challenges encountered after the change of our publisher. However, looking at the current list of top-ranking Polish scientific journals that have received their IFs (Table 1), *Kardiol Pol* has defended its position of the best cardiology journal. Notably, several Polish medical journals have suffered 10%–20% decreases in their IFs in the latest Clarivate reports. Undoubtedly COVID-19 articles contributed substantially to the total citation counts in our journal (Table 2), and less interest in this disease affected the 2022 IF. On the other hand, the best general medicine journals (with the best example of *The Lancet*, which in 2023, with IF of 202, outperformed for the first time the long-standing leader, *The New England Journal of Medicine,* with IF of 158.5) experienced an important change due to COVID-19 papers. Interesting changes in the ranking can be also observed in the cardiology category. Now the top-ranked cardiology journal is *Nature Reviews in Cardiology* (2022 IF 49.6) followed by *Circulation* (IF 39.9) and *European Heart Journal* (IF 35.8).

Table 1. List of Polish journals with the highest 2022 IF (based on the 2023 Journal Citation Reports issued by Clarivate Analytics)

Journal	2022 Impact Factor
Oeconomia Copernicana	8.5
Nonlinear Engineering — Modeling and Application	8.3
Cellular & Molecular Biology Letters	8.3
Biocybernetics and Biomedical Engineering	6.4
Equilibrium-Quarterly Journal of Economics and Economic Policy	5.7
Biology of Sport	5.6
Polish Archives of Internal Medicine — Polskie Archiwum Medycyny Wewnętrznej	4.8
Archives of Civil and Mechanical Engineering	4.4
Pharmacological Reports	4.4
Entrepreneurial Business and Economics Review	3.8
Archives of Medical Science	3.8
Pediatria i Medycyna Rodzinna — Paediatrics and Family Medicine	3.6
Reviews on Advanced Materials Science	3.6
Studies in Second Language Learning and Teaching	3.4
Kardiologia Polska (Polish Heart Journal)	3.3

The 2022 IF of 3.3 is good news since our predicted value was 3.2. The whole Society, editors, and publisher are extremely grateful to all our supporters who contributed to our present standing in 2022. The top citing investigators are as follows: Maciej Lesiak (56 citations), Mariusz Gąsior (38 citations), and Stanisław Bartuś (26 citations). We

Table 2. Eleven papers published in our journal in 2020 or 2021, which were most cited in 2022 and most contributed to the 2022 IF of 3.3

Title	Authors	Reference	2022 citation count
Association between cardiovascular disease, cardiovascular drug therapy, and in-hospital outcomes in patients with COVID-19: data from a large single-center registry in Poland	Terlecki M, Wojciechowska W, Klocek M, et al.	Kardiol Pol. 2021; 79 (7–8): 773–780	13
Dietary interventions in blood pressure lowering: current evidence in 2020	Strilchuk L, Cincione RI, Fogacci F, Cicero AFG	Kardiol Pol. 2020; 78 (7–8): 659–666	13
Every rose has its thorns — acute myocarditis following COVID-19 vaccination	Sokolska JM, Kurcz J, Kosmala W	Kardiol Pol. 2021; 79 (10): 1153–1154	12
Current challenges in the diagnosis and treatment of cardiac myxoma	Samanidis G, Khoury M, Balanika M, Perrea DN	Kardiol Pol. 2020; 78 (4): 269–277	9
The association of acute-to-chronic glycemic ratio with no-reflow in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention	Şimşek B, Çınar T, Tanık VO, et al.	Kardiol Pol. 2021; 79 (2): 170–178	8
Telemedicine solutions in cardiology	Piotrowicz R, Krzesiński P, Balsam P, et al.	Kardiol Pol. 2021; 79 (2): 215–229	8
Acute myocarditis associated with the Pfizer/BioNTech vaccine	Shumkova M, Vassilev D, Karamfiloff K, et al.	Kardiol Pol. 2021; 79 (11): 1282–1283	8
Effects of the coronavirus disease 2019 pandemic on the number of hospitalizations for myocardial infarction: regional differences. Population analysis of 7 million people	Gąsior M, Gierlotka M, Tycińska A, et al.	Kardiol Pol. 2020; 78 (10): 1039–1042	7
Identification of potential novel biomarkers and therapeutic targets involved in human atrial fibrillation based on bioinformatics analysis	Fan G, Wei J	Kardiol Pol. 2020; 78 (7–8): 694–702	7
Reaching the left bundle branch pacing area within 36 heartbeats	Jastrzębski M, Moskal P	Kardiol Pol. 2021; 79 (5): 587–588	7
Feasibility of the intravascular lithotripsy in coronary artery disease. Short-term outcomes of the Lower-Silesia Shockwave Registry	Rola P, Włodarczak A, Kulczycki JJ	Kardiol Pol. 2021; 79 (10): 1133–1135	7

appreciate every researcher who referenced our materials in 2022. We are indebted to all authors who entrusted their work, which gained much interest in 2022, to us (Table 2).

We remain committed to high-quality publishing and strive to choose articles that present novel findings of potential interest for other researchers, supported by sound methodology, in particular appropriate statistical analysis. Now we are thinking of the 2023 IF, which should be higher, proportionally to our aspirations and potential. The 2023 IF will be generated based on the total number of our citations in 2023 (regardless of the type of articles cited and including self-citations) divided by the total number of so-called citable items (including articles and reviews) published in our journal in 2021 or 2022. Therefore, we strongly encourage all our supporters, authors, and reviewers to read and cite our material starting from editorials, through reviews, original articles, and clinical vignettes, while working on new articles. Every single citation matters and without continued support of our readers, our ambitions will not be achieved in the near future.

Our society has decided to switch the titles of our journal as of January 1, 2024. The English title — *Polish Heart Journal* — will be provided first while the Polish title — *Kardiol Pol* — will be in second place. According to Clarivate Analytics, such a switch will ensure the journal will maintain its IF and avoid the risk of having to build its standing from scratch. The existence of these 2 titles (Polish and English) is likely to be challenging for authors referencing our articles; therefore, a higher IF next year is desirable. Intensified efforts to achieve, in 2023, a higher IF than in 2022 are ongoing.

During the 2023 International Congress of the Polish Cardiac Society in Poznan, we hope for inspiring discussions on how to improve our journal. All comments will be welcome so we can achieve, next year, an IF of 4 or more.

Article information

Conflict of interest: None declared.

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Fibrosis-specific biomarkers and interstitial fibrosis in hypertrophic cardiomyopathy

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Related article
by Karabinowska-Małocha et al.

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Hypertrophic cardiomyopathy (HCM) is a cardiac muscle disorder characterized by generally asymmetric abnormal hypertrophy of the left ventricle without abnormal loading conditions (such as hypertension or valvular heart disease) [1]. HCM is an autosomal-dominant genetic cardiomyopathy, and mutations in the genes encoding sarcomeric proteins are identified in 30%–60% of cases [1]. The presence of this genetic mutation carries more than a 2-fold increased risk of ventricular arrhythmias. Genetic and myocardial substrates, including fibrosis, ventricular hypertrophy, and microvascular ischemia, play a role as arrhythmogenic determinants [1].

Cardiopulmonary exercise testing seems to improve contemporary strategies for SCD risk stratification [2–4]. However, the development of new drugs for HF and cardiomyopathies should focus on the direct effect on cardiomyocytes, coronary microcirculation, and the myocardial interstitium. Detailed knowledge of interstitium and cardiomyocyte biology becomes essential [5]. The myocardial interstitium is an elaborate and active micro-habitat within the myocardium [6]. HF fibrotic changes in the interstitium and near capillaries are featured by extracellular matrix (ECM) expansion and myofibroblast secretion of type I collagen [5]. A cardiac magnetic resonance imaging technique, T1 mapping, which measures extracellular volume fraction [ECV] in the human myocardium, permits the distinction of different components of the interstitium (cardiomyocytes and connective tissue) and a more precise definition of myocardial fibrosis [5].

To develop new drugs for HF and cardiomyopathies, it is fundamental to identify and match the drugs with the most suitable patient population. In this way, biomarkers might better characterize different patients and who could benefit most from novel drugs and treatments [7]. Biomarkers of extracellular matrix remodeling may be important for the prediction of heart failure with the development of preserved ejection fraction (HFpEF) [8]. Levels of both C-terminal propeptide and C-terminal telopeptide of type-1 collagen as well as N-terminal peptide of procollagen type III show the presence of fibrosis in HF [9]. Both matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) are involved in cardiac remodeling; MMP2, MMP3, and MMP9 seem to play a role in the development of HF [10]. MMP2 may make an early prediction of the cardiovascular prognosis [11].

The protein galectin-3 (gal-3) is a biomarker of fibrosis, inflammation, and oxidative stress. In a failing heart, gal-3 is released by activated cardiac macrophages and cardiac fibroblasts, which take part in ventricular remodeling [12].

In this issue of *Kardiologia Polska* (*Polish Heart Journal*), Karabinowska-Małocha et al. [13] present an interesting prospective single-center observational study. They hypothesized that cardiac- and fibrosis-specific biomarkers might also be related to interstitial fibrosis in HCM. Their study aimed to compare the circulating levels of cardiac- and fibrosis-specific biomarkers between

HCM patients and patients with high and low burdens of interstitial fibrosis.

The topic of interstitial fibrosis and its relationship with serum biomarkers is little studied, with few publications centered on cardiac-specific markers in the setting of interstitial fibrosis in HCM. The choice of this topic is one of the main merits of the article written by Karabinowska-Małocha et al. [13].

The final study population, in which ECV and biomarkers values were obtained, included 49 patients. Patients were divided based on their median ECV value, which was 28.1%. So, HCM patients stratified according to median ECV differed in terms of body mass index (BMI), late gadolinium enhancement (LGE) extent and mass, as well as N-terminal pro-B-type natriuretic peptide (NT-proBNP) and gal-3 levels.

The authors [13] demonstrated that cardiac-specific biomarkers (troponin T [TnT], NT-proBNP) are weakly related to both replacement and interstitial fibrosis, and markers of collagen turnover, as well as transforming growth factor-β1 (TGF-β1) seem to be inadequate as fibrosis-related biomarkers in HCM. On the other hand, gal-3 appears to be strongly related to interstitial fibrosis in HCM, making it a strong candidate for being a potential biomarker in this setting.

In particular, cardiac-specific (NT-proBNP and TnT) as well as gal-3 correlated with ECV, whereas only TnT correlated with LGE extent. Gal-3 and BMI were found to be independently associated with interstitial fibrosis (ECV). In this study [13], the authors showed a positive correlation between LGE extent and TnT levels (in agreement with data derived from other studies) [14, 15]. The authors did not observe any correlation between NT-proBNP levels and LGE, similar to previous researchers. Additionally, in the plasma fibrosis-specific biomarkers, no association with LGE was observed [13]. No such associations have been found in HCM between fibrosis-specific markers and replacement fibrosis [13].

Aleksandra Karabinowska-Małocha et al. confirmed the lack of associations between collagen turnover-related biomarkers (PICP, PIIINP) and TGF-β1 with interstitial fibrosis. These data are consistent with other studies conducted so far. This is the first study to reveal a relatively strong relationship between gal-3 and interstitial fibrosis in HCM. The observed association between gal-3 and ECV (interstitial fibrosis) and the lack of any relationship between gal-3 and LGE (replacement fibrosis) points to distinct metabolic pathways and the significance of these two types of fibrosis in HCM. However, this relationship needs further attention and in-depth research.

Article information

Conflict of interest: None declared.

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Education in cardiovascular disease prevention

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Related article
by Cicha-Mikołajczyk et al.

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Favorable lifestyle changes to reduce well-known cardiovascular disease (CVD) risk factors, i.e., smoking, blood cholesterol, and physical activity explained most of the decline in coronary heart disease (CHD) mortality in Poland between 1991 and 2005 [1]. After 2005, despite the rapid increase in access to modern treatments for acute CHD, the decline in CVD mortality has slowed down [2]. At that time, studies in CHD patients and the general population showed that the decline in exposure to main risk factors was slower than expected, and the prevalence of obesity and diabetes increased further. Only a small proportion of the general population remained free of risk factors, and most of the rest had risk factors uncontrolled [3, 4].

Prevention, which aims to reduce CVD risk factors, is the most effective and economical method to decrease the incidence and mortality from CVD [5]. In CVD prevention, health education is a key element for both the high-risk group and the general population. The recent European guidelines on CVD prevention emphasize the importance of media to educate the population about smoking, physical activity, diet, and alcohol abuse, in addition to educating patients and high-risk individuals by clinicians and general practitioners [5]. The education should provide cardiovascular knowledge, motivate people to change their lifestyles and adhere to medical recommendations. A Polish study confirmed that not knowing risk factors increases the risk of death. However, a lower level of knowledge of risk factors was associated with higher risk of death only in men with secondary or higher education [6].

Knowledge of risk factors is likely related to higher education. On the other hand, a high level of education is associated with a higher social and economic status and with better access to medical care. Low social status has to be regarded as an independent CVD risk factor, and the relationships between education, low social status, and CVD risk were also confirmed in Poland [5, 7]. Nevertheless, a lower CVD risk observed in people with higher education can be, partially at least, attributed to better knowledge about the disease, its symptoms, and risk factors. Knowledge of risk factors is also related to other important factors, including female sex, family history of CVD, and residence in rural areas and small towns [8]. In an experimental population study, which was carried out in the Małopolska Voivodeship, people who watched educational TV programs on CVD prevention had better knowledge of CVD risk factors, such as hypertension, diabetes, obesity, smoking, low physical activity, and unhealthy diet. However, watching such programs was not equally popular across the entire population. Women, older people, people with low education, and those with a personal or family history of CVD were more likely to watch educational programs [9].

The article "Disparities in knowledge of cardiovascular risk factors and prevention methods related to cardiovascular status and functional health literacy. Poland 2020–2021" by Alicja Cicha-Mikołajczyk et al. [10] shed more light on this complicated net of interrelations by underlining the effect of health literacy on CVD knowledge. Health literacy, which is defined as "a person's ability to read and comprehend information and instructions in health settings" [11], can be expected to correlate with social status, and, in particular, with education and may mediate the impact of socioeconomic status on CVD risk.

The article presented partial results of the WOBASZ II Study, which involved 2827 adult residents from 8 voivodeships (Dolnoslaskie, Kujawsko-pomorskie, Lubuskie, Opolskie, Podkarpackie, Warminsko-mazurskie, Wielkopolskie, Zachodniopomorskie) [10]. The findings are, in particular, important for health education and prevention. The authors postulate that screening for health literacy should be part of prevention programs to better understand patient needs, reduce health inequalities, and increase effectiveness. The postulate seems reasonable, but such screening may not be feasible with the current organization and funding of CVD prevention in Poland. Even though there is a large body of evidence that comprehensive and structured educational and rehabilitation programs have great potential to reduce exposure to CVD risk factors and deaths, no such educational program was adopted in clinical practice on a larger scale, despite the 2016 recommendation by the expert panel of the Polish Cardiac Society and the Agency for Health Technology Assessment and Tariff System [12].

The European guidelines for CVD prevention recommend integration of nurse-coordinated prevention programs into healthcare systems, and nurses, together with general practitioners and allied health professionals, should deliver those programs for high-risk patients within primary care [5]. In Poland, prevention is an important part of the mission of individual and group nursing practices [13]. However, no state-funded CVD prevention program was addressed to nurses at the national level. The lack of a comprehensive structured educational program might explain why the effectiveness of the CVD prevention program supported by the Polish National Health Fund was below expectations [14]. Also, no such program was adopted in the nationwide system of coordinated care after myocardial infarction (MI), which imposed on hospitals the responsibility for patient care for up to 1 year after hospitalization for MI [12].

Nevertheless, education of CHD patients and high-risk individuals is recommended by international and Polish scientific societies [5, 12], and comprehensive and structured programs might appear as local initiatives. In such circumstances, the suggestion to prepare separate programs, both in primary and secondary prevention, for various sectors of the population under care according to their level of health literacy would be the next step.

Article information

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REVIEW ARTICLE

Blood pressure and hypertension in relation to lead exposure updated according to present-day blood lead levels

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ABSTRACT

Lead is an environmental hazard that should be addressed worldwide. Over time, human exposure to lead in the Western world has fallen drastically to the levels comparable to those in humans living in the pre-industrial era, who were mainly exposed to natural sources of lead. To re-evaluate the health risks possibly associated with present-day lead exposure, a three-pronged approach was applied. First, we critically assessed the recently published population metrics describing the adverse health effects associated with lead exposure at the population level. Next, we summarized the key results of the Study for Promotion of Health in Recycling Lead (SPHERL; NCT02243904) and analyzed these results in the context of the published population metrics. Last but not least, we performed a brief literature review on the present-day lead exposure level in Poland. To our best knowledge, SPHERL is the first prospective study that accounted for interindividual variation in vulnerability to the toxic effects of lead exposure by assessing the participants' health status before and after occupational lead exposure, with blood pressure and hypertension as the primary outcomes. The overall conclusion of this comprehensive review on blood pressure and hypertension is that mainstream ideas about the public and occupational health risks related to lead exposure need to be urgently updated because a large part of the available literature has become obsolete given present-day exposure levels that sharply declined over the past 40 years.

Key words: blood pressure, environmental medicine, hypertension, lead, occupational medicine

INTRODUCTION

Lead is an environmental toxicant. At high exposure, as observed in the past in occupational settings or in the general population due to, for instance, the consumption of moonshine whiskey, lead causes hypertension and renal failure [1, 2]. However, the National Health Examination Survey (NHANES) demonstrated that mean blood lead levels in American adults have dramatically dropped from 13.1 µg/dl in NHANES II (1976–1980) [3] to 2.76 µg/dl in NHANES III (1988–1994) [3] and further to 1.64 µg/dl in NHANES IV (1999–2002) [4, 5]. Over time, increasingly tighter environmental regulations led to the prohibition on lead-containing paint (1976) [6], phasing out of leaded gasoline (1995) [6], elimination of lead as construction material, replacement of lead pipes in drinking water distribution, eliminating lead solder in food cans, and compulsory and systematic recycling of lead batteries and other lead waste. In developed nations, the average blood lead concentration in the general population currently approaches 1.5 µg/dl. As estimated by the Global Burden of Disease (GBD) Consortium [7], this level is close to the estimated blood lead concentration of 2 µg/dl in pre-industrial humans, who were only exposed to natural sources.

Our studies in the field of environmental medicine span over the past 40 years but did not provide convincing evidence supporting the thesis that environmental lead exposure is causally related to hypertension [8–10], renal dysfunction [11–13], or cardiovascular disease [14, 15]. Given this research track record, this review aimed to identify sources of bias in recent publications [16] associating adverse health outcomes with lead exposure, to summarize the key results of the Study for Promotion of Health in Recycling Lead (SPHERL; NCT02243904) [17], and to provide an overview on the contemporary lead exposure level in Poland. To our best knowledge, SPHERL is the first prospective study that accounted for individual variation in vulnerability to the toxic effects of lead exposure by assessing the participants' health status before and after lead exposure [17], which was an issue identified as a research priority in a meta-analysis published in 2002 [18]. As an introduction to the field, the toxicokinetics of lead in humans are first summarized.

TOXICOKINETICS OF LEAD IN HUMANS

Lead enters the body primarily through inhalation and ingestion. Today, adults are mainly exposed by breathing in lead-contaminated fine particulates and fumes in occupational settings or during leisure time activities. Exposure in the general population via ambient air is generally due to respirable particles capable of deep lung penetration and deposition [19]. Once the finest dust particles reach the lung alveoli, they readily pass the air-blood barrier and are subsequently system-wide distributed via the bloodstream. Occupational exposure entails coarser aerosols that deposit in the upper airways and then translocate to the gastrointestinal tract by mucociliary clearance, where gastrointestinal uptake kinetics prevail (5%–10% uptake). The lead in air to lead in blood slope is around 2 for ambient and 0.05 for occupational exposure [19].

Lead is a cumulative toxicant, 90%–95% of which is stored in bone, from where it is recirculated with a half-life of 20–25 years [20, 21]. Blood lead, in 99% carried by red blood cells, reflects recent exposure over the past 1–2 months and the amount of lead released and recirculated from bone stores [20]. Both bone [21, 22] and blood [11, 21, 22] lead levels increase with advancing age. Bone lead is associated with blood lead [21, 22] and explains around 20% of the variance in blood lead, depending on seasonality [21], hormonal, and other endogenous and environmental stimuli influencing the balance between bone formation and resorption [22]. Recirculation of lead from bone explains why there is a lag time for blood lead to decline when environmental [9] or occupational [20] lead exposure decreases.

SOURCES OF BIAS IN THE LITERATURE

Relevant publications are the NHANES III results and the articles published by the GBD consortium.

MORTALITY IN RELATION TO BLOOD LEAD IN NHANES III

The cross-sectional NHANES III survey (1988–1994) involved the collection of clinical variables, questionnaire data, and biochemical measurements, including blood lead, in a representative sample of the adult population of the United States (US) [23–25]. The method of blood lead measurement was graphite furnace atomic absorption spectrophotometry with the detection limit set at 1.0 µg/dl. For the 8% of participants with blood lead levels below the detection limit, a level of 0.7 µg/dl was imputed [23–25]. These NHANES III baseline data were linked with the National Death Index, using probabilistic matching based on 12 identifiers for each participant to ascertain vital status and cause of death. Follow-up (FU) was the time between the baseline examination date, date of death, or the participant's 90th birthday, whichever came first. The censoring date was 31 December 2011 in the latest NHANES III report [25].

In 1489 individuals (Table 1 [25]), the multivariable-adjusted hazard ratios expressing the risk of an increase in blood lead from the 10th to the 90th percentile (1.0 to 6.7 µg/dl) were 1.37, 1.70, and 2.08 for total, cardiovascular, and coronary mortality, respectively. From individual measures of blood lead and their associated hazard ratios, the population attributable fraction (PAF [26, 27]), i.e., the adverse health outcomes attributable to lead exposure, was then computed as the integral of the hazard ratios at each blood lead level weighted by the logarithmically transformed population distribution of blood leads over the total range from 0.70 to 56.0 µg/dl. The PAFs amounted to 18.0% (CI, 10.9%–26.1%) for total mortality, 28.7% (CI, 15.5%–39.5%) for cardiovascular mortality, and 37.4% (CI, 23.4%–48.6%) for coronary mortality. Given the overall annual mortality (n = 2 288 888), cardiovascular mortality (n = 891 896), and coronary mortality (n = 494 652) in the US and assuming that blood lead concentrations might be reduced to 1.0 µg/dl or less, the number of preventable deaths amounted to 412 000 (CI, 250 000–598 000) for total mortality, 256 000 (CI, 138 000–352 000) for cardiovascular mortality, and 185 000 (CI, 116 000–241 000) for coronary mortality.

That 2018 NHANES report (Table 1 [25]), based on historical blood lead from the year 1988 to 1994, has little relevance for public health policies in the third decade of the twenty-first century for the reasons listed below. First, the blood lead levels, as recorded in NHANES III, were not representative of current lead exposure. To a large extent, these levels reflected the recirculation of lead from earlier bone stores, which in many participants accrued from the first decades of the twentieth century onwards, when lead was still highly prevalent in the environment in the US. In our analyses of 12 725 NHANES IV participants examined from 2003 until 2010 [5], the geometric mean blood lead concentration in all participants was 1.41 µg/dl, with lower

Table 1. Mortality in 14 289 NHANES III participants followed up until December 31, 2011

Variable	All participants	Results by thirds of the blood lead distribution			*P*-value
Blood lead range, µg/dl	0.7–56.0	<2.0	2.0–3.7	≥3.8	
Risk factors					
Black, %	10.2	9.1	9.2	12.1	0.0004
Men, %	47.9	24.6	49.2	68.3	<0.0001
Age, years	44.1	37.8	44.8	48.2	<0.0001
Body mass index					
<25 kg/m^2, %	44.6	49.4	42.8	42.0	<0.0002
25–29.9 kg/m^2, %	33.0	27.0	24.5	36.9	<0.0001
≥30 kg/m^2, %	22.4	23.6	22.7	21.1	0.13
Current smoking, %	34.9	23.0	33.0	47.8	<0.0001
Alcohol consumption, %					
<4 units per month, %	63.2	73.3	62.3	54.8	<0.0001
≥4 units per month, %	36.8	26.7	37.7	45.2	<0.0001
Hypertension, %	17.5	9.6	18.0	24.3	<0.0001
<$20 000 annual income, %	31.9	27.7	24.0	37.4	<0.0001
Total mortality					
Deaths, n (%)	4422 (30.9)	631 (13.2)	1340 (28.1)	2451 (51.5)	
Hazard ratios (95% CI)					
Primary analysis	1.37 (1.17–1.60)	–	–	–	–
Sensitivity analyses					
Blood lead <5 µg/dl	1.38 (1.15–1.66)	–	–	–	–
HT + treatment status	1.38 (1.18–1.61)	–	–	–	–
SBP + DBP (continuous)	1.36 (1.16–1.58)	–	–	–	–
Cardiovascular mortality					
Deaths, n (%)	1801 (12.6)	218 (4.6)	552 (11.6)	1031 (21.6)	
Hazard ratios (95% CI)					
Primary analysis	1.70 (1.30–2.22)	–	–	–	–
Sensitivity analyses					
Blood lead <5 µg/dl	1.95 (1.46–2.60)	–	–	–	–
HT + treatment status	1.73 (1.32–2.27)	–	–	–	–
SBP + DBP (continuous)	1.68 (1.28–2.19)	–	–	–	–
Coronary mortality					
Deaths, n (%)	988 (6.9)	112 (2.4)	284 (6.0)	592 (12.4)	
Hazard ratio (95% CI)					
Primary analysis	2.08 (1.52–2.85)	–	–	–	–
Sensitivity analyses					
Blood lead <5 µg/dl	2.57 (1.56–4.52)	–	–	–	–
HT + treatment status	2.13 (1.55–2.93)	–	–	–	–
SBP + DBP (continuous)	2.07 (1.55–2.84)	–	–	–	

HT, SBP, and DBP indicate hypertension, systolic blood pressure, and diastolic blood pressure, respectively. Data were extracted from reference [16]. Of 18 825 participants enrolled, 1795 had no medical examination or home visit, 1419 were excluded because of missing blood lead or urinary cadmium, 1314 because of missing covariables, and 8 because of missing identifiers to match with the national registry, leaving 14 289 for statistical analysis. Hazard ratios, given with a 95% confidence interval, represent the relative risk for an increase in blood lead from 1.0 to 6.7 µg/dl (10th–90th percentile interval). Hazard ratios accounted for ethnicity (White, Black, or Mexican-American), sex, the linear and squared terms of age, body mass index (categorical), hypertension (blood pressure ≥140 mm Hg or ≥90 mm Hg diastolic), smoking status (never, current, or former), alcohol consumption (<4 vs. ≥4 units per month), serum cholesterol, glycated hemoglobin, urinary cadmium (categorized), physical activity (categorized into none, 1–14 and ≥15 times in the previous month), annual income (< vs. ≥$20 000), and the healthy eating index (categorized). Sensitivity analyses were conducted by including only participants with blood lead <5 µg/dl (relative risk given for the 10th–80th percentile interval), considering treatment status in the definition of hypertension, and entering systolic and diastolic blood pressure as continuous covariables in the models to replace hypertension (categorical). To convert blood lead concentration from µg/dl to µmol/l, multiply by 0.0483. An ellipsis indicates that in reference [16], hazard ratios were not given for increasing categories of blood lead. Reproduced from reference [16], which was published as an open access article under the Creative Commons Attribution Non-Commercial-NoDerivs License

Abbreviations: DBP, diastolic blood pressure; HT, hypertension; SBP, systolic blood pressure

levels in women (1.25 µg/dl) than men (1.80 µg/dl) and in Whites (1.46 µg/dl) compared to Blacks and Hispanics (1.57 µg/dl). All blood lead levels were below 30 µg/dl [5]. Second, PAF was calculated as the proportional decline in mortality that would occur if the blood lead concentrations of all participants were reduced to a reference level of 1.0 µg/dl or lower [25], which is an unfeasible target, given lead exposure from natural sources and food. This very low null-effect blood lead concentration substantially inflated the hazard ratios and PAFs associated with blood lead. Third, hypertension as the causal pathway linking mortality to environmental or occupational lead exposure is a deeply rooted paradigm based on research dating back more than half a century ago [28, 29]. The NHANES III report itself [25] argued against this mechanistic pathway, given that models accounting for hypertension and hypertension treatment or adjusted for systolic and diastolic blood pressure (BP) as continuously distributed variables barely affected the hazard ratios (Table 1). Along similar lines, a meta-analysis of 31 studies published before

February 2001 involving 58518 participants [30] indicated the doubling of blood lead was only associated with a marginally higher BP. The pooled estimates averaged 1.0 mm Hg (confidence interval [CI], 0.5–1.4 mm Hg) systolic and 0.6 mm Hg (CI, 0.4–0.8 mm Hg) diastolic. Furthermore, in a prospective population study of 728 individuals (50.7% women; age range, 20–82 years), BP was measured conventionally at baseline (1985–1989) and at FU (1991–1995), and by 24-hour ambulatory BP monitoring at FU [9]. Over a median FU of 5.2 years (range, 3.5–8.4 years), the geometric mean blood lead concentration dropped by 32% from the baseline level of 8.7 µg/dl (range, 1.7–72.5 µg/dl). The small changes in systolic/diastolic BP on conventional measurement (–1.5/+1.7 mm Hg) were unrelated to the blood lead concentration at baseline or to the changes in this exposure biomarker over FU. Similarly, 24hour ambulatory BP was not associated with blood lead at baseline or FU [9]. A recent NHANES report covering the data from 1999 to 2016 [31] included 30 467 participants at the age range of 20-79 years. Non-Hispanic Black men (n = 3006) had the highest mean blood lead level (2.20 µg/dl), compared to 3 814 Hispanic men (2.18 µg/dl), and 6989 non-Hispanic White men (1.89 µg/dl). A similar ethnic gradient in blood lead was observed in women: 1.49 µg/dl in 3256 non-Hispanic Black women, 1.30 µg/dl in 4130 Hispanic women, and 1.30 µg/dl in 7078 non-Hispanic White women. In the multivariable-adjusted logistic regression models [31], hypertension was not associated with blood lead (odds ratio, 1.002; CI, 0.983–1.021).

The percentage of all-cause mortality was 55.4% in the top third of the NHANES III blood lead distribution (Table 1) [25]. The 2011 National Vital Statistics Report [32] listed cause-specific mortality corresponding in time with the end of the 20-year FU of the NHANES III participants [25]. Malignancies, standardized per 100 000 deaths from 45 up to 84 years, contributed 434 more deaths to all-cause mortality than cardiovascular disease, whereas from the age of 85 onwards, heart disease overtook malignant disease, contributing 2435 extra deaths. The NHANES III models [25] did not account for the competing risks of fatal cardiovascular and non-cardiovascular diseases, both contributing to all-cause mortality [33, 34]. Finally, a major limitation of the NHANES III studies [23–25] was their focus on mortality. The introduction of stroke units and the wide availability of invasive coronary care, thrombolysis, and percutaneous vascular interventions have reduced the case-fatality rate of most cardiovascular complications of hypertension. Not accounting for nonfatal events, therefore, limits the generalizability of the NHANES III reports [23–25].

THE GLOBAL BURDEN OF DISEASE REPORTS

A disability-adjusted life year (DALYs) is a summary metric that reflects the sum of years lived with a disability and the years of life lost. It, therefore, reflects both quality of life and premature mortality [35]. From the age of 25 years onwards, there is a causal association between systolic BP and lead exposure, as proposed by the GBD consortium [36, 37]. Mediated-via-BP lead exposure was unrealistically assumed to cause a wide range of cardiovascular diseases, including right heart disease; ischemic heart disease; ischemic, hemorrhagic, and other non-ischemic strokes; hypertensive heart disease; aortic aneurysm; the aggregate of cardiomyopathy, myocarditis, and endocarditis; the aggregate of atrial fibrillation and flutter; pulmonary vascular disease; other cardiovascular diseases; and chronic kidney disease [38]. If evidence was only available for the relative risk of either morbidity or mortality, the assumption was that estimates of relative risk would equally apply to both fatal and nonfatal outcomes. In 2010, high BP was the leading single risk factor globally, accounting for 9.4 million deaths (95% uncertainty interval [UI], 8.6–10.1 million) and 7.0% (UI, 6.2%–7.7%) of global DALYs [35]. For environmental lead exposure, these estimates were 0.67 million deaths (UI, 0.58–0.78 million) and 0.56% of DALYs lost (UI, 0.47%–0.66%) [35]. Worldwide, for both sexes and all ages combined, high BP moved up in the global risk factor ranks from rank 4 in 1990 to rank 1 in 2010 and environmental lead exposure from rank 30 to rank 25 [35].

The GBD investigators listed among possible limitations of their results: (1) residual confounding; (2) uncertainty as to the extent to which effect sizes were generalizable; (3) and the impossibility to account for temporal changes in the exposure to risk factors. Thus, the GBD statistics fell short of accounting for the steady global decline in environmental lead exposure. This might explain why globally, regardless of declining environmental exposure [3–5, 9], environmental lead exposure moved up in the risk factor ranks from rank 30 in 1990 to rank 25 in 2010 [35]. Furthermore, PAF for clusters of risk factors, rather than for a single risk indicator, has to be calculated because of the issue of residual confounding. Indeed, cardiovascular risk factors [39–41] and exposures to various environmental pollutants [8, 12, 42] cluster within individuals, such as, for instance, poverty, unhealthy lifestyle habits, poor housing conditions, and lead exposure in the NHANES surveys. The GBD estimates did not account for co-exposures to risk factors and environmental pollutants. According to the World Health Organisation demographic data, in 2010, the population of the US (309 million) represented approximately 4.5% of the world's population (6.9 billion). Interestingly, if the statistics of the 2012 GBD report are truly generalizable (PAF, 0.67 deaths worldwide [35]), preventable deaths related to environmental lead exposure in the US would amount to approximately 30 150 per year, an estimate more than 10-fold smaller than that proposed in the NHANES III report [25].

SPHERL

SPHERL is a longitudinal study of newly hired lead workers without known previous occupational exposure. They were employed at battery manufacturing and lead recycling plants in the US. SPHERL complies with the Helsinki Decla-

ration for investigations in humans. The Ethics Committee of the University Hospitals Leuven (Belgium) approved the study protocol (Nº B322201421631), which has been published in detail [17]. The co-primary endpoints for which SPHERL was powered [17] were the changes in BP and renal function. The secondary endpoints included the autonomous nervous regulation of the cardiovascular system, as captured by heart rate variability (HRV), neurocognitive function, and peripheral nerve conduction.

The workers underwent FU visits 1 and 2 years after enrollment. Detailed diagrams describing the flow of participants and the number of workers excluded from the statistical analyses have been published for BP and hypertension [43]. In the most recently published SPHERL article focusing on BP [43], the geometric mean blood lead concentration was 4.1 µg/dL (interquartile range [IQR], 2.3–8.1 µg/dl) at baseline, and 13.5 µg/dl (IQR, 10.1–22.8 µg/dl) at last FU in the office BP cohort (n = 267). The last follow-up-to-baseline blood lead concentration ratio averaged 3.3 (IQR, 3.0–3.8; $P = 0.036$; Figure 1). Changes in the blood lead concentration were similar in the ambulatory BP cohort (n = 137).

At the study sites, office BP was measured at the brachial artery by trained nurses according to the current guidelines [44]. After the workers had rested for 5 minutes in the sitting position, the nurses obtained five consecutive BP readings to the nearest 2 mm Hg by auscultation of the Korotkoff sounds, using standard mercury sphygmomanometers. For analysis, the five readings were averaged. Ambulatory BP was recorded on the same arm as office BP with similarly sized cuffs, using validated [45] oscillometric Mobil-O-Graph 24-h PWA monitors (I.E.M. GmbH, Stolberg, Germany). The monitors were programed to obtain readings at 15-minute intervals during waking hours and every 30 minutes during sleep. Mean 24-hour BP was the average of the awake and asleep BPs weighted for the duration of the awake and asleep periods. Office and ambulatory BP were categorized according to the 2017 American College of Cardiology/American Heart Association (ACC/AHA) guidelines [44].

Office BP was measured in 267 participants (11.6% women, mean baseline age, 28.6 years) and 24hour ambulatory BP in 137 participants at two FU visits. Fully adjusted changes in systolic/diastolic BP associated with a doubling of the blood lead ratio were 0.36/0.28 mm Hg (CI, 0.55 to 1.27/0.48 to 1.04 mm Hg) for office BP and 0.18/0.11 mm Hg (CI, 2.09 to 1.74/1.05 to 1.27 mm Hg) for the 24-hour ambulatory BP. The adjusted hazard ratios for moving up hypertension categories associated with a doubling of the blood lead concentration were 1.13 (CI, 0.93–1.38) for office BP and 0.84 (CI, 0.57–1.22) for the 24-hour ambulatory BP. Heat maps demonstrated, in line with all clinical measurements [46], that baseline BP was the main determinant of BP at FU (Figure 2). Due to regression to the mean, workers with low BP at enrollment were more likely to experience an increase in their office and ambulatory BP or to move up across hypertension categories according to the ACC/AHA

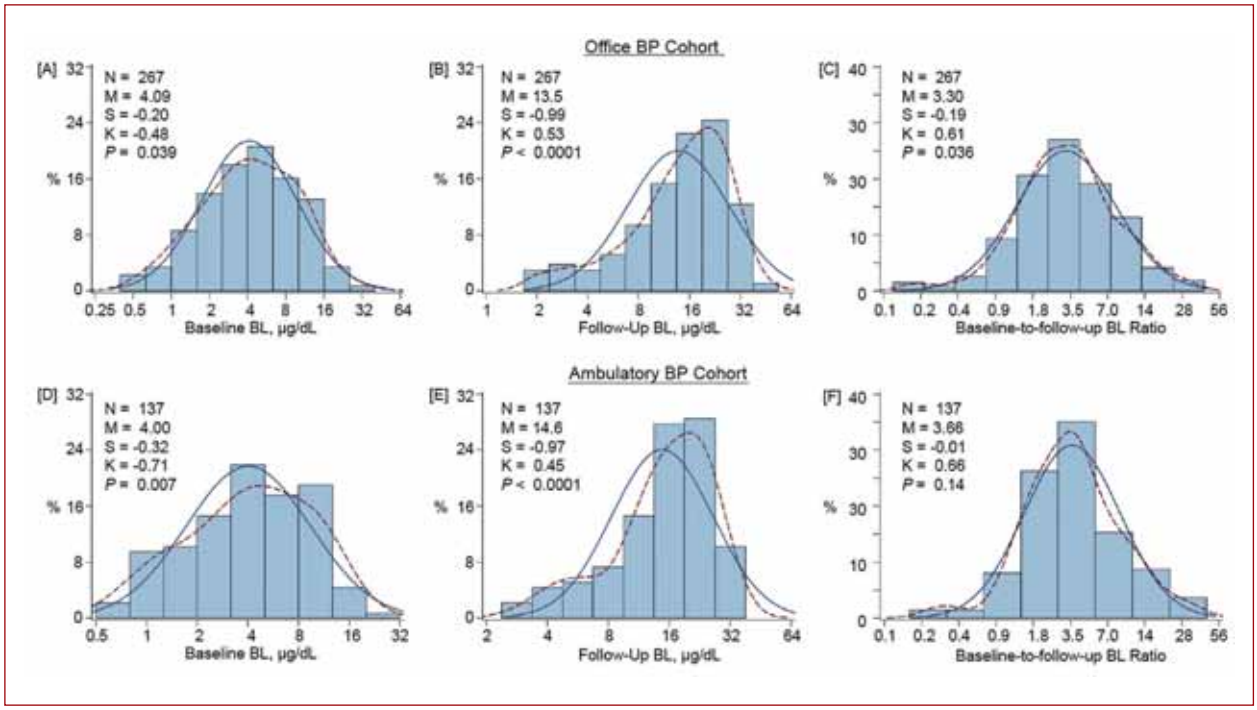

Figure 1. Distributions of the blood lead concentration at baseline (**A, D**), at the last follow-up visit (**B, E**), and the last-follow-up-to-baseline blood lead ratio (**C, F**) in the office (**A–C**) and ambulatory (**D–E**) blood pressure cohorts. N, M, S, and K indicate the number of workers, geometric mean, and coefficients of skewness and kurtosis. The solid and dotted lines represent the normal and kernel density distributions. The *P*-values are for departure of the observed distribution from normality according to the Shapiro-Wilk statistic.

Abbreviations: BP, blood pressure; BL, blood lead

guidelines, whereas the opposite was true for workers in the top tail of the baseline BP distribution. However, there was no systematic shift in BP distributions from baseline to last FU. During the 2-year FU, there was not a single case of the wide array of cardiovascular diseases to be associated with lead exposure, according to the 2012 GBD report [38].

LEAD EXPOSURE IN POLAND

We performed a literature review on lead exposure in Poland by searching PubMed from January 2018 to June 2023, using "lead", "lead poisoning", "occupational exposure", "environmental exposure", and "Poland" as keywords and MeSH (Medical Subject Headings) terms. After excluding the articles unrelated to humans, 9 articles were left, including 5 studies in adults, 2 studies in children, 1 in-vitro experiment, and 1 literature review. We did not find any recently reported Polish occupational lead exposure study. In the studies conducted in Polish adults, the mean blood lead levels ranged from 1.16 to 7.25 µg/dl in the general population under environmental exposure [47–50]. Blood lead was significantly and positively associated with the severity of anxiety in healthy postmenopausal women [47] and the percentage of monocytes and cortisol levels in blood in women with metabolic syndrome [48]. However, given their observational nature, these studies cannot establish a causal relation with lead exposure. A cross-sectional study [51] recruited 1141 schoolchildren (551 boys and 590 girls, at average age of 10.79 years) in an industrialized mining area in southwestern Poland. The mean blood lead level was 3.76 µg/dl (range, 1.7–15.2 µg/dl). The boys with a blood lead level above median (>3.7 µg/dl) had significantly lower body mass index, mid-upper arm circumference, and skinfold thickness (P <0.01), while these associations were not significant in girls (P >0.05) [51]. However, nutritional status was not accessed, and the co-exposure to other heavy metal pollutants in the industrialized area could

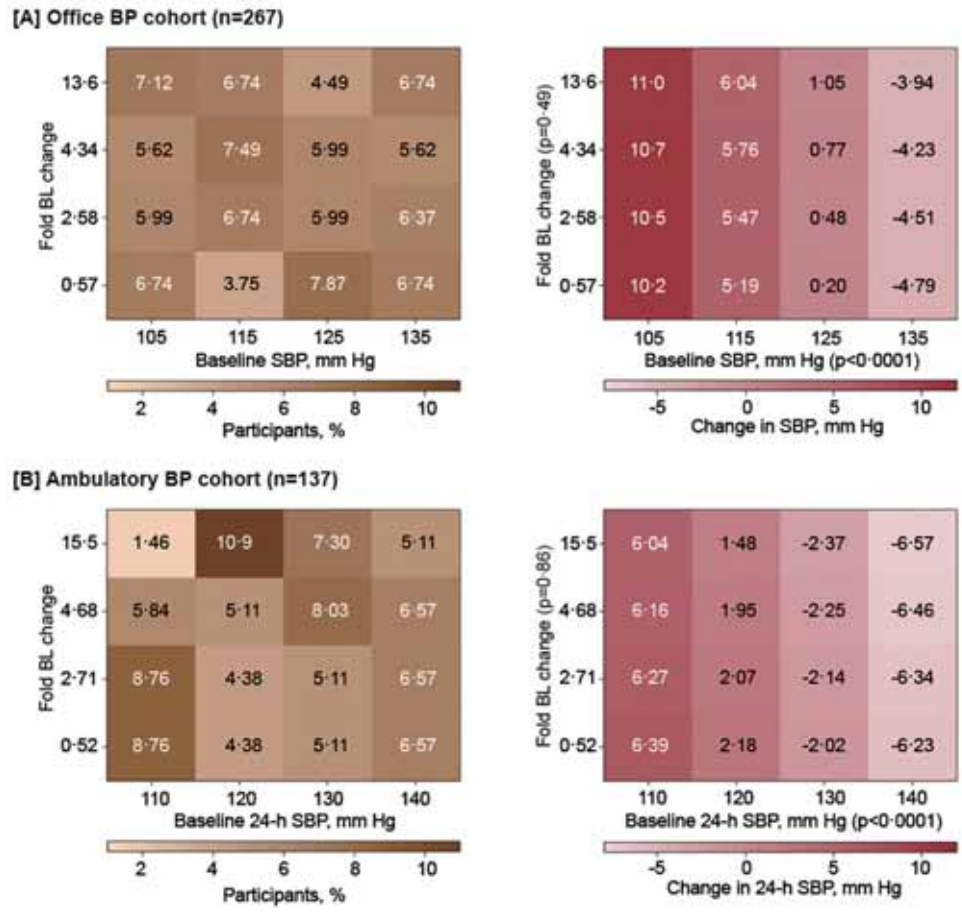

Figure 2. Heat maps relating the change in office (**A**) and 24-hour ambulatory (**B**) systolic blood pressure to the change in blood lead multiple from baseline to last follow-up. SBP refers to systolic blood pressure. Associations were derived by mixed models, including the individual as a random effect. Models were adjusted for ethnicity (white vs. other), sex, age, body mass index at baseline, change in body weight during follow-up, the baseline value of blood lead, and the baseline values of and changes during follow-up in heart rate, smoking status, total-to-HDL serum cholesterol ratio, γ-glutamyltransferase, and serum creatinine. The percentage of workers contributing to the cross-classification between the baseline blood pressure (horizontal axis) and the fold change in blood lead was given for each analysis run. Reproduced from reference [43], which was published as an open access article under the Creative Commons Attribution Non-Commercial-NoDerivs License

Abbreviations: see Table 1 and Figure 1

not be excluded [51]. Another study reported geometric mean blood lead levels of 2.54 and 2.39 µg/dl in 3–7 year-old environmentally exposed boys and girls, respectively [52]. The blood lead level was significantly higher in the children whose fathers had higher education attainments, whose mothers smoked cigarettes, and those living in the neighborhood with some environmental hazards [52]. In a society with a life expectancy of more than 74 years, biomarkers in young people show recent exposure, which is particularly relevant for pollutants, such as lead, a heavy metal accumulating during life [12, 53]. Although lead exposure is still a contributor to adverse health outcomes, the aforementioned studies demonstrated a substantially lower blood lead level in the environmental setting compared with the historic high exposure levels in Poland (the year 1997, blood lead ranged from 1.9 to 28.1 µg/dl in 155 children aged 4–14 years) [54]. The blood lead levels in Polish children reflected the current environmental exposure level in Poland and were lower than 5 µg/dl, the target level as suggested by the Centers for Disease Control and Prevention (CDC) [55].

PERSPECTIVES

Lead exposure represents an environmental risk that should be addressed worldwide. To re-evaluate the health risks possibly associated with present-day lead exposure, a three-pronged approach was applied, first assessing recently published population metrics [23–25], next summarizing the SPHERL results on BP and hypertension [43, 56–58], and third performing a brief literature review on the present-day lead exposure in Poland. Considering health preservation at the population level, health metrics might gain credibility by addressing the following issues: (1) ensuring use of health data (e.g., BP) in relation to present-day lead exposure levels; (2) retesting the presumed pathogenic pathway leading from hypertension to both fatal and nonfatal adverse health outcomes; (3) narrowing the range of cardiovascular complications potentially associated with lead exposure; (4) developing risk models accounting for multimodal exposure to risk factors and pollutants, thereby reducing residual confounding; and (5) setting no-risk thresholds at blood lead levels that are not lower than what is achievable given the naturally occurring background sources of lead exposure.

SPHERL was an ethically endorsed real-world experiment. The major strength of that cohort study was that it accounted for interindividual variability in the responses to an over 3-fold blood lead increase with full documentation of the baseline values in the biomarkers of effect and exposure. Additionally, although residual confounding by unmeasured risk factors can never be excluded in observational studies, SPHERL did address a wide array of potential confounders. Nevertheless, the limitations of SPHERL should be addressed in future research. First, the attrition rate among the workers who participated in the baseline examination but defaulted from FU amounted to over 40% mainly because they left employment. According to the published SPHERL protocol [17], the anticipated attrition rate was 50%. To meet the sample size required to address hypertension and renal dysfunction as the primary endpoint, 500 workers were enrolled. Second, the small sample size and limited 2-year FU of the current SPHERL cohort warrant a cautious interpretation of the findings. Third, the healthy worker effect [59] might partially account for the nonsignificant results in relation to lead exposure in this occupational cohort, as the mean age of the workers was 28.6 years. The current observations should not be unthinkingly generalized and might, therefore, not apply to older individuals or patients with comorbidities, such as diabetes [60], in whom renal function is more vulnerable. Finally, co-exposure to other metals, such as cadmium, is common in lead recycling plants. Lead accumulates in the kidneys, with a half-life exceeding 30 years [61]. Cadmium is an established renal toxicant, adversely affecting renal tubular and glomerular function [62], which would affect BP and hypertension.

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REVIEW ARTICLE

How to predict prognosis in patients with acute pulmonary embolism? Recent advances

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ABSTRACT

Pulmonary embolism (PE) is the third most frequent cardiovascular disease, characterized by a wide range of presentations and clinical courses. Prognostic assessment is a cornerstone of PE management as it determines the choice of both diagnostic and therapeutic strategies. During the previous decades significant efforts have been made to safely select patients for early discharge or home treatment, but appropriate risk stratification, particularly of intermediate-risk patients, remains challenging. In addition to the guideline-recommended clinical prediction rules, such as Pulmonary Embolism Severity Index (PESI), simplified PESI (sPESI), and/or Hestia criteria, a multimodality approach based also on biomarkers and cardiac imaging is crucial for risk-stratification and for selecting appropriate management of patients. In this review article, we discuss the current methods for predicting short and long-term prognosis in PE patients, focusing on the current guidelines, but also on the most recently proposed clinical prediction rules, biomarkers, and imaging parameters.

Key words: mortality, pulmonary embolism, prognosis, risk stratification, venous thromboembolism

INTRODUCTION

Pulmonary embolism (PE) is the third most frequent cardiovascular disease, accounting for approximately 300 000 deaths in Europe every year [1, 2]. It has various presentations, ranging from an asymptomatic incidental finding to circulatory collapse.

In the past, PE patients were traditionally hospitalized for the indication of intravenously anticoagulation and concerns about a high risk of death [3]. Since oral anticoagulants demonstrated their efficacy and safety, PE can nowadays often be treated on an outpatient basis. However, appropriate patient selection remains debatable. Risk stratification is a cornerstone in managing several conditions, including PE. It determines the need for urgent reperfusion therapy in high-risk patients and identifies low-risk patients that can be safely treated at home. The major challenge in managing PE patients is for the remaining group of intermediate-risk patients, which is highly heterogeneous. Although most of those patients experience favorable outcomes, a small, albeit significant, proportion will need rescue reperfusion [4].

In this article, we discuss the current models for predicting short- and long-term prognosis for PE patients and the decision-making process for PE management, particularly regarding the decision on inpatient vs. outpatient treatment.

INSTRUMENTS USED FOR PROGNOSIS ASSESSMENT IN PE

Clinical scores

The Pulmonary Embolism Severity Index (PESI) and Geneva score were the first to be proposed and validated for acute PE risk stratification.

The Geneva prediction rule was developed to identify PE patients who are at low risk of

Table 1. Summary of prognostic clinical scores for pulmonary embolism

Geneva [5]	PESI [6]	Simplified PESI [7]	Hestia criteria [9]
Cancer Heart failure Previous DVT Documented DVT SBP <100 mm Hg Arterial PaO_2 <60 mm Hg (8 kPa)	Cancer Chronic heart failure Chronic obstructive pulmonary disease Male sex SBP <100 mm Hg Arterial oxyhemoglobin saturation <90% Respiratory rate >30 bpm Pulse rate ≥110 bpm Temperature <36° C Altered mental status Age in years	Cancer Chronic heart failure or chronic pulmonary disease Pulse rate ≥110 bpm SBP <100 mm Hg Arterial oxyhemoglobin saturation <90% Age >80 years	Hemodynamic instability Need for thrombolysis or embolectomy Active bleeding or high bleeding risk Oxygen supply to maintain oxygen >90% for >24 hours PE diagnosed during anticoagulant treatment Severe pain needing IV medication >24 hours Medical or social reasons for hospital treatment Creatinine clearance <30 ml/min Severe liver impairment or disease Pregnancy Documented history of HIT

Abbreviations: DVP, deep vein thrombosis; HIT, heparin-induced thrombocytopenia; IV, intravenous; PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index; SBP, systolic blood pressure

death, recurrent venous thromboembolism (VTE), or major bleeding at three months [5]. This score is based on 6 predictors, including cancer, heart failure, previous deep vein thrombosis (DVT), documented DVT, systolic blood pressure (SBP) <100 mm Hg, and arterial PaO_2 <60 mm Hg (8 kPa). About two-thirds of patients achieve a score of two or less, which is associated with a 2% risk of adverse outcomes.

The Pulmonary Embolism Severity Index (PESI) comprises 11 clinical variables and stratifies patients into five severity classes [6]. A simplified PESI score (sPESI) version includes only six variables and two risk classes [7]. A PESI risk of I or II indicates a low-risk population (as does a simplified PESI [sPESI] of zero), with a 30-day mortality rate of less than 3%. According to a meta-analysis including 50 021 patients, the area under the curve (AUC) of sPESI was 0.79 for all-cause mortality with pooled sensitivity and specificity of 0.92 and 0.38, respectively, which was similar to the original PESI score [8]. That study documented pooled mortality of 2% in patients with PESI class I or II, and 1.8% in patients with 0 points on sPESI [8].

The Hestia criteria represent an alternative approach to identifying low-risk patients and selecting those who can be safely treated at home [9]. This approach consists of eleven criteria on the patient's clinical presentation, comorbidities, and familial and social factors. In a prospective study, 90-day mortality was 1% for patients with acute PE and no Hestia criteria for hospitalization who were managed as outpatients.

Table 1 summarizes the most frequently used clinical prognostic scores.

To re-stratify patients with intermediate risk, several scores have been developed. One of the most often used is the BOVA score, which includes parameters such as heart rate (HR), SBP, biomarkers, and transthoracic echocardiography (TTE) [10]. The primary composite outcome was PE-related death, hemodynamic collapse, or recurrent PE at 30 days. Thirty-day complications differed significantly across categories of the model (0–2 points: 4%; 3–4 points: 11%; >4 points: 29%), with an AUC of 0.73 (95% confidence interval [CI], 0.68–0.77). Other scores, such as TELOS, CAPE, and SHIeLD scores, were also developed for additional risk stratification in normotensive patients [11–13]. The variables comprised in those scores are summarized in Table 2.

The shock index (SI) includes information about the patient's HR and SBP (shock index = HR/SBP) to assess hemodynamic status. A SI ≥0.9 indicates a high-risk population. The shock index was demonstrated to be an independent predictor of 30-day mortality, and it performed better than SBP alone for discrimination of low-risk patients [14]. However, while the SI had higher sensitivity compared to SBP (31% vs. 14% for SBP <100 mm Hg and 8% for SBP <90 mm Hg, respectively), it was associated with lower specificity (86% vs. 93 and 97%, respectively) [15]. The sPESI was demonstrated to outperform the SI in predicting 30-day mortality [16].

Biomarkers

Biomarkers were traditionally included as part of the risk stratification of PE patients. Although in initial studies, elevated troponin was associated with poor outcomes, including mortality, subsequent studies have questioned its predictive value. Nowadays, the recommendation is that it should be combined with other prognostic markers [17, 18]. The prognostic value of natriuretic peptides has also been demonstrated, and it seems to have an additive predictive value when combined with troponin measurements. In the PROTECT study, a combination of sPESI with troponin and N-terminal prohormone B-type natriuretic peptide (NT-proBNP) measures had a higher positive predictive value for adverse outcomes than the sPESI alone [19]. The current guidelines recommend employing NT-proBNP to identify normotensive patients with an expected benign disease course.

Elevated plasma lactate signalizes patients with organ dysfunction and is associated with increased mortality in patients with acute PE [13, 20]. The FAST score is a clinical predicting rule that includes heart fatty acid-binding protein (H-FABP), syncope, and HR. The positive predictive value was 20.5%, and the AUC was 0.85 (95% CI, 0.75–0.95). A meta-analysis of 9 studies including 1680 patients found that elevated H-FABP levels were associated with 30-day PE-related mortality [21]. Although a promising biomarker, H-FABP is not routinely available. Other biomarkers,

Table 2. Summary of prognostic clinical scores for normotensive patients with pulmonary embolism

BOVA score [10]	CAPE score [12]	TELOS score [40]	SHIELD [11]
SBP 90–100 mm Hg	SBP 90–100 mm Hg	Elevated lactate[d]	Lactate[f]
HR ≥100 bpm	HR ≥100 bpm	HR ≥100 bpm	Shock index ≥1.0
RV dysfunction[a]	Right-to-left ventricular ratio 1.5[c]	RV dysfunction[e]	Cardiovascular dysfunction[g]
Cardiac troponin elevation[b]	Presence of central pulmonary artery clot		Hypoxaemia (PaO_2/FiO_2 ratio)

[a]RV dysfunction defined as echocardiographic assessment RV/LV >0.9, systolic pulmonary artery pressure >30 mm Hg, RV end-diastolic diameter >30 mm, RV dilatation or RV free-wall hypokinesis; or on CT scan as an RV/LV ratio >1 [10]. [b]Based on standard manufacturer assays and cut-off values [10]. [c]Evaluated on cardiac CT [12]. [d]Elevated plasma lactate is defined as plasma lactate levels ≥2 mmol/l [40]. [e]RV dysfunction defined as the presence of at least one of the following: (1) RV dilatation (end-diastolic diameter >30 mm or right-to-left ventricular end-diastolic diameter ≥1 mm in apical four-chamber view); (2) pulmonary hypertension (estimated RV-right atrial gradient over 30 mm Hg); (3) Hypokinesis of the RV free wall [40]. [f]Absolute value in mmol/l [11]. [g]Cardiovascular dysfunction is defined as the cumulative presence of elevated troponin, elevated NT-proBNP, and an RV/LV ratio ≥1.0 [11]

Abbreviations: CT, computed tomography; HR, heart rate; LV, left ventricle; RV, right ventricle; SBP, systolic blood pressure

such as copeptin, have also been studied but are less extensively validated and not readily available in clinical practice [22–24].

Cardiac imaging

Right ventricular (RV) dysfunction has been associated with increased risk of death [4]. Computed tomography pulmonary angiography (CTPA) has the advantage of combining both diagnostic and prognostic features at once [4]. CTPA signs of RV dysfunction include septal bulging, pulmonary artery enlargement, elevated right-to-left ventricular end-diastolic diameter ratio, and retrograde contrast reflux into the vena cava [4]. CTPA also assesses PE extension, and due to high sensitivity, it contributes to an increased incidence of subsegmental PE diagnosis. The clinical significance of subsegmental PE remains uncertain, and recommendations are extrapolated mainly from historical ventilation-perfusion lung scan trials. In the PIOPED study, 17% of patients had defects isolated to the subsegmental pulmonary arteries [25]. A systematic review and meta-analysis showed no difference between patients with subsegmental PE treated with anticoagulation and those not treated, with regard to the pooled outcomes of a 3-month incidence of recurrent VTE and all-cause mortality [26]. Thus, the indication of anticoagulation should be individualized in patients with incidentally diagnosed PE who have no additional risk factors such as cancer.

TTE is a readily available examination that can be easily performed at the patient's bedside. Although according to the European Society of Cardiology (ESC) guidelines on PE, TTE is not a mandatory part of the routine diagnostic workup in hemodynamically stable patients, several parameters have been proposed for risk stratification [4]. Prognostic markers include an increased right-to-left ventricular ratio, ratio of tricuspid annular plane systolic excursion (TAPSE) to pulmonary arterial systolic pressure, 60/60 sign, and RV wall hypokinesis (including McConnell's sign) [27]. Considering that TAPSE cannot be measured in some patients, subcostal echocardiographic assessment of tricuspid annular kick (SEATAK) was demonstrated to be an accurate alternative, reflecting RV systolic function and demonstrating a prognostic value [28].

A clot in transit, defined as a free-floating thrombus within cardiac chambers, represents a potential source of recurrent embolism and is associated with higher short-term all-cause mortality and PE-related mortality [29]. The prevalence of TTE detection of right heart thrombi was 3.1% (95% CI, 2.8–3.4) [29]. Besides the prognostic value, there was no significant difference in outcomes between treatment with anticoagulation alone or reperfusion strategy in these patients [30]. A multicenter prospective cohort study including 490 normotensive PE patients managed according to the current ESC guidelines proposed an optimal definition of RV dysfunction for prognostic assessment. In this study, the multivariable analysis identified SBP, right-to-left ventricular ratio, and TAPSE as independent predictors of adverse outcomes or rescue thrombolysis within the first 30 days [21].

New echocardiographic parameters have reinforced the role of TTE in risk assessment of acute PE. Right ventricular outflow tract velocity time integral <9.5 cm was associated with increased PE-related mortality [31]. RV strain assessed with speckle-tracking echocardiography is an independent prognostic marker for in-hospital events in patients with acute non-massive PE [31]. The ratio of tricuspid annular plane systolic excursion to pulmonary arterial systolic pressure (TAPSE/PASP) predicts adverse outcomes in PE better than each measurement individually [31]. Pulmonary artery systolic pressure/left ventricular stroke volume (PASP/LVSV) performs better compared to BOVA and PESI in predicting adverse events in intermediate risk of PE [32].

Although markers of RV dysfunction have a consistent association with short-term mortality, they have poor diagnostic performance when used as a stand-alone test, requiring combination with other parameters [33]. In some patients with suspected acute PE, TTE and CTPA may be useful tools to identify pre-existing chronic thromboembolism pulmonary hypertension [4].

Electrocardiogram

The electrocardiogram (ECG) is a quickly interpretable, low-cost, and widely available tool that could be used for prognostic stratification of PE patients. The Daniel score was developed as a scoring system for the severity of pulmonary hypertension in PE patients. However, since

its publication, several studies have investigated the use of ECG as a risk-stratification tool for PE. A systematic review and meta-analysis identified S1Q3T3, complete right bundle branch block, and right axis deviation as the best predictors for in-hospital mortality [15]. T wave inversion and atrial fibrillation were also identified as predictors of negative outcomes [15].

RISK-STRATIFICATION IN PE PATIENTS

Identification of high-risk patients

Identifying a high risk of mortality in patients should be the first step in PE risk stratification. According to the ESC criteria, high-risk patients include those who present with cardiac arrest, hemodynamic instability (defined as SBP less than 90 mm Hg for more than 15 minutes in the absence of other explanation), and/or the need for vasopressors in combination with end-organ hypoperfusion, or persistent hypotension not caused by new-onset arrhythmia, hypovolemia, or sepsis [4]. This subgroup of patients corresponds to 4% of PE patients, with documented short-term mortality of 16% to 19% [34, 35]. These patients' management relies on organ support and prompt reperfusion with thrombolytic therapies or thrombectomy.

In a hemodynamically compromised patient with suspected PE, if immediate CTPA is not possible, bedside TTE echocardiography is the most useful test to evaluate signs of RV pressure overload. Some specific TTE findings (60/60 sign, McConnell's sign, or right-heart thrombi) justify emergency reperfusion treatment for PE, without further tests.

Identification of low-risk patients

Low-risk PE corresponds to about 40% of acute PE patients [36]. Although historically, all patients with acute PE were admitted to the hospital, in the last decades, several prediction rules have been developed to identify patients that can be safely treated as outpatients [3]. Home treatment seems feasible in approximately 30% of normotensive patients with acute PE [37].

The safety of these scoring systems was further investigated in the HOME-PE (Hospitalization or Out-treatment Management of PE) study, which directly compared the sPESI and Hestia criteria. This study demonstrated that both strategies had similar safety and effectiveness and may be used for PE risk stratification. In that study, Hestia criteria identified a lower proportion of patient candidates for home treatment compared to the sPESI (39.4% vs. 48.4%). Still, the proportion of patients managed at home was similar in the two-triaging group (38.4% vs. 36.3% in the Hestia and sPESI groups, respectively) [37]. The incidence of recurrent VTE, major bleeding, or death in patients who were qualified for home treatment by the Hestia or sPESI strategy and were treated at home was as low as 1.3% and 1.1%, respectively. Thirty-day mortality was 0.27% and 0.28%, respectively [37]. The HOT-PE (Home Treatment of Patients with Low-risk PE with the Oral Factor Xa inhibitor Rivaroxaban) trial investigated the safety and efficacy of home treatment of PE using rivaroxaban in low-risk patients, defined by the adapted Hestia criteria and the absence of RV enlargement or dysfunction, and of free-floating thrombi on TTE or CTPA. From the reported initial population of 2854 patients with objectively confirmed PE, 300 patients had either RV dysfunction or free-floating thrombi despite not meeting any of the Hestia criteria. A recent meta-analysis of 3295 patients from 21 studies showed that RV dysfunction, primarily defined by RV pressure overload assessed on imaging tests, alternatively by elevated cardiac biomarkers, may have a significant impact on the early prognosis of patients classified as low-risk based on PESI, sPESI, or Hestia criteria [21]. Thus, outpatient treatment appears to be safe for truly low-risk patients identified by PESI, sPESI, or Hestia criteria combined with the exclusion of RV dysfunction by either imaging studies or cardiac biomarkers. Data show that these instruments are similarly reliable in identifying low-risk patients in terms of prognosis [38].

Re-stratifying intermediate-risk patients

The intermediate-risk patients represent a highly heterogenous group of patients, with a 30-day mortality risk varying between 5% and 15% [6, 7]. Data from the FLASH (FlowTriever All-Comer Registry for Patient Safety and Hemodynamic) registry showed that over one-third of these patients were in normotensive shock, described as the presence of SBP higher than 90 mm Hg in patients with a cardiac index ≤2.2 l/min/m^2 (invasive evaluation). This subgroup of patients is at higher risk of hemodynamic deterioration and in-hospital mortality. For this reason, in the last decade, efforts have been made to identify the subgroup of patients at higher risk who mainly benefit from close in-hospital monitoring. Several markers have been investigated as potential tools to stratify intermediate-risk patients, such as troponin and natriuretic peptides and detection of RV dysfunction. However, when considered in isolatation, none of those markers exceeded specificity of 70% (ranging from 56% for CT-documented RV dysfunction to 70% for natriuretic peptides) [3]. Based on expert opinions, the current guidelines proposed a subdivision into intermediate-high and intermediate-low-risk patients, as the first represents a high 30-day mortality risk subgroup (10% vs. 4%) [39]. Normotensive patients with an sPESI <1 or PESI II-II are considered low-risk patients without further risk stratification; those with an sPESI ≥1 or those with either RV dysfunction or elevated cardiac biomarkers are considered intermediate-low-risk patients; and those with sPESI ≥1 and both RV dysfunction and elevated cardiac biomarkers are considered intermediate-high risk patients. However, the currently available tools for the stratification of this subgroup of patients still have some limitations. The PESI and sPESI scores have a high negative predictive value but a low positive predictive value.

They do not adequately identify those normotensive patients who are at a higher risk and require intensive monitoring [3, 26]. For this purpose, alternative scores such as the BOVA, TELOS, and CAPE scores seem more appropriate [26].

The TELOS score was derived from a prospective cohort of 496 patients and includes RV dysfunction, troponin, and plasma lactate elevation as predictors of death or hemodynamic collapse at 7 days. In a prospective validation of this score, 5.9% of patients were assigned to the intermediate-high-risk category, with a cumulative incidence of death or hemodynamic collapse at 7 days of 21% [3, 40].

The CAPE (Calgary Acute Pulmonary Embolism) score consists of a simple four-variable risk score (comprising computed tomography right-to-left ventricular ratio ≥1.5, presence of central clot, HR ≥100 beats per minute, and SBP <90–100 mm Hg), and demonstrated high predictive value for adverse outcomes in normotensive patients [12].

The SHIeLD score was created and validated to predict 30-days PE-related mortality and/or rescue thrombolysis and comprises four prognostic factors: a shock index ≥1, hypoxemia, lactate, and cardiovascular dysfunction (defined as elevated troponin and NT-proBNP and right-to-left ventricular ratio >1) [11].

Furthermore, both biomarkers and cardiac imaging can be useful for additional risk stratification [12]. In a cohort of 688 normotensive patients with acute PE, NT-proBNP, and echocardiography had a prognostic impact in addition to the sPESI. The risk of adverse outcomes in patients with an sPESI ≥1 with normal NT-proBNP and normal echocardiography was 2.5%, while the risk increased to 5.8% and 5.6% in patients with either NT-proBNP elevation or evidence of RV dysfunction, respectively. For those with both elevated NT-proBNP and RV dysfunction, the risk increases to 10.8%. In the PROTECT study, in normotensive patients with sPESI ≥1, the risk of adverse events was 6.1% in patients with normal biomarkers, 13.8% in patients with elevated BNP, and 20.4% in patients with both elevated troponin and natriuretic peptides [19].

Despite current advances, re-stratification of intermediate-risk patients remains a challenging and important area of research as it may impact not only treatment decisions but also decisions about in- or out-of-hospital care. The use of systemic thrombolysis in normotensive patients considered as being at high risk of decompensation has been evaluated in several trials. The European Pulmonary Embolism Thrombolysis (PEITHO) trial included 1005 patients with intermediate-high risk PE, defined by the evidence of myocardial injury (documented by elevated troponin) and RV dysfunction on imaging. It demonstrated that the incidence of hemodynamic collapse or death within one week was substantially lower in patients in whom tenecteplase plus unfractionated heparin (UFH) was administered compared to those who received UFH alone (2.6% vs. 5.6%; $P = 0.02$). However, this benefit was mainly driven by reducing the risk of hemodynamic decompensation, while mortality did not significantly differ. In addition, the risk of major bleeding was significantly higher in patients who had thrombolysis. Based on these findings, bleeding risks seem to outweigh potential benefits of full-dose systemic thrombolysis, which highlights that more refined strategies are necessary to re-stratify patients at higher risk. The ongoing PEITHOS-3 trial will evaluate whether a reduced dosage of alteplase may be superior to heparin without excessive risk of major bleeding in these patients [41].

One possibly safer alternative to systemic thrombolysis in intermediate-risk PE patients may be catheter-directed PE treatment using lower thrombolytic doses, which has been the focus of recently published small randomized and cohort studies. The results are promising, although only surrogate endpoints were used [42–45]. A larger randomized ongoing ultrasound-facilitated catheter-directed thrombolysis vs. anticoagulation alone for acute-intermediate-high-risk pulmonary embolism (HI-PEITHO) study will evaluate catheter-directed treatment (CDT), and particularly ultrasound-assisted CDT vs. isolated anticoagulation in selected patients with intermediate-high risk acute PE [46]. In this trial, the investigators are using the National Early Warning Score (NEWS), an objective assessment and monitoring of each patient's vital status to enable early detection of patients who may benefit from prompt initiation of rescue therapy before hemodynamic collapse occurs.

Bleeding risk as an additional prognostic factor

Aside from the thrombotic risk, bleeding risk also impacts the prognostics for PE patients. Major bleeding was identified as a predictor of short and midterm mortality in the Rejestr ZATorowósci plucnej w POLsce (ZATPOL) and as a predictor of 1-year mortality in the Registro Inormatizado Enfermedad TromboEmbolica (RIETE). The VTE-BLEED score was developed in the dabigatran arms of the pooled RE-COVER studies and identified six variables as predictors of major bleeding in VTE patients on stable oral anticoagulation: active cancer, males with uncontrolled hypertension, anemia, history of bleeding, age ≥60 years, and renal dysfunction. This score was externally validated in HOKUSAI-VTE, and its prognostic value was further demonstrated in a real-world prospective cohort study [47].

A systematic review evaluated the ability of different bleeding risk tools to predict major bleeding. Most scores showed a moderate ability to predict major bleeding events in VTE patients. The VTE-BLEED score was the most sensitive in forecasting major bleeding events in patients treated with direct oral anticoagulants [48].

Specific populations: Patients with cancer

Venous thromboembolism is a frequent complication in cancer patients and represents the second cause of death after cancer itself. Pulmonary embolism attributable to neoplasia is associated with 3-fold increased mortality compared to a non-neoplastic condition [49, 50]. Approximately 80% of patients with acute PE attributable to cancer died after 1 year of follow-up [49]. Although it is associated with significant

mortality, there is considerable heterogeneity in prognosis, and prognostic tools adapted to this population are lacking.

The most frequently used non-cancer-specific prediction rules, such as the PESI, sPESI, and Geneva score, include cancer as a relevant predictor of mortality, even though these patients may be at low risk and successfully treated as outpatients [26]. Those prediction rules fail to account for cancer-specific disease characteristics by including cancer as a generic variable. Particularly, sPESI automatically classifies all cancer patients as high-risk individuals, limiting its usefulness in this setting. Previous studies have demonstrated that the performance of those non-cancer-specific clinical prediction rules could not be relied on to predict 30-day mortality in cancer patients with acute PE [51]. Recognizing that the existing clinical prediction rules likely require modification in cancer patients, Carmona-Bayonas et al. [51] adapted the commonly used Hestia, PESI, and sPESI by replacing the typical "history of cancer" variable with "metastatic cancer". While these score adaptations demonstrated acceptable predictive accuracy, these rules categorize only a small portion of patients at low risk [51, 52].

As an alternative to the generic risk scores, there are two cancer-specific risk-stratification rules: the RIETE and POMPE-C scores. The RIETE score uses 6 variables (age >80 years, HR ≥110/min, SBP <100 mm Hg, weight <60 kg, immobilization, and presence of metastases) [7]. The POMPE-C calculates the probability of death based on respiratory rate, O_2 saturation, weight, pulse, altered mental status, respiratory distress, do-not-resuscitate status, and unilateral limb swelling [53]. In their original studies, both rules classified 22% to 38% of patients as low risk with sensitivity >95%. When cancer-specific risk-stratification tools were compared to cancer-adapted generic prediction rules (adapted PESI and sPESI), RIETE and POMPE-C demonstrated better discriminatory ability [51].

A meta-analysis performed to assess the prognostic accuracy of clinical prediction rules for mortality in patients with cancer and PE concluded that the highest sensitivity was observed with Hestia criteria (98.1%; 95% CI, 75.6%–99.9%) [54]. Other clinical prediction rules, such as POMPE-C, PESI, sPESI, modified PESI, and RIETE, displayed sensitivity between 87.8% and 93.8% [54]. Considering all the clinical prediction rules with sensitivity equal to or higher than 95%, all had specificity lower than 33% [54]. Thus, further studies are necessary to define specific predictors of mortality in this heterogenous group of patients.

LONG TERM PROGNOSIS

In addition to minimizing short-term mortality, PE management should focus on long-term prognosis and reducing the risk of VTE recurrence. Although the risk of recurrence is low during anticoagulant treatment, it increases after interruption of anticoagulation to as much as 10% in the first year and more than 30% within 5 years. Currently, most guidelines recommend balancing the risk of bleeding with the risk of recurrence after an initial treatment period of three to six months based on the etiology and presence of modifiable risk factors. The provoked (e.g., by a transient risk factor such as major surgery) or unprovoked nature of PE also impacts prognosis, as patients with unprovoked PE are at higher risk of recurrence and represent a heterogenous subgroup of patients, in which further risk-stratification is needed.

Previous studies have suggested that D-dimer testing after three to six months of treatment can help identify patients with unprovoked PE with low risk of VTE recurrence. The PROLONG study demonstrated that patients with elevated D-dimer levels after an initial treatment period who had stopped using anticoagulation had an annualized PE recurrence of 11%. In comparison, the rate was 2% among patients who resumed treatment [55].

The Vienna model is a prediction model for assessing the risk of recurrence in patients with unprovoked VTE; it comprises male sex and the absolute D-dimer level as predictors. Based on this score, the expected rate of recurrent VTE at one year is below 5%, 5%–10%, and > 10% for patients with low, moderate, or high risk, respectively [56].

USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence (AI) is having a significant impact on healthcare. In the past few years, investigation of new AI-based PE tools has focused on diagnosis, using deep-learning models to improve time and diagnostic accuracy based on CTPA and also ECG-signals [57–59]. Few studies are available regarding the use of AI models for risk stratification, although they demonstrate that machine learning models have notable potential for PE prediction [21]. Based on the knowledge that the clot burden is related to the prognosis of acute PE, Liu la et al. [21] developed a deep framework based on U-Net to conduct pulmonary emboli segmentation and quantification on CTPA. Thus, artificial intelligence is taking the first steps aiming at new applicability in the future, but it has already shown promising results in this field.

CONCLUSION

The management of patients with acute PE requires accurate step-by-step risk stratification. Hemodynamic instability allows identifying high-risk patients who will benefit from thrombolytic therapy, while the clinical prediction rules such as PESI, sPESI, and Hestia criteria will enable identifying low-risk patients who can safely be treated as outpatients. The approach to intermediate-risk patients could be most challenging, and no single parameter could be recommended. In these patients, a multimodal approach should be encouraged based on PESI, sPESI or Hesta criteria, biomarkers, and cardiac imaging.

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Link between fibrosis-specific biomarkers and interstitial fibrosis in hypertrophic cardiomyopathy

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Editorial
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ABSTRACT

Background: Cardiac fibrosis is a hallmark of hypertrophic cardiomyopathy (HCM) and has confirmed unfavorable clinical significance. Replacement fibrosis is better known and has already been studied on a larger scale, whereas interstitial fibrosis is less explored.

Aims: We aimed to analyze the relationship between serum biomarkers and interstitial fibrosis, as assessed with cardiac magnetic resonance (CMR) in HCM patients.

Methods: We performed 3T CMR scans in 50 HCM patients to assess interstitial fibrosis as expressed by extracellular volume (ECV). In all patients, we determined levels of serum cardiac-specific (troponin T [TnT], N-terminal prohormone of brain natriuretic peptide [NT-proBNP]) and fibrosis-specific (procollagen I C-terminal propeptide, procollagen III N-terminal propeptide, transforming growth factor β1, galectin-3) biomarkers. Patients were divided based on their median value of ECV.

Results: The final study population included 49 patients. The median value of ECV in our cohort was 28.1%. Patients stratified according to median ECV differed in terms of several variables: body mass index, late gadolinium extent, NT-proBNP, and galectin-3 levels (all P <0.05). Cardiac biomarkers (TnT and NT-proBNP) and galectin-3 were significantly correlated with ECV (r_S = 0.34; P = 0.02; r_S = 0.39; P = 0.006; r_S = 0.43; P = 0.002, respectively). Galectin-3 and body mass index were found to be independent predictors of ECV (odds ratio [OR], 2.29 [1.07–4.91]; P = 0.03; OR, 0.81 [0.68–0.97]; P = 0.02, respectively).

Conclusions: Galectin-3 was an independent predictor of interstitial fibrosis in HCM patients expressed as elevated ECV values. The other measured fibrosis-specific biomarkers were not useful in detecting interstitial fibrosis in HCM. In addition, there was a positive correlation between classical cardiac biomarkers and interstitial fibrosis in HCM patients.

Key words: ECV, galectin-3, hypertrophic cardiomyopathy, myocardial fibrosis

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is one of the most common inherited myocardial diseases in the general population with a prevalence of approximately 1 in 500 [1]. Pathogenic mutations in sarcomeric genes are responsible for the great majority of HCM cases [2]. The diagnosis of HCM is based on the detection of left ventricular hypertrophy (LVH), which cannot be explained by abnormal loading conditions [3, 4], via echocardiography or cardiac magnetic resonance (CMR). Besides LVH, myocardial fibrosis is also a hallmark of HCM, being a risk factor for ventricular arrhythmias,

WHAT'S NEW?

Cardiac fibrosis is present in many cardiovascular diseases and leads to numerous negative consequences such as cardiac remodeling, systolic and diastolic dysfunction, as well as life-threatening arrhythmias. Cardiac fibrosis is also present in hypertrophic cardiomyopathy (HCM), the most common genetic disease. This fibrosis can be assessed invasively and non-invasively with cardiac magnetic resonance (CMR). Moreover, the use of blood parameters that could be indicative of fibrosis is constantly being investigated. We distinguish two types of fibrosis — replacement and interstitial. While replacement fibrosis is largely explored, the interstitial type is much less studied. In this study, we observed an association between one of the plasma markers of fibrosis — galectin-3 and interstitial fibrosis as assessed in CMR studies in HCM patients. This study could enable us to better understand the course of pathology leading to cardiac fibrosis, and further the development of a more effective fibrosis treatment in the future.

diastolic dysfunction, and end-stage heart failure [3]. There are two types of fibrosis which differ from each other in terms of pathology and clinical significance: replacement and interstitial fibrosis [5]. Necrosis of myocytes leads to replacement (or local/reparative) fibrosis while general processes, such as hypertension, genetic mutations, and inflammation, result in the interstitial (or diffuse/reactive) type. Both types of fibrosis are present in HCM. The negative effects of replacement fibrosis and its clinical significance have already been studied extensively, leading, for instance, to the recognition of qualitative evaluation of replacement fibrosis using CMR-based late gadolinium enhancement (LGE) in the American College of Cardiology guidelines on HCM, as an established and validated risk factor for sudden cardiac death (SCD) [4]. On the other hand, interstitial fibrosis is far less studied and understood.

Nowadays, thanks to tremendous strides in hardware and software development, CMR is becoming the preferable and most frequently utilized diagnostic modality in the detection and quantification of cardiac fibrosis. Both replacement fibrosis (via LGE quantification) and interstitial fibrosis (using T1 mapping) can be assessed. T1-based assessment of extracellular volume (ECV) allows for the precise evaluation of global and regional (segmental) interstitial fibrosis. However, due to costs, limited availability, and the infeasibility of performing the CMR exams in certain groups of patients (e.g. with claustrophobia, hemodynamic compromise, certain ferromagnetic implants, etc.), there is ongoing research on the potential role of serum fibrosis biomarkers in the diagnosis and monitoring of the fibrosis process. Cardiac fibrosis itself is very complex, hence there are specific groups of biomarkers related to it, including markers of collagen metabolism (procollagen I C-terminal propeptide [PICP], procollagen III N-terminal propeptide [PIIINP]) or fibrosis-controlling and regulating factors (among these, transforming growth factor β1 [TGF-β1] or galectin-3 [gal-3]) [6, 7]. Although still not fully uncovered, associations between cardiac-specific (i.e. natriuretic peptides, troponin) and fibrosis-specific markers and replacement fibrosis (expressed as LGE) have already been explored to some extent in HCM. In contrast, any relationships between circulating fibrosis-specific biomarkers and interstitial fibrosis in HCM have been much less studied, and the results obtained thus far are rather unclear.

Given that there are already some confirmed relationships between fibrosis-specific biomarkers and LGE, we hypothesized that cardiac- and fibrosis-specific biomarkers may also be related to interstitial fibrosis. Thus, the primary aim of the study was to compare the circulating levels of cardiac- and fibrosis-specific biomarkers between HCM patients with high and low burdens of interstitial fibrosis.

METHODS

Study population

In this prospective single-center observational study, we included 50 HCM patients. The study took place between December 2019 and April 2021. The diagnosis of HCM was made based on the current guidelines of the European Society of Cardiology. Exclusion criteria were patients with previously implanted cardiac devices, severely reduced kidney function (GFR <30 ml/min/1.73 m^2), or HCM phenocopies, such as amyloidosis or hemochromatosis, Fabry disease, etc. All the patients underwent the following procedures: laboratory tests, echocardiography, a six-minute walk test, electrocardiographic Holter monitoring, and CMR. Echocardiographic examinations were performed on commonly available machines in accordance with the current European and American guidelines [8]. We received informed consent from all of the patients enrolled. The study was conducted in accordance with the Declaration of Helsinki, and before the study, the protocol was approved by the Jagiellonian University Ethical Committee (protocol number 1072.6120.237.2019; date of approval: October 24, 2019).

Cardiac magnetic resonance (CMR)

CMR imaging with cine CMR, native and post-contrast T1 mapping, and LGE imaging was performed on a 3T CMR scanner (Magnetom Skyra, Siemens, Erlangen, Germany) according to local imaging protocols, as previously described [9]. The analyses were conducted with Syngo. VIA software, version VB 40 (Siemens, Erlangen, Germany). The CMR studies were analyzed based on the guidelines of the Society of Cardiovascular Magnetic Resonance [10].

The short-axis LGE scans were obtained approximately 15 min after the intravenous application of 0.1 mmol/kg of body weight of gadolinium-based contrast agent. The presence of LGE in both short and perpendicular long-axis images indicated fibrosis. The quantitative extent of LGE was assessed with a 5-standard-deviation threshold in consecutive short-axis images, and its value was computed as a percentage of the total left ventricular (LV) mass [10]. T1 mapping was acquired using a Modified Look-Locker Inversion Recovery sequence before, and 15 mins after, gadolinium-based contrast agent administration. The following parameters of the sequence were used: breath-hold TR/TE of 281/1.1 ms, slice thickness of 8 mm, matrix of 144 × 256 pixels, FOV from 320 × 260 mm^2, and a flip angle of 35°. The native and post-contrast T1 values were obtained by drawing regions of interest in the mid-wall regions of every segment according to the American Heart Association (AHA) 16-segment model. Drawings from the center of the LV cavity determined T1 blood pools. Between the pre- and post-contrast, T1 maps of the regions of interest were copied. We excluded artifact segments. The global values of native and post-contrast T1 times were computed as the means of all segments. ECV was calculated with the formula [10]: ECV = (1/[post-contrast T1] − 1/[native T1])/(1/[blood post-contrast T1] − 1/[blood native T1]) × (1 − Hct).

Laboratory measurements

The blood samples were centrifuged (1600 × g) for 10 min at 4°C. The material was stored at –20°C until the analysis. The quantification of collagen type I and III synthesis markers in blood samples was performed using an Enzyme-Linked Immunosorbent Assay (ELISA) according to the manufacturer's instructions (Bioassay Technology Laboratory, Shanghai, China). The level of sensitivity of the assays was 2.26 ng/ml for PICP, and 2.52 ng/l for PIIINP. The detection range for the PICP ELISA kit was 5–1500 ng/ml and for the PIIINP ELISA kit 5–2000 ng/l. The intra-assay and inter-assay coefficients of variation were <8% and <9% for PICP, and <7% and <10% for PIIINP, respectively. Plasma concentrations of gal-3 and TGF-β1 were assessed using the Nori Human ELISA Kit in line with the manufacturer's instructions (Genorise Scientific, Inc.; Glen Mills, PA, US). The assay sensitivity of the Nori Human TGF-β1 ELISA Kit was 6 pg/ml, and the detection range was 31–2000 pg/ml. The sensitivity of the Nori Human gal-3 ELISA Kit was 30 pg/ml, and the detection range was 156–10000 pg/ml. Following the standards of our laboratory, normal values for N-terminal prohormone of brain natriuretic peptide (NT-proBNP) were defined as <125 pg/ml and for troponin T (TnT) <14 pg/ml.

Statistical analysis

Values were presented as percentages (counts) or mean (standard deviations [SD]) or median (interquartile range [IQR]). The Shapiro-Wilk test was used for the assessment of the normal distribution of quantitative variables. The continuous variables were compared with a t-test or Mann-Whitney U test when appropriate, and the qualitative ones with the χ^2 test or Fisher's exact test. The correlation analyses were performed based on the Spearman rank correlation. All parameters (presented in Tables 1 and 2) differentiating groups by their ECV median with *P*-values <0.1 were included in the regression analyses. Uni- and multivariable logistic regression methods were used to analyze the associations between the analyzed parameters and greater ECV burdens. Redundant parameters (correlated with other predictors with R >0.4) were not included in multivariable logistic regression models. The results were statistically significant if the *P*-value was <0.05. The analysis was performed with the Statistica package, version 13.3 (StatSoft, TIBCO Software Inc., Palo Alto, CA, US).

RESULTS

Baseline characteristics

Due to incomplete data, the final study population from whom ECV and biomarker values were obtained consisted of 49 patients. One patient was not included in the analysis because we could not obtain complete CMR data. Patients were assigned into groups based on their median value of ECV, which was 28.1%. The comparison of the baseline parameters between the groups with lower and higher values of ECV is presented in Table 1. Patients with higher ECV had a lower body mass index (BMI) (mean [SD], 28.2 [5.4] kg/m^2 vs. 31.9 [5.7] kg/m^2; $P = 0.03$) and larger LGE extent (median [IQR], 5.21% [1.6%–9.38%] vs. 2.82% [0%–4.83%]; $P = 0.04$).

Relationships between cardiac-specific/fibrosis-specific markers and fibrosis

Among established cardiac-specific markers, NT-proBNP was more elevated in patients with higher ECV (median [IQR], 823 [440–1465] pg/ml vs. 199.5 [116–817.5] pg/ml; $P = 0.007$), and TnT showed a trend towards significance ($P = 0.08$) (Table 2) in these patients in comparison to those with lower ECV. As for serum fibrosis biomarkers, only gal-3 clearly distinguished the groups (median [IQR], 2.93 [1.9–4.25] ng/ml vs. 1.93 [1.68–2.97] ng/ml; $P = 0.03$), whereas all other fibrosis-specific markers were comparable between the groups. In the correlation analysis between biomarkers and ECV, a moderate correlation between gal-3 and ECV ($r_S = 0.43$; $P = 0.002$), and also weaker correlations both between NT-proBNP and ECV ($r_S = 0.39$; $P = 0.006$) and, TnT and ECV ($r_S = 0.34$; $P = 0.02$) were observed (Table 3). Only TnT weakly correlated with the LGE extent ($r_S = 0.35$; $P = 0.01$). Neither cardiac-specific nor fibrosis-specific markers correlated with LV mass (Table 3). LGE and ECV were correlated with each other ($r_S = 0.47$; $P < 0.001$).

Table 1. Baseline characteristics. Comparison of HCM patients stratified according to ECV

Parameter	All (n = 49)	ECV <28.1% (n = 24)	ECV ≥28.1% (n = 25)	*P*-value
Age, years, mean (SD)	51.9 (14.4)	53 (15.2)	50.8 (13.8)	0.59
Male sex, n (%)	34 (69.4)	18 (75)	16 (64)	0.4
BMI, kg/m^2, mean (SD)	30.0 (5.8)	31.9 (5.7)	28.2 (5.4)	0.03
NYHA class, median (IQR)	1 (1–2)	1.5 (1–2)	1 (1–2)	0.61
Left ventricular outflow track obstruction, n (%)	18 (36.7)	11 (45.8)	7 (28)	0.2
Family history of sudden cardiac death, n (%)	4 (8.2)	2 (8.3)	2 (8)	1
Ventricular tachycardia, n (%)	14 (28.6)	7 (29.2)	7 (28)	0.93
Syncope, n (%)	6 (12.2)	4 (16.7)	2 (8)	0.42
Estimated 5-year risk of sudden cardiac death, %, median (IQR)	2.8 (1.9–4.5)	3.0 (2–3.9)	2.4 (1.4–5)	0.33
Diabetes mellutis, n (%)	6 (12.2)	2 (8.3)	4 (16)	0.67
Coronary artery disease, n (%)	8 (16.3)	5 (20.8)	3 (12)	0.46
Hypertension, n (%)	29 (59.2)	17 (70.8)	12 (48)	0.1
Atrial fibrillation, n (%)	6 (12.2)	4 (16.7)	2 (8)	0.42
Dyslipidemia, n (%)	23 (46.9)	13 (54.2)	10 (40)	0.32
SBP, mm Hg, mean (SD)	131.2 (21.6)	136.6 (20.7)	126 (21.7)	0.09
6MWT distance, m, mean (SD)	431.5 (121.2)	447.5 (101.4)	416.2 (138.1)	0.39
Hb, g/dl, median (IQR)	14.4 (13.6–15.4)	14.6 (13.8–15.6)	14.3 (13.4–15.2)	0.25
Creatinine, µmol/l, median (IQR)	84 (78–94)	83.5 (78–90)	85 (78–94)	0.62
Echocardiographic data				
Indexed LVEDd, mm/m^2, mean (SD)	22.5 (3.4)	21.8 (3)	23.2 (3.6)	0.14
Max wall thickness, mm, mean (SD)	19.9 (4.0)	19.5 (3.8)	20.3 (4.2)	0.48
Left atrium diameter, mm, mean (SD)	43.5 (6.6)	44.3 (6.6)	42.8 (6.7)	0.43
Left atrial volume index, ml/m^2, median (IQR)	41.6 (33.7–64.3)	51.7 (33.7–67.6)	40.5 (33.5–56.5)	0.36
Max LVOT gradient, mm Hg, median (IQR)	20 (8–55)	37 (11.5–78.5)	15 (8–36)	0.07
E/A, median (IQR)	1.05 (0.76–1.83)	0.97 (0.7–1.76)	1.1 (0.77–1.9)	0.66
E' intraventricular septum, m/s, median (IQR)	0.06 (0.04–0.08)	0.07 (0.06–0.08)	0.05 (0.04–0.07)	0.05
E/E', median (IQR)	10.1 (8–14)	8.8 (6.8–13.9)	11.3 (8.8–14)	0.21
Right ventricular systolic pressure, mm Hg, median (IQR)	23 (16–28)	20 (15–26)	24 (19–29)	0.14
Cardiac magnetic resonance data				
Indexed LVED volume, ml/m^2, mean (SD)	79.7 (12.4)	79.8 (13.6)	79.6 (11.4)	0.96
Indexed LVES volume, ml/m^2, median (IQR)	23.9 (20.5–30.6)	25.3 (21.6–30.6)	23.3 (19.9–30.3)	0.71
Indexed stroke volume, ml/m^2, mean (SD)	53.1 (10.3)	53.6 (10.4)	52.6 (10.4)	0.73
EF, %, median (IQR)	69 (61–73)	68.5 (61–72.5)	69 (63–74)	0.8
Left ventricular mass, grams, mean (SD)	196.5 (53.3)	205.8 (54.4)	187.8 (51.8)	0.25
LGE presence, n (%)	37 (75.5)	16 (66.7)	21 (84)	0.16
LGE mass, grams, median (IQR)	6.65 (0.5–13)	5.6 (0–8.65)	8.65 (2.55–20.5)	0.05
LGE extent, %, median (IQR)	3.80 (0.45–8.29)	2.82 (0–4.83)	5.21 (1.6–9.38)	0.04
Native T1 time, ms, median (IQR)	1262.4 (1238.8–1315)	1241 (1217.1–1275.7)	1289.2 (1258–1326.6)	0.002
Post-contrast T1 time, ms, mean (SD)	470.4 (55.5)	479.4 (53.1)	461.6 (57.4)	0.27
Native blood T1 time, ms, median (IQR)	1851.7 (1820.3–1919.3)	1836.2 (1787.3–1903.5)	1854.7 (1825.3–1960.7)	0.12
Post-contrast blood T1 time, ms, mean (SD)	306.8 (43.2)	289.9 (42.4)	323 (38)	0.006
ECV, %, median (IQR)	28.1 (25.6–30.2)	25.5 (23.4–26.6)	30.2 (29–32.1)	<0.001
Pharmacotherapy				
BB, n (%)	42 (85.7)	22 (91.7)	20 (80)	0.42
Diltiazem/verapamil, n (%)	7 (14.3)	4 (16.7)	3 (12)	0.7
ASA, n (%)	8 (16.3)	4 (16.7)	4 (16)	1
ACEi/ARB, n (%)	22 (44.9)	12 (50)	10 (40)	0.48
MRA, n (%)	14 (28.6)	7 (29.2)	7 (28)	0.93
Loop diuretics, n (%)	14 (28.6)	6 (25)	8 (32)	0.59
Amiodarone, n (%)	2 (4.1)	2 (8.3)	0	0.23
OAC, n (%)	6 (12.2)	4 (16.7)	2 (8)	0.42
Statins, n (%)	20 (40.8)	9 (37.5)	11 (44)	0.64

Abbreviations: 6MWT, 6-minute walk test; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; ASA, acetylsalicylic acid; BB, beta-blocker; BMI, body mass index; E/A, ratio of early mitral inflow E-wave and late mitral inflow A-wave velocity; ECV, extracellular volume; E/E', ratio of early mitral inflow velocity to early mitral myocardial velocity; EF, left ventricular ejection fraction; Hb, hemoglobin; LGE, late gadolinium enhancement; LVED, left ventricular end-diastolic; LVEDd, left ventricular end-diastolic diameter; LVES, left ventricular end-systolic; LVOT, left ventricular outflow tract; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association class; SBP, systolic blood pressure; OAC (VKA and non-VKA) oral anticoagulants; VKA, vitamin K antagonist

Table 2. Comparison of biomarkers between HCM patients, stratified according to ECV

Parameter	All (n = 49)	ECV <28.1% (n = 24)	ECV ≥28.1% (n = 25)	*P*-value
Troponin T, pg/ml	15 (8–25)	13 (7.5–19)	20 (8–28)	0.08
NT-proBNP, pg/ml	481 (197–1117)	199.5 (116–817.5)	823 (440–1465)	0.007
PICP, ng/ml	268.9 (203.7–350.2)	267.7 (201.6–350)	268.9 (228.3–354.1)	0.73
PIIINP, ng/l	399.6 (328.2–476.8)	408.4 (335.8–469.4)	376.2 (328.2–546)	0.98
Gal-3, ng/ml	2.40 (1.83–3.38)	1.93 (1.68–2.97)	2.93 (1.9–4.25)	0.03
TGF-β1, pg/ml	50.5 (21.6 -110.1)	51.2 (21.4–126.9)	50.5 (28.7–110.1)	0.9

Values are presented as median (IQR)

Abbreviations: Gal-3, galectin-3; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PICP, procollagen I C-terminal propeptide; PIIINP, procollagen III N-terminal propeptide; TGF-β1, transforming growth factor β1

Table 3. Correlation between biomarkers and selected CMR data

	LV mass		LGE extent		ECV	
	r_s	*P*-value	r_s	*P*-value	r_s	*P*-value
Troponin T	0.18	0.21	0.35	0.01	0.34	0.02
NT-proBNP	–0.005	0.97	0.16	0.26	0.39	0.006
PICP	–0.06	0.7	0.15	0.3	0.06	0.67
PIIINP	–0.17	0.25	–0.04	0.81	-0.04	0.79
Gal-3	0.02	0.87	0.11	0.45	0.43	0.002
TGF-β1	–0.1	0.5	0.01	0.94	0.07	0.62

Abbreviations: LV, left ventricular; r_s, R Spearman coefficient; other — see Table 1 and 2

Table 4. Uni- and multivariable regression models for presence of higher value of ECV.

	Univariable		Multivariable	
Parameter	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
BMI	0.89 (0.79–0.99)	0.03	0.81 (0.68–0.97)	0.02
SBP	0.97 (0.95–1.005)	0.09	—	—
LGE extent	1.16 (1.006–1.34)	0.04	1.24 (0.996–1.55)	0.05
Max. LVOT gradient	0.98 (0.96–0.999)	0.03	0.98 (0.96–1.006)	0.13
E' intraventricular septum	2.66 (0.003–2610.67)	0.78	—	—
Troponin T	1.03 (0.99–1.07)	0.1	—	—
NT-proBNP	1.0002 (0.9997–1.0007)	0.41	—	—
Gal-3	1.73 (1.03–2.89)	0.03	2.29 (1.07–4.91)	0.03

Abbreviations: see Table 1 and 2

Predictor factors for elevated ECV

Among all the parameters differentiating patients with lower and higher ECV values, univariable regression analysis revealed significant associations between ECV and BMI, LGE extent, left ventricular outflow tract gradient, and gal-3 (Table 4). However, in the multivariable regression model, only BMI and gal-3 were independently associated with ECV (odds ratio [OR], 0.81 [0.68–0.97]; *P* = 0.02; OR, 2.29 [1.07–4.91]; *P* = 0.03, respectively) (Table 4). Nonetheless, it is worth highlighting that the LGE extent was also very close to being statistically significant.

Parameters associated with higher LGE extent

In the group of patients with confirmed LGE (n = 37), we conducted an analysis aimed at identifying parameters associated with higher LGE extent, defined as equal to or greater than the median in our subgroup, which was 5.21%. In the univariable analysis, the following variables were associated with the LGE extent: ejection fraction (EF) (OR, 0.91 [0.84–0.99]; *P* = 0.03), ventricular tachycardia (VT) (OR, 5.56 [1.14–27.16]; *P* = 0.03), with TnT being the only biomarker differing between the groups and showing a trend toward significance (OR, 1.06 [0.999–1.12]; *P* = 0.05) (Supplementary material, *Tables S1, S2*). Due to the small size of the subgroup, we did not perform a multivariable analysis identifying independent predictors of higher LGE extent.

DISCUSSION

The study findings can be summarized as follows. Firstly, HCM patients stratified according to median ECV differed in terms of several key clinically relevant variables, such as BMI, LGE extent, and mass, as well as NT-proBNP and gal-3 levels. Secondly, cardiac-specific (NT-proBNP and TnT), as well as fibrosis-related (gal-3) markers, were correlated with ECV, whereas only TnT was correlated with LGE extent. Thirdly, EF and VT were found to be associated with replacement fibrosis (LGE extent), whereas gal-3 and BMI were found to be independently associated with interstitial fibrosis (ECV).

Biomarkers and replacement fibrosis

So far, the issue of the relationship between cardiac-specific biomarkers and replacement fibrosis expressed as LGE has been quite widely studied, mainly due to the fundamental role of replacement fibrosis in HCM pathology. Despite this extensive investigation, the topic is still far from being resolved, with conflicting results being reported. In our study, we observed a positive correlation between LGE extent and TnT levels. In the sub-analysis involving only patients with LGE presence, troponin levels presented a tendency to predict higher LGE extent in the univariable analysis, and only EF and VT were associated with LGE extent. It is worth remarking that this observed association could well be interpreted in the following way: LGE extent is a VT predictor (which we and others have shown previously), not the other way round [9, 11]. Several authors have also observed higher levels of TnT in HCM patients with LGE presence [12, 13], and yet in other studies, there have been associations reported between TnT levels and LGE mass or extent [14, 15]. However, Kawasaki et al., despite the presence of higher troponin levels in LGE-positive HCM patients, observed no correlation between TnT and LGE extent [12]. Interestingly, Gommans et al. [16] observed the association between LGE extent and elevated TnT in their whole group of HCM patients; however, this association was no longer seen when only patients with LGE were considered.

Moving on to the question of natriuretic peptides, numerous authors have found that there is a higher level of BNP or NT-proBNP in LGE-positive patients (e.g. via qualitative classification into LGE-positive and negative patients) as well as a relationship between quantitative LGE evaluation (LGE extent or LGE mass) and NT-proBNP [12, 14, 17]. Despite that, we did not observe any correlation between NT-proBNP levels and LGE, which is similar to the report of Miyaji et al., who showed no differences in the percentage of LGE extent among the tertiles of BNP levels in HCM patients [18]. In the study by Roldan et al. [19], NT-proBNP was increased in fibrosis patients assessed by CMR; still, NT-proBNP values did not correlate with LGE extent. Similarly, Gommas et al. did not report differences in the NT-proBNP levels in the patients with LGE extent <15% and ≥15% [15].

Significantly, among the plasma fibrosis-specific biomarkers analyzed in our study, no association with LGE was observed, nor have other researchers shown such a relationship with respect to gal-3, PICP, PIIINP, or TGF-β1 [14, 15, 20]. Thus, the question concerning the relationship between fibrosis-specific markers and replacement fibrosis seems to have been answered to a certain degree by this and previous studies since no such associations have been found in HCM.

Biomarkers and interstitial fibrosis

As previously mentioned, the topic of interstitial fibrosis and its relationship with serum biomarkers is much less studied, with few articles focused on cardiac-specific markers in the setting of interstitial fibrosis in HCM. Neubauer et al. presented data from a large registry on HCM and reported a significant trend of higher NT-proBNP values with increasing ECV quartiles as well as a significant trend of higher TnT with higher ECV quartiles, but only in males rather than in females [21]. Ho et al. [22] reported correlations between ECV and NT-proBNP, but no relations were observed between ECV or LGE and serum PICP or troponin levels in a cohort of 77 subjects including sarcomere mutation carriers with and without LVH. Importantly, we found that TnT and NT-proBNP were elevated in HCM patients. Similarly, we found higher values of NT-proBNP in those with higher ECV values. In terms of troponins, we noted only a trend towards significance in patients with higher ECV, and a weak but significant correlation with ECV. In the recent article on this topic by Shi et al. [23], no differences within LGE, native T1, and ECV were observed in HCM patients stratified into normal and elevated troponin levels.

Our observations on the lack of associations between collagen turnover-related biomarkers (PICP, PIIINP) and TGF-β1 with interstitial fibrosis are consistent with other studies conducted so far. Apart from the work cited above by Ho et al. [22], Fang et al. [24], who studied a population of a similar size to ours, observed no differences in levels of PINP and PIIINP in patients with lower and higher ECV values. In another article, Ellims et al. reported no correlations between PINP or PIIINP levels, CMR-determined replacement (LGE extent), and diffuse (post-contrast T1 mapping) fibrosis [25].

Our observation on the association of lower BMI with higher ECV values is consistent with the study by Neubauer et al. [21]. Since, apart from gal-3, only BMI emerged as a predictor of ECV, this observation requires further study.

Galectin-3 in HCM

Galectin-3 has recently become a "hot topic", being a key molecule integrating cardiac stress injury, inflammation, and fibrosis. As such, its significance and role has been studied in various cardiovascular diseases, including heart failure and cardiomyopathies. In our previous study in dilated cardiomyopathy (DCM) patients, we observed no correlation between gal-3 and biopsy-determined fibrosis while circulating gal-3 was independently associated with cardiovascular outcomes in DCM; its serial measurements also correlated with markers of fibrosis, including markers of collagen synthesis [26]. Several studies reported gal-3 levels to be significantly higher in patients with HCM than in controls [27, 28]. Data regarding gal-3 and fibrosis assessed by CMR in HCM are scarce. Gawor et al. [14] reported no correlation between gal-3, sST2, GDF-15 levels, and LGE extent in 60 HCM patients. Also, in the study by Hu et al. [29], HCM patients with and without LGE did not differ in terms of gal-3 levels. Thus, our observations on the lack of association between gal-3 and LGE are consistent with the above-mentioned authors. To the best of our knowledge, our study is the first to reveal a relatively strong relationship

between gal-3 and interstitial fibrosis in HCM. The observed association between gal-3 and ECV (interstitial fibrosis) and the lack of any association between gal-3 and LGE (replacement fibrosis) clearly points to distinct metabolic pathways and the significance of these two types of fibrosis in HCM. In our opinion, this relationship deserves further attention and in-depth research, especially bearing in mind that the data on the relationship between gal-3 and HCM SCD-risk are, to date, contradictory — while Gawor et al. [27] observed no significant relationships between sST2 and gal-3 levels and HCM SCD-risk, Emet et al. [30] found a significant correlation between the estimated 5-year risk of SCD and serum levels of gal-3.

Limitations

We admit that there are several limitations to our study. First, our study group was relatively small, and this was a single-center study. Second, due to the impaired quality of T1 mapping images in patients with implantable devices, we excluded such high-risk patients; still, a sub-analysis of such patients would probably be valuable. Third, blood marker concentrations may vary daily or weekly; thus, sequential measurements could provide additional data. Fourth, due to the low number of cases with LGE, we did not perform a multivariable analysis and the results of the univariable logistic regression analysis could be less sound, and the conclusion should be interpreted with caution.

CONCLUSIONS

Cardiac-specific biomarkers (troponin, NT-proBNP) are weakly related with both replacement and interstitial fibrosis, and markers of collagen turnover as well as TGF-β1 seem to be inadequate as fibrosis-related biomarkers in HCM. On the other hand, Galectin-3 appears to be strongly related to interstitial fibrosis in HCM, making it a strong candidate for being a potential biomarker in this setting.

Supplementary material

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

Article information

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Disparities in knowledge of cardiovascular risk factors and prevention methods related to cardiovascular status and functional health literacy in Poland, 2020–2021

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Editorial
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ABSTRACT

Background: Numerous studies have reported a significant role of health literacy (HL) in the prevention or treatment of various diseases. However, in Poland, there was no scientific research involving simultaneously the status of cardiovascular disease (CVD) and HL in assessment of health knowledge; therefore, it became the objective of our study.

Aims: We aimed to evaluate the level of CVD knowledge depending on CVD status and functional HL in the Polish population.

Methods: The study population consisted of 2827 participants from the WOBASZ II Survey aged 20–89 years: 2266 were CVD-free (non-CVD), 361 were hospitalized for CVD (CVDH[+]), and 200 were diagnosed with CVD but not hospitalized (CVDH[-]). The Newest Vital Sign test (NVS) was applied to determine functional HL. Self-reported knowledge of CVD risk factors (RFs) and prevention methods (PMs) in participants with different CVD status depending on HL was estimated. Multivariable ordinal and binary logistic regression analyses were performed to find predictors of RFs and PMs knowledge.

Results: The knowledge of CVD RFs and/or PMs was strictly related to HL and CVD status. Inadequate HL decreased the satisfactory (≥5 RFs/PMs) knowledge of RFs (odds ratio [OR], 0.50; 95% confidence interval [CI], 0.40–0.62) and PMs (OR, 0.56; 95% CI, 0.45–0.71). CVDH(-) participants were more likely to have satisfactory PMs knowledge (OR, 1.49; 95% CI, 1.02–2.16), while CVDH(+) participants satisfactory RFs knowledge (OR, 1.85; 95% CI, 1.35–2.53).

Conclusions: HL and CVD status are the key determinants of CDV RFs/PMs knowledge. Functional HL significantly affects health knowledge; therefore, HL screening should be recommended in primary care to increase the effectiveness of primary CVD prevention.

Key words: cardiovascular disease, health inequalities, health literacy, health promotion, risk factors

INTRODUCTION

Cardiovascular disease (CVD) is the main cause of mortality and disability throughout the world and in Poland. It caused 17.9 million deaths (32% of all global deaths) in 2019 [1]. Forty percent of deaths in Poland are due to CVD. One of the biggest threats to global health that occurred in the last 10 years was the high number of deaths from ischemic heart disease and stroke [2]. One way to reverse this unfortunate situation would be to place more emphasis on primary prevention, which refers to the steps taken by individuals to prevent the onset of CVD. Knowlege of risk factors (RFs) and non-pharmacological prevention methods (PMs) is required to take these steps.

Individuals cannot change unmodifiable CVD RFs (age, sex) but can modify their lifestyle by making proper choices such as a healthy diet, exercise, no tobacco use, no excessive alcohol drinking, and avoiding

WHAT'S NEW?

Cardiovascular disease (CVD) knowledge is associated with health literacy (HL): the higher level of HL, the better CVD knowledge. The novelty of this study is in-depth analysis of the knowledge of CVD risk factors and prevention methods in people with different CVD status (free from CVD, diagnosed with CVD, or hospitalized for CVD) and adequate or inadequate HL, simultaneously. The most important findings were differences between persons with varying CVD status within the HL subgroups. Our study revealed that CVD status plays a crucial role in acquiring knowledge of particular CVD risk factors and prevention methods — the greatest knowledge was mostly observed in hospitalized CVD patients with inadequate HL and in non-hospitalized CVD patients with adequate HL. These findings may be particularly important in public health practice because they show that patients' HL may affect CVD prevention and/or development. Therefore, HL screening should be recommended in primary care to better understand patient needs, reduce health inequalities, and increase the effectiveness of CVD prevention and/or treatment.

chronic stress. Lifestyle change is possible at every stage of life, both among CVD-free or CVD-diagnosed people and can bring tangible benefits.

Numerous studies report a helpful role of functional health literacy (HL) [3, 4], defined as "a person's ability to read and comprehend information and instructions in health settings" [5]. An adequate level of HL can significantly contribute to maintaining a healthy lifestyle, increasing detection of CVD, and the effectiveness of CVD treatment [6]. Limited HL has been shown to result in "an increased risk of morbidity and premature death in older adults independent of age, socioeconomic position, cognitive function and pre-existing illness" [7].

CVD RFs and/or PMs knowledge has also been shown to depend on CVD status [3, 4]. However, to our best knowledge, there was no scientific research involving simultaneously different CVD status and HL in the assessment of CVD health knowledge in Poland.

Therefore, the purpose of our study was to investigate and describe similarities and disparities between individuals with different CVD status and with adequate and inadequate functional HL.

METHODS

Study population

The current study related to the assessment of functional HL in participants with different CVD status was conducted in 2020–2021. We used data from the National Multicenter Health Examination Survey (Polish acronym WOBASZ II), which took place in 2013–2014 in a randomly selected sample of 6170 respondents; details are available elsewhere [8]. A pilot study on the evaluation of HL was included in the WOBASZ II Survey in 2014 among participants from 8 voivodeships (dolnoslaskie, kujawsko-pomorskie, lubuskie, opolskie, podkarpackie, warminsko-mazurskie, wielkopolskie, zachodniopomorskie). There were 2868 respondents who completed the main questionnaire of the WOBASZ II Survey and participated in the HL test. Finally, our study was based on 2827 interviewees aged 20–89 years, 1270 (44.9%) men, and 1557 (55.1%) women, after excluding 39 of the respondents who did not provide information about their CVD status. Both studies were approved by the Bioethics Committee of the National Institute of Cardiology (current study: no. 1857/2020, WOBASZ II: no. 1344/2012). Written informed consent was obtained from all participants.

Identifying CVD status

We classified the interviewees as free from CVD if they answered "no" to the question about being diagnosed or hospitalized for CVD (non-CVD group, n = 2266) and as having CVD if they answered "yes" to the same question (CVD group, n = 561). Then we assigned participants into two CVD subgroups: the group hospitalized for CVD (CVDH[+], n = 361) and the group diagnosed with CVD but not hospitalized (CVDH[-], n = 200). Respondents were diagnosed with any of the following CVDs: coronary heart disease (n = 214, 38.1%), myocardial infarction (n = 95, 16.9%), atrial fibrillation (n = 144, 25.7%), abnormal heart rhythm or other cardiac arrhythmias (n = 204, 36.4%), peripheral vascular disease of the lower limbs (n = 135, 24.1%), and stroke (n = 69, 12.3%). CVD-related hosptializations were due to acute coronary heart disease (n = 138, 38.3%), myocardial infarction (n = 100, 27.8%), atrial fibrillation (n = 119, 33.1%), abnormal heart rhythm or other cardiac arrhythmias (n = 107, 29.7%), heart failure (n = 96, 26.7%), stroke (n = 72, 20.0%), coronary angioplasty or coronary artery bypass grafting (n = 54, 15.0%), an implanted pacemaker or cardioverter-defibrillator (n = 25, 6.9%).

Measurement of health literacy

From many validated instruments used to assess HL skills [5], the Newest Vital Sign Test (NVS) was applied to determine functional HL [9, 10]. Respondents completed the 6-question test in the Polish language version, which was adopted for the first time during the European Health Literacy Survey (HLS-EU) in 2011 [11]. We applied the bivalent classification to convert the NVS score from a seven-point scale. An adequate level of HL was assigned to the respondent if he/she achieved a score of 4–6 in NVS and an inadequate (limited) level of HL if his/her result was in the range of 0–3.

Assessment of knowledge of CVD risk factors and non-pharmacological prevention methods

A multistage approach was applied to evaluate the level of CVD RFs/PMs knowledge based on open-ended questions. First, we estimated the knowledge of single CVD RFs or PMs. We classified respondents as knowing relevant CVD RFs if they listed any of the following modifiable RFs: hypertension, tobacco smoking, increased alcohol consumption, overweight and/or obesity, improper diet, low physical activity, chronic stress, diabetes mellitus (DM), increased total cholesterol (T-Chol), increased low-density lipoprotein cholesterol (LDL-C), and decreased high-density lipoprotein cholesterol (HDL-C). We classified participants as knowing relevant CVD PMs if they mentioned any of the following non-pharmacological modifiable PMs: tobacco smoking cessation, alcohol consumption reduction, regular physical activity, weight reduction in persons with overweight or obesity, leading a regular lifestyle and/or avoiding chronic stress, fat intake reduction, salt intake reduction, and regular consumption of fruits and vegetables.

Respondents could obtain one point for each correct answer, and a composite knowledge index was created by summing the responses for each item. CVD RFs and PMs knowledge indices were calculated separately and were in the range of 0–11 and 0–8, respectively. Furthermore, they were converted to a 4-point scale: poor (0–1 points), moderate (2–3 points), good (4–5 points), and very good (≥6 points). The method of recoding reflected the degree of dissemination of knowledge; therefore, the same scale was used for CVD RFs/PMs despite the different ranges of the original scales. We also defined a satisfactory level of CVD RFs/PMs knowledge (≥5 points). The threshold value was arbitrarily determined as the value equal to the upper limit of good CVD RFs/PMs knowledge.

Statistical analysis

First, the prevalence of CVD RFs and PMs knowledge was estimated between different CVD status groups depending on functional HL. Second, multivariable ordinal (a partial proportional odds model) and binary logistic regression analyzes were performed to find potential predictors of CVD RF/PM knowledge, respectively, for four-level (very good, good, moderate, poor) and two-level (satisfactory, unsatisfactory) dependent variables.

Descriptive statistics were presented as means (standard deviation [SD]) for continuous data and numbers (percentages) for categorical data, and the Kruskal-Wallis test or χ^2 test was applied for comparisons between groups, respectively. Percentages and means with a 95% confidence interval (CI) related to the level of CVD RFs/PMs knowledge were adjusted for age, sex, education, and size of the place of residence in a general linear model with the Tukey-Kramer adjustment for multiple comparisons. The determinants of CVD RFs/PMs knowledge were expressed as the odds ratio (OR) with 95% CI. The level of significance was assumed at P <0.05. Data analyzes were performed using SAS9.4 software (SAS Institute Inc., Cary, NC, US).

RESULTS

The mean age (SD) of the study population was 49.7 (16.3) years. Respondents with different CVD status varied in the background variables: sex, age, education, some categories of marital status or place of residence, and HL (Table 1). The respondents with CVDH(+) status were the oldest (64.5 [13.0] years vs. CVDH[-], 58.9 (14.9) years, and non-CVD, 46.5 (15.2) years; P <0.001), with the lowest level of secondary and higher education (40.1% vs. CVDH[-], 56.5% and non-CVD, 62.3%; P <0.001) and with the highest percentage of individuals with inadequate functional HL (65.7% vs. CVDH[-], 44.0% and non-CVD, 42.5%; P <0.001).

First, the relationships between knowledge of CVD RFs/PMs were found separately either for the HL level of the respondent or the presence or absence of CVD. As expected, participants with adequate HL or positive CVD status had better knowledge than participants with inadequate HL and non-CVD status.

The differences in CVD knowledge by HL were statistically significant for the following RFs: hypertension, tobacco smoking, increased alcohol consumption, overweight and/or obesity, improper diet, low physical activity, chronic stress, and increased T-Chol, and for the following PMs: tobacco smoking cessation, alcohol consumption reduction, regular physical activity, weight reduction, leading a regular lifestyle, fat or salt intake reduction (Supplementary material, *Figure S1A* and *S1B*, respectively).

The differences in CVD knowledge between non-CVD and CVD persons were significant for the following RFs: hypertension, tobacco smoking, increased alcohol consumption, DM, and increased T-Chol, and for the following PMs: tobacco smoking cessation, weight reduction, fat intake reduction, and regular consumption of fruits and vegetables (Supplementary material, *Figure S1A* and *S1B*, respectively).

Secondly, the knowledge of CVD RFs/PMs was investigated simultaneously by CVD status and HL level. The detailed data and distribution of 2 to 4 most frequently mentioned CVD RFs/PMs, and their sums are presented in Supplementary material, *Table S1* and *Figure S2*, respectively. Additionally, the graph shows the level of ignorance about CVD RFs/PMs (no CVD RFs or PMs known).

There were two different patterns of CVD RFs knowledge distribution between respondents with different CVD status within each HL subgroup.

Subgroup with inadequate health literacy

In the subgroup with inadequate HL, the highest knowledge was observed in CVDH(+) participants almost for all significantly different RFs: hypertension (47.3%; 95% CI, 40.8%–53.9%), overweight and/or obesity (36.7%; 95% CI, 30.8%–42.6%), increased T-Chol (31.1%; 95% CI, 26.6%–37.6%), except for DM (the highest knowledge

Table 1. Baseline characteristics of respondents by CVD status

	Total	Cardiovascular disease status			
		Non-CVD	CVD		*P*-value
			CVDH(-)	CVDH(+)	
Respondents, n (%)	2827 (100.0)	2266 (80.1)	200 (7.1)	361 (12.8)	—
Sex, n (%)					
Male	1270 (44.9)	1015 (44.8)	67 (33.5)	188 (52.1)	<0.001
Female	1557 (55.1)	1251 (55.2)	133 (66.5)	173 (47.9)	
Age, years					
Mean (SD)	49.7 (16.3)	46.5 (15.2)	58.9 (14.9)	64.5 (13.0)	<0.001
Age group, n (%)					
20–44 years	1149 (40.6)	1086 (47.9)	34 (17.0)	29 (8.0)	<0.001
45–59 years	822 (29.1)	683 (30.1)	59 (29.5)	80 (22.2)	
60–74 years	646 (22.9)	404 (17.8)	75 (37.5)	167 (46.3)	
≥75 years	210 (7.4)	93 (4.1)	32 (16.0)	85 (23.5)	
Marital status, n (%)					
Married/cohabited	1856 (65.7)	1487 (65.6)	129 (64.5)	240 (66.5)	<0.001
Single	493 (17.4)	456 (20.1)	22 (11.0)	15 (4.1)	
Widowed	317 (11.2)	189 (8.3)	40 (20.0)	88 (24.4)	
Divorced/separated	161 (5.7)	134 (5.9)	9 (4.5)	18 (5.0)	
Education, n (%)					
Primary	490 (17.3)	312 (13.7)	50 (25.0)	128 (35.5)	<0.001
Vocational	669 (23.7)	544 (24.0)	37 (18.5)	88 (24.4)	
Secondary	1023 (36.2)	844 (37.3)	72 (36.0)	107 (29.6)	
Higher	645 (22.8)	566 (25.0)	41 (20.5)	38 (10.5)	
Size of the place of residence, n (%)					
Small community (<8000 inhabitants)	933 (33.0)	764 (33.7)	51 (25.5)	118 (32.7)	0.017
Medium community (8000–40 000 inhabitants)	940 (33.3)	739 (32.6)	65 (32.5)	136 (37.7)	
Large community (≥40 000 inhabitants)	954 (33.7)	763 (33.7)	84 (42.0)	107 (29.6)	
Health literacy, n (%)					
Inadequate	1289 (45.6)	964 (42.5)	88 (44.0)	237 (65.7)	<0.001
Adequate	1538 (54.4)	1302 (57.5)	112 (56.0)	124 (34.3)	

Abbreviations: CVD, cardiovascular disease; SD, standard deviation

Definitions: non-CVD, without CVD; CVDH(-), CVD-diagnosed but not hospitalized; CVDH(+), CVD-diagnosed and hospitalized; education: primary, none, partial or completed primary school; vocational, after completed primary or middle school; secondary, high or post-secondary school, higher, bachelor's degree or tertiary education

in CVDH[-] subjects [21.6%; 95% CI, 14.5%–28.6%]). No significant differences were noticed in the knowledge of singular CVD PMs, except knowledge of the necessity for weight reduction.

There was a difference between participants with different CVD status (non-CVD, CVDH[-], CVDH[+]) in the average and satisfactory levels of CVD RF knowledge (2.3 [95% CI, 2.1–2.5]; 2.7 [95% CI, 2.2–3.2]; 3.0 [95% CI, 2.7–3.3]; P <0.001, and 14.8% [95% CI, 12.5%–17.2%]; 21.1% [95% CI, 14.2%–28.0%]; 21.2% [95% CI, 16.7%–25.7%]; P = 0.02, respectively), but not in the average or satisfactory levels of CVD PMs knowledge. The lowest percentage of participants with poor CVD RFs knowledge was in the CVDH(+) subgroup (31.6% [95% CI, 25.0%–38.2%]) (Supplementary material, *Table S1*).

Subgroup with adequate health literacy

In the subgroup with adequate HL, the greatest CVD RF knowledge was noticed in CVDH(-) respondents in relation to the following significantly different RFs: tobacco smoking (56.1% [95% CI, 46.4%–65.8%]), improper diet (54.4% [95% CI, 46.2%–64.5%]), and low physical activity (33.1% [95% CI, 24.3%–42.0%]), except increased alcohol consumption (the highest knowledge in CVDH(+) subjects (43.2% [95% CI, 34.1%–52.3%]). Furthermore, CVDH(-) respondents had the greatest PMs knowledge, although not statistically significant, except knowledge of the requirement for fat intake reduction and regular consumption of fruits and vegetables.

There was no significant difference in the average number of self-reported CVD RFs between participants with different CVD status (non-CVD, CVDH[-], CVDH[+]), although it was in the average and satisfactory levels of CVD PMs knowledge (3.3 [3.2–3.4], 3.9 [3.5–4.2], 3.4 [3.0–3.7]; P = 0.005 and 21.8% [18.8%–24.8%], 32.7% [24.3%–41.1%], 26.2% [18.1%–34.3%]; P = 0.03, respectively). The lowest percentage of participants with poor CVD RFs and PMs knowledge was in the CVDH(-) subgroup (17.3% [9.4%–25.2%] and 5.7% [0%–12.0%], respectively) (Supplementary material, *Table S1*).

Predictors of knowledge of CVD risk factors and prevention methods

HL and CVD status impacted the knowledge of CDV RFs/PMs. Inadequate HL reduced the knowledge by 51% and 48% (Table 2, model 1) for RFs and PMs, respectively, while the presence of CVD increased the knowledge about RFs/PMs. Participants diagnosed or hospitalized for CVD were more likely to have a higher level of knowledge of RFs and PMs (by 48% and 62%, and by 65% and 32%, respectively).

Education also impacted CVD RFs/PMs knowledge: the lower the educational level, the lower knowledge (Table 2). Furthermore, the place of residence had a substantial impact on RFs/PMs knowledge. Living in a medium community substantially increased only the possibility of a very good level of RFs knowledge (OR, 1.74; 95% CI, 1.38–2.20), while living in a small community significantly decreased the knowledge (OR, 0.80; 95% CI, 0.67–0.96) regardless of its level. In turn, living in a medium community increased the level of PMs knowledge by 28%, 48%, and 86% for moderate, good, and very good levels of knowledge, respectively. Living in a small community did not affect CVD PMs knowledge.

Additionally, participants aged 45–59 years were more likely to have a higher level of RFs knowledge (by 47%), while persons aged 75 years and older were more likely to have a lower level of PMs knowledge (by 42%). In our study, neither RFs knowledge nor PMs knowledge was sex-dependent (Table 2).

Similar results were obtained for satisfactory knowledge of RFs/PMs in relation to HL, education, and sex (Table 2, model 2). Living in a small community did not impact RFs knowledge, while living in a medium community increased by 43% and 81% the possibility of achieving satisfactory RFs and PMs knowledge, respectively. Participants aged 45–59 years were more likely to obtain satisfactory RFs knowledge, whereas age did not affect the achievement of satisfactory PMs knowledge.

The ability to achieve satisfactory RFs knowledge was significantly higher only in CVDH(+) subjects (OR, 1.85; 95% CI, 1.35–2.53) and satisfactory PMs knowledge only in CVDH(-) subjects (OR, 1.49; 95% CI, 1.02–2.16). It was the main difference in the influence of CVD status on RFs/PMs knowledge.

DISCUSSION

The overall level of adequate HL (54.4%), measured by the NVS test, in the adult Polish population in 2014 was noticeably higher than the level of adequate HL (42.2%) in the HLS-EU in 2011 [12]. The increasing percentage of adults with adequate HL appears to be a good prognosis for the future, also compared to other European countries. A meta-analysis of low HL in Europe showed the middle position of Poland among European countries with low HL of 45% (95% CI, 41%–48%) against the highest level of low HL of 62% (95% CI, 59%–65%) in Bulgaria and the lowest level of low HL of 29% (95% CI, 26%–32%) in the Netherlands [13].

The percentage of participants without CVD who did not know any RFs changed from 20.8% to 37.1% in the subgroups with adequate and inadequate HL, respectively. Our results are consistent with those of the Brazilian study [14], where one-third of the respondents were unable to identify at least one CVD RF. The results of other Polish studies also confirm the low level of health knowledge, especially in people with CVD or at risk of CVD [15].

A little knowledge of the impact of DM on CVD and the relationship between cholesterol fractions and CVD was also observed, whereas, at that time, 8.4% and 67.1% of Polish adults were affected by DM or hypercholesterolemia, respectively [16, 17].

In general, knowledge of CVD PMs and RFs seemed to be closely related, but it was not reflected in everyday life. In our study, more than 50% of respondents with inadequate HL and more than 60% with adequate HL knew that regular physical activity could reduce CVD risk, but only 27.3% of men and 28.7% of women participated in recommended physical activity (exercises lasting ≥30 min/day at least 5 times per week) [18]. Furthermore, the focus on one PM does not result in compliance with other recommendations: knowledge of recommended daily sodium intake and/or harmful use of excessive amounts of sodium contributed to the control of dietary salt intake but did not affect awareness of other PMs [19].

The knowledge of CVD RFs/PMs was found to be related to HL, CVD status, and education, as previously demonstrated by other researchers [5, 6]. In Poland, better-educated patients (>11 years) who participate in cardiac rehabilitation within comprehensive, coordinated care after myocardial infarction achieve more effective results compared to non-participants [20].

The relationship between HL and education requires additional attention. The final level of formal education is an attribute acquired by a person at a young adult age. When HL was based on the concept of traditional and functional literacy, there was a simple dependence: adults with limited functional literacy skills had difficulties in maintaining well-being.

Nowadays, general HL refers to personal "knowledge, motivation and competencies to access, understand, appraise and apply information to make judgments and take decisions in everyday life concerning healthcare, disease prevention, and health promotion to maintain and improve quality of life during the life course" [5]. The broadening of HL definition and the rapid development of medical science and technology in the 21st century mean that yesterday's knowledge may be outdated and insufficient today.

Living in a medium size community may be pivotal for good and very good level of CVD RFs/PMs knowledge. We suppose that in large communities, the fast pace of life does not encourage mutual integration and active participation

Table 2. Predictors of CVD risk factors or non-pharmacological CVD prevention methods knowledge

	Model 1			
Level of knowledge	**Risk factors**		**Prevention methods**	
Very good, n (%)	410 (14.5)		275 (9.8)	
Good, n (%)	618 (21.9)		719 (25.4)	
Moderate, n (%)	839 (29.7)		1216 (43.0)	
Poor, n (%)	960 (33.9)		617 (21.8)	
	Ordinal logistic regression			
Predictor	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Sex				
Female	1 [Reference]	—	1 [Reference]	—
Male	0.90 (0.78–1.04)	0.14	0.93 (0.80–1.07)	0.28
Age, years				
20–44	1 [Reference]	—	1 [Reference]	—
45–59	1.47 (1.23–1.74)	<0.001	1.10 (0.93–1.31)	0.26
60–74	1.10 (0.90–1.35)	0.36	0.96 (0.78–1.18)	0.68
≥75	0.84 (0.60–1.19)	0.32	0.58 (0.41–0.81)	0.002
Education				
Higher	1 [Reference]	—	1 [Reference]	—
Secondary	0.48 (0.40–0.58)	<0.001	0.55 (0.46–0.67)	<0.001
Basic vocational	0.30 (0.24–0.37)	<0.001	0.38 (0.30–0.47)	<0.001
Primary	0.17 (0.13–0.23)	<0.001	0.18 (0.13–0.23)	<0.001
Size of the place of residence[a]				
Large	1 [Reference]	—	1 [Reference]	—
Medium Very Good	1.74 (1.38–2.20)	<0.001	1.86 (1.42–2.44)	<0.001
Medium Good	1.17 (0.97–1.41)	0.11	1.48 (1.23–1.79)	<0.001
Medium Moderate	0.99 (0.81–1.20)	0.89	1.28 (1.02–1.60)	0.04
Small	0.80 (0.67–0.96)	0.01	1.05 (0.88–1.26)	0.57
CVD status				
Non-CVD	1 [Reference]	—	1 [Reference]	—
CVDH(-)	1.48 (1.12–1.94)	0.005	1.65 (1.26–2.17)	<0.001
CVDH(+)	1.62 (1.30–2.04)	<0.001	1.32 (1.05–1.66)	0.02
Health literacy				
Adequate	1 [Reference]	—	1 [Reference]	—
Inadequate	0.49 (0.42–0.57)	<0.001	0.52 (0.44–0.61)	<0.001
	MODEL 2			
Level of knowledge	**Risk factors**		**Prevention methods**	
Satisfactory	622 (22.0)		541 (19.1)	
Unsatisfactory	2205 (78.0)		2286 (80.9)	
	Binary logistic regression			
Predictor	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Sex				
Female	1 [Reference]	—	1 [Reference]	—
Male	0.91 (0.75–1.10)	0.32	0.91 (0.75–1.12)	0.38
Age, years				
20–44	1 [Reference]	—	1 [Reference]	—
45–59	1.41 (1.13–1.77)	0.003	1.15 (0.91–1.46)	0.24
60–74	0.89 (0.66–1.20)	0.46	0.94 (0.70–1.28)	0.70
≥75	0.80 (0.46–1.39)	0.42	0.63 (0.34–1.16)	0.14
Education				
Higher	1 [Reference]	—	1 [Reference]	—
Secondary	0.52 (0.41–0.65)	<0.001	0.49 (0.39–0.63)	<0.001
Basic vocational	0.30 (0.22–0.41)	<0.001	0.40 (0.29–0.54)	<0.001
Primary	0.18 (0.12–0.27)	<0.001	0.21 (0.13–0.33)	<0.001
Size of the place of residence				
Large	1 [Reference]	—	1 [Reference]	—
Medium	1.43 (1.15–1.79)	0.002	1.81 (1.43–2.30)	<0.001
Small	0.98 (0.76–1.26)	0.86	1.28 (0.98–1.67)	0.07
CVD status				
non-CVD	1 [Reference]	—	1 [Reference]	—
CVDH(-)	1.35 (0.93–1.95)	0.12	1.49 (1.02–2.16)	0.04
CVDH(+)	1.85 (1.35–2.53)	<0.001	1.16 (0.83–1.64)	0.39
Health literacy				
Adequate	1 [Reference]	—	1 [Reference]	—
Inadequate	0.50 (0.40–0.62)	<0.001	0.56 (0.45–0.71)	<0.001

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; OR, odds ratio; PM, prevention method; RF, risk factor; SE, standard error; other abbreviations and definitions — see Table 1

[a]Levels of CVD RFs/PMs knowledge: very good ≥6 RFs/PMs; good 4–5 RFs/PMs; moderate 2–3 RFs/PMs; poor 0–1 RFs/PMs; satisfactory ≥5 RFs/PMs; unsatisfactory 0–4 RFs/PMs

in CVD prevention programs, while in small communities, public access to expert knowledge and preventive programs is not as common as in larger centers. Some sociological studies indicate that environmental and cultural factors, and social capital, are the reasons for differences between municipalities in Poland. Mantaj et al. [21] observed similar dependencies: self-monitoring of health and intensity of preventive examinations were the highest in medium cities (<50 000) compared to rural areas and larger cities (>50 000), respectively, 72.7% vs. 43.8% and 44.7%. However, this interesting phenomenon would require further in-depth research.

Undeniably, the crucial findings of our study were the differences between persons with different CVD status within HL subgroups. Among respondents with adequate HL, the lowest percentage of participants who had poor knowledge of CVD RFs was in CVDH(-) respondents, which could suggest a good implementation of primary prevention. In turn, among the respondents with inadequate HL, the lowest percentage of participants who had poor knowledge of CVD RFs was in CVDH(+) respondents, which could suggest that they acquired and/or deepened their knowledge in secondary prevention.

People, even those who participate in prevention programs, do not comply with the advice they receive from healthcare professionals. Moreover, older patients (65+ years) are 50% less likely to recollect information compared to younger patients [22]. Probably, in patients with inadequate HL, this percentage would be higher. Therefore, optimal patient-doctor communication, adapted to the patient's HL and actual perception capacity, becomes an urgent need. Furthermore, age-related and HL-dependent individual cognitive competence [23] leads to higher mortality in people with lower HL [24].

There was a verification of the usefulness of HL during the COVID-19 pandemic. The growing threat of SARS-CoV-2 infection, high morbidity, and mortality due to COVID-19 disease limited access to traditional medical care and created the need for e-health and telemedicine systems. Higher HL significantly impacted user satisfaction and ease of use of remote visits in Polish patients (OR, 1.12; 95% CI, 1.08–1.16 and OR, 1.18; 95% CI, 1.14–1.22, respectively) [25].

Knowledge of CVD RFs and PMs was of particular importance during the pandemic. Smoking and obesity, and CVD itself significantly increased COVID-19 mortality (OR, 2.24; 95% CI, 1.4–3.58; OR, 2.28; 95% CI, 0.76–6.90 and OR, 7.87; 95% CI, 2.12–28.57 at maximum estimate, respectively) [26]. The high prevalence of CVD RFs in the Polish population and decreased attention to CVD prevention during the COVID-19 pandemic led to the development of modern prevention programs.

In conclusion, it seems that patients' HL may be a key determinant of CVD prevention, development, treatment, and positive health outcomes [27], also in Poland. Initial evaluation of patient HL will allow for personalized and tailored doctor-patient contact and choice of an appropriate way of providing medical information, especially for patients from vulnerable groups (i.e., with low educational level, advanced age, and poor handling of new technologies). This is particularly important in aging societies accompanied by a progressive increase in non-communicable diseases. Therefore, HL screening is recommended in primary cardiac care to better understand patients' needs, provide adequate medical care, and reduce health inequalities.

Our conclusions are in line with the findings of a systematic review of HL measurement in CVD patients by Elbashir et al. [4] and their suggestion that healthcare professionals should consider HL assessment as a routine practice in CVD patients. Furthermore, necessary actions should still be taken to intensify health promotion and improve the quality of primary CVD prevention. We believe that our findings can facilitate future actions, especially since taking HL into account in creating social environments by both national and local authorities has been recommended in the 2021 ESC Guidelines on CVD prevention in clinical practice [28].

Our study has several limitations. First, it was a cross-sectional study; therefore, we could not investigate the relationship between HL and CVD status. Second, only 8 of 16 voivodeships and only some of the diseases classified as CVD were included in the study, so we cannot generalize the results to the entire population of Poland. However, the main strength of our study is the large number of participants and the simultaneous consideration of many factors that affect CVD knowledge (sex, age, education level, place of residence, HL, CVD status).

Supplementary material

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

Article information

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Long-term results of pediatric heart transplantations: Single-center experiences

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ABSTRACT

Background: Heart failure (HF) is characterized by significant mortality in both adults and children. Characteristics of pediatric HF are feeding problems, poor weight gain, exercise intolerance, or dyspnea. These changes are often accompanied by endocrine disorders. The main causes of HF are congenital heart defects (CHD), cardiomyopathies, arrhythmias, myocarditis, or heart failure secondary to oncological treatment. Heart transplantation (HTx) is the method of choice for treatment of end-stage HF in pediatric patients.

Aims: This article aimed to summarize the single-center experience in heart transplantation in children.

Methods: Between 1988 and 2021 in the Silesian Center for Heart Diseases in Zabrze, 122 pediatric cardiac transplantations were performed. In the group of recipients with failing Fontan circulation, HTx was performed in 5 children. The study group was evaluated for the postoperative course: rejection episodes depending on the medical treatment scheme, coinfections, and mortality.

Results: One-, 5-, and 10-year survival rates between 1988 and 2001 were 53%, 53%, and 50%, respectively. One-, 5-, and 10-year survival rates between 2002 and 2011 were 97%, 90%, and 87%, respectively; between 2012 and 2021 (1-year of follow-up), the survival rate was 92%. The main cause of mortality both in early and late periods after transplantation was graft failure.

Conclusions: Cardiac transplantation in children remains the main method of treatment for end-stage heart failure. Our results at both early and long-term posttransplant periods are comparable to those obtained in the most experienced foreign centers.

Key words: cardiomyopathy, congenital heart defect, heart failure, pediatric heart transplantation

INTRODUCTION

Heart failure (HF) in children is a clinical and pathophysiological syndrome resulting from ventricular dysfunction and pressure or volume overload of the circulatory system. Characteristics of pediatric heart failure include feeding problems, poor weight gain, exercise intolerance, or dyspnea. These changes are often accompanied by changes in the endocrine system. There is a complex etiology of HF in children. The main causes are congenital heart disease (CHD) and cardiomyopathies. Less frequent causes are cardiac arrhythmias and acquired heart diseases, such as myocarditis, Kawasaki disease, or heart failure secondary to oncological treatment. In the United States, 12 000 to 35 000 children suffer from heart failure caused by CHD or cardiomyopathy. This gives an incidence of HF in the pediatric population of 16.4–48 cases per 100 000 children [1]. Each year, these patients require 14 000 hospital admissions, of which 65% are caused by CHD. According to a Belgian study, CHD accounts for about 50% of all hospital ad-

WHAT'S NEW?

This article presents an overview of the unique pediatric heart transplant program in Poland. Heart transplantation is the method of choice for treatment of end-stage heart failure in pediatric patients. This is a rare pediatric procedure, related to high operational risk. This article presents the valuable Polish operating and immunosuppression treatment protocol. The results obtained in the second and third periods are consistent with the data presented by leading centers in the world.

missions for HF exacerbation. Fourteen percent of patients with single ventricle physiology require multiple hospital stays due to HF exacerbations. Many of these patients will require mechanical circulatory support (MCS) or HTx qualification in the future [2]. Cardiomyopathies occur with a frequency of 1.13–1.24 cases per 100 000 children. They are especially frequent in the group <1 year of age, where the prevalence of cardiomyopathy is estimated at 7.8–8.3 cases per 100 000 infants. Severe HF is also more common in this age group [3, 4]. Not all patients with cardiomyopathy will develop HF. The prevalence of HF in children with cardiomyopathy is estimated at 0.87 cases per 100 000 children under 16 years of age. Seventy-one percent of HF episodes occur in patients with dilated cardiomyopathy (DCM) [5]. Heart transplantation (HTx) is considered the method of choice for the treatment of end-stage HF in pediatric patients.

Historical overview

In 1960, Lower and Shumway [6] published the results of experiments with orthotopic cardiac transplantation in dogs using an oxygenator. They described the technique of preparation of the recipient and donor atrium (Shumway's technique), which is still used but not commonly. On December 3, 1967, Christian Bernard performed the first successful heart transplant in humans in Groote Schuur Hospital in Cape Town (Republic of South Africa). Despite the use of advanced immunosuppression (local irradiation, azathioprine, prednisolone, and actinomycin C) and the sanitary regime, the patient died 18 days after the transplant due to infection caused by *Pseudomonas Pneumoniae* [7]. Three days later, on December 6, 1967, Adrian Kantrovitz of the Maimonides Medical Center in Brooklin (US) performed the first successful heart transplant in a child. Kantrovitz assumed that the underdevelopment of the immune system of the infant would facilitate surgery and subsequent treatment. The patient was a 3-week-old infant with critical CHD (tricuspid atresia type IA). The procedure was performed in deep hypothermia with full cardiac arrest. Due to post-transplant complications, the patient died after 6 hours [8].

Heart transplantation in the world

The introduction of effective and safe immunosuppressive drugs directly increased the number of successful transplants and extended patients' survival time [9, 10]. According to data from the International Society for Heart and Lung Transplantation (ISHLT) in 1982, 187 heart transplants were performed in the world, including 10 in children. In 1992, the number of transplanted hearts was 4 735, of which 406 were performed in children. This represented a 40-fold increase in the number of heart transplantations in children compared to the year 1982 in fewer than 10 years. Twenty-five percent of transplanted pediatric patients were under one year old. According to data for 2021, the total number of heart transplants in children from 1992 ranged from 458 to 663 per year. With the increase in transplant procedures, the number of pediatric centers where this procedure is performed has also grown. Currently, there are 120 pediatric centers in the ISHLT database, of which 54% are located in North America (US and Canada). Indications for cardiac transplantation in children include three main types of diseases: myocardial diseases such as dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), and arrhythmogenic ventricular cardiomyopathy (AVC); congenital heart defects (including hypoplastic left heart syndrome [HLHS]), Ebstein's anomaly, transpositions of the great arteries (TGA), and other diseases that impair heart function, such as myocarditis. Retransplantations account for 2%–3% of indications for HTx in children [11, 12]. The main indication for HTx in children under 1 year of age is CHD (53% of indications). In older pediatric recipients, this relation changes to cardiomyopathy, which accounts for 55% of indications in patients in the 11–17 age group [13]. The increase in the experience of transplantation teams and the improvement of immunosuppressive treatment noticeably influenced recipient survival time. In the years 1982–1989, 1-, 5-, and 10-year survival rates in the pediatric population were 63.7%, 57.2%, and 51.6%, respectively. In the years 2004–2008, they increased to 81.8%, 70.8%, and 66.2%, respectively. In the years 2009–2015, the 1- and 5-year survival rates were 87.1% and 80.0%, respectively. The observed mean (standard deviation [SD]) survival time increased from 9.9 (6.9) years in 1982–1991 to 14.3 (3.4) years in the next decade. Mean survival time in the years 1982–2015 was: 22.3 years in the group of children <1 year of life, 18.4 years in the group aged 1–5 years; 14.4 years in the group aged 6–10 years, and 13.1 years in the group aged 11–17 years. Longer survival time occurs in patients who received transplants due to cardiomyopathy compared to patients with congenital heart disease, regardless of the age at which HTx was performed [11]. The type of induction and immunosuppression as well as complications influenced the mean survival time. The most common complications after HTx are primary graft failure, acute

rejection, coronary artery disease (CAV), severe renal insufficiency, or posttransplant lymphoproliferative disorder (PTLD). Early mortality during the first 30 days after transplantation is caused by graft failure and corresponds to 36.2% mortality. This often occurs in the group of children <5 years old, where it corresponds to 45% mortality. The next causes are stroke episodes (15.1%), multiple organ failure (11.2%), acute rejection of the transplanted heart (7.3%), and non-cytomegalovirus infections (6.5%). From the 3rd to the 5th and from the 5th to the 10th year after HTx, the main cause of mortality is graft failure, corresponding to 36.4% and 40.5% mortality, respectively. The episode of acute rejection as well as an increasing percentage of CAV are responsible for poor outcomes in those groups (15.3% and 11.7%, respectively) and also responsible for nearly 25% mortality in children 10 years after HTx [11].

Heart transplantation in Poland

The first Polish heart transplant was performed on April 1, 1969, by Jan Moll, Antoni Dziatkowiak, and Kazimierz Rybiński at the S. Sterling Clinical Hospital in Łódź. Due to unrecognized pulmonary hypertension associated with heart failure, the recipient died shortly after surgery [14]. The development of the Polish heart transplant program is related to Zbigniew Religa, who on December 5, 1985, together with the team of the Provincial Cardiology Center in Zabrze (currently the Silesian Center for Heart Diseases in Zabrze), performed the first successful heart transplant in an adult in Poland. Three years later, on February 8, 1988, in the same Center, a team of cardiac surgeons under the leadership of Zbigniew Religa performed the first successful heart transplant in a pediatric patient. In subsequent years, HTx was performed in increasingly younger patients. In 1998, a heart transplant program was initiated for the youngest children (R. Przybylski, M. Zembala, B. Chodór). In 2008, HTx was performed in 2 infants at the age of 9 and 10 months (R. Przybylski, Sz. Pawlak). In 2010, the 5th and youngest infant (6-month-old) received a transplant due to severe HF in the course of DCM. Currently, in Poland there is one center performing heart transplants in children: the Silesian Center for Heart Diseases in Zabrze. In the period between the years 2010 and 2021, 1333 heart transplants were performed in Poland, of which 609 (45.7%) were in our Center and 75 were pediatric patients. Pediatric heart transplantations in our country remain low, at about 6.9% of all heart transplants. The average number of HTx performed per year was 73 in adults and 7 in children in the last decade (2012–2021) in Poland [15]. The number of potential donors has remained stable for many years but is still not sufficient.

METHODS

Study group

Between 1988 and 2021 in the Silesian Center for Heart Diseases in Zabrze (formerly the Provincial Center of Cardiology in Zabrze), 122 pediatric cardiac transplantations were performed: 30 in the first period before the year 2001, 31 in the second period (2002-2011), and 61 in the third period (2012–2021). The median age of the patients for the whole group was 12.3 (8.0–14.7) and in the individual periods: period I — 13.3 (6.4–14.8), period II —12.7 (8.9–16.1), period III — 11.5 (8.0–14.5) years. The age of the patients ranged from 6 months to 17 years and 10 months. The main indication for HTx in the period between 2002 and 2021 (n = 92) was severe HF as a consequence of cardiomyopathy (n = 66, 71.7 %). In 25 recipients (27.2%), severe HF resulted from a congenital heart defect. Primary and post-inflammatory dilated cardiomyopathy was the most common indication (n = 59; 57.6%); hypertrophic cardiomyopathy (n = 13; 14.1%), restrictive cardiomyopathy (n = 10; 10.9%), arrhythmogenic ventricular cardiomyopathy (n = 1; 1.1%), and heart failure after oncological treatment (n = 1; 1.1%) caused heart failure requiring HTx. In the group of recipients with failing Fontan circulation, HTx was performed in 5 children (5.4%). The endpoint of the study was the time when medical follow-up was completed or the patient died. The death was confirmed in the personal identification number database. It was a retrospective study, and the institutional review board, ethics committee, and patient written informed consent were not required.

Induction and immunosuppression

From 2006 to August 2014, basiliximab (Simulect), a chimeric human-mouse monoclonal antibody administered on day 0 and day 5 after HTx was used as the induction of immunosuppression as a standard procedure until the manufacturer recommended withdrawal. Triple-drug immunosuppressive therapy included the administration of methylprednisolone infusion in the operating room before reperfusion. The infusions were continued for 5 days and then changed to the oral form of prednisone. All recipients were treated with cyclosporine A (CyA) and mycophenolate mofetil (MMF) intravenously in 24 hours after HTx. After the beginning of oral feeding, they were switched to oral forms of the drugs under the control of serum drug levels measured regularly (Table 1). In 2006, CyA was changed to tacrolimus (TAC).

Rejections

Rejection assessment was based on endomyocardial biopsies (EBM). The full EBM protocol is shown in Table 2. EBM was performed by puncturing a peripheral vein: the internal jugular or femoral vein using the Seldinger method. After assessing the pressure in the right atrium and right ventricle, 5 to 10 fragments of myocardium were collected from the interventricular septum. The myocardial fragments were fixed with 4% formalin and then stained with hematoxylin and eosin (HE) according to the standard protocol. Specimens were evaluated for the presence of acute cellular rejection (ACR) using the ISHLT 1995 classification (Table 3) [16, 17].

Table 1. Immunosuppressive drugs levels

Drug	0–6 months	6–10 months	>12 months
Cyclosporine A (CyA)	200–300 ng/ml	150–200 ng/ml	100–150 ng/ml
Mycophenolate mofetil (MMF)	1.5–2.0 ng/ml	1.5–2.0 ng/ml	1.5–2.0 ng/ml
Tacrolimus (TAC)	10–15 ng/ml	10–12 ng/ml	8–10 ng/ml

Table 2. EBM protocol

Days after HTx	
0–30	4 EBM every 7 days
31–60	2 EBM every 14 days
61–180	1 EBM every month
181–270	1 EBM
271–360	1 EBM
720	1 EBM with coronary angiography
Additional EBM	3–5 days after rejection treatment

Abbreviations: EBM, endomyocardial biopsies

Rejection episodes were treated with 3-day use of methylprednisolone infusions and enlarged MMF and TAC dosages. In the group of patients under 5 years of age, either a single EBM or no EBM was performed (n = 12; 13%). In those cases, rejection screening was based on echocardiography evaluation and blood levels of biochemical markers: N-terminal prohormone of brain natriuretic peptide (NT-pro BNP), highly-sensitive troponin T, creatine kinase (CK-MB), and lactate dehydrogenase (LDH).

Statistical analysis

Data were presented as median with interquartile range for quantitative variables with other than normal distribution and mean SD for variables with normal distribution. The number and percentage of cases with percent was presented for qualitative ones. A test for two proportions was used to assess the significance of differences between percentages. The Shapiro-Wilk test was used for the normality assumption check.

The Kaplan-Meier curves displayed the estimated survival probability. Differences in survival between groups were estimated using the Mantel test for more than two groups. Statistical analysis was performed using the statistical package SOFA Statistic (open source AGPL3 license). Survival analysis was performed using R language in Rstudio Environment (RStudio Team [2020]). RStudio is the Integrated Development for R (RStudio, PBC, Boston, MA, US, www.rstudio.com/), with additional packages survimner and survarium (https://cran.rproject.org/package=survminer, https://cran.r-project.org/package=survival). Five-year survival with *P*-value <0.05 was considered statistically significant.

RESULTS

One-, 5-, and 10-year survival rates between 1988 and 2001 were 53%, 53%, and 50%, respectively. One-, 5-, and 10-year survival rates between 2002 and 2011 were 97%, 90%, and 87%, respectively; between 2012 and 2021 (1--year follow-up), the survival rate was 92%. Median survival time in the years 2002–2011 was 9.2 (0.03–22.3) years, and 2012–2021 — 11.6 (10.2–13.7). Median survival was not analyzed in the years 2012-2021 because not all of the patients completed the 10-year follow-up. The main cause of mortality both in early and late periods after transplantation was graft failure (n = 5, 6.4% and n = 5, 6.4%, respectively). In the study group, primary graft failure was the cause of 57% of hospital deaths. In two cases (2.5%) the cause of mortality was PTLD. The distribution of HTx indications, characteristics of the study group, survival

Table 3. Comparison of the ISHLT 2004 and 1995 standardized EBM grades of acute cellular rejection (ACR) [16, 17]

ISHLT 2004		ISHLT 1995	
Grade	**Description**	**Grade**	**Description**
0R	No rejection	0	No rejection
1R, mild	Interstitial and/or perivascular infiltrate with at least one focus of myocyte damage	1, mild	
		A – focal	Focal perivascular and/or interstitial infiltrate without myocyte damage
		B – diffuse	Diffuse infiltrate without myocyte damage
		2, moderate (focal) diffuse	One focus infiltrate with associated myocyte damage
2R, moderate	Two or more foci of infiltrate with associated myocyte damage	3, moderate	
		A – focal	Multifocal infiltrate with myocyte damage
3R, severe	Diffuse infiltrate with multifocal damage and/or edema and/or hemorrhage and/or vasculitis	B – diffuse	Diffuse infiltrate with myocyte damage
		4, severe	Diffuse, polymorphous infiltrate with extensive myocyte damage and/or edema and/or hemorrhage and/or vasculitis

Abbreviations: EBM, endomyocardial biopsies; ISHLT, International Society for Heart and Lung Transplantation

Table 4. Demographic characteristics of the recipients

		Sex	
		Male	Female
n		67	55
%		54.9	55.1
Age of HTx, years			
Median (IQR)	12.3 (8.0–14.7)	14.0 (10.4–15.8)	10.2 (6.2–13.4)
Min	0.54	0.54	0.76
Max	17.82	17.82	17.41
Weight, kg			
Median (IQR)	38.9 (24.0–53.8)	44.6 (29.0–57.0)	30.0 (22.0–46.0)
Min	6.00	6.00	11.00
Max	110.00	110.00	66.00
Height, cm			
Median (IQR)	147 (131–165)	152 (133–170)	138 (122–159)
Min	65.0	65.0	84.0
Max	195.0	195.0	170.0

Abbreviations: HTx, heart transplantation

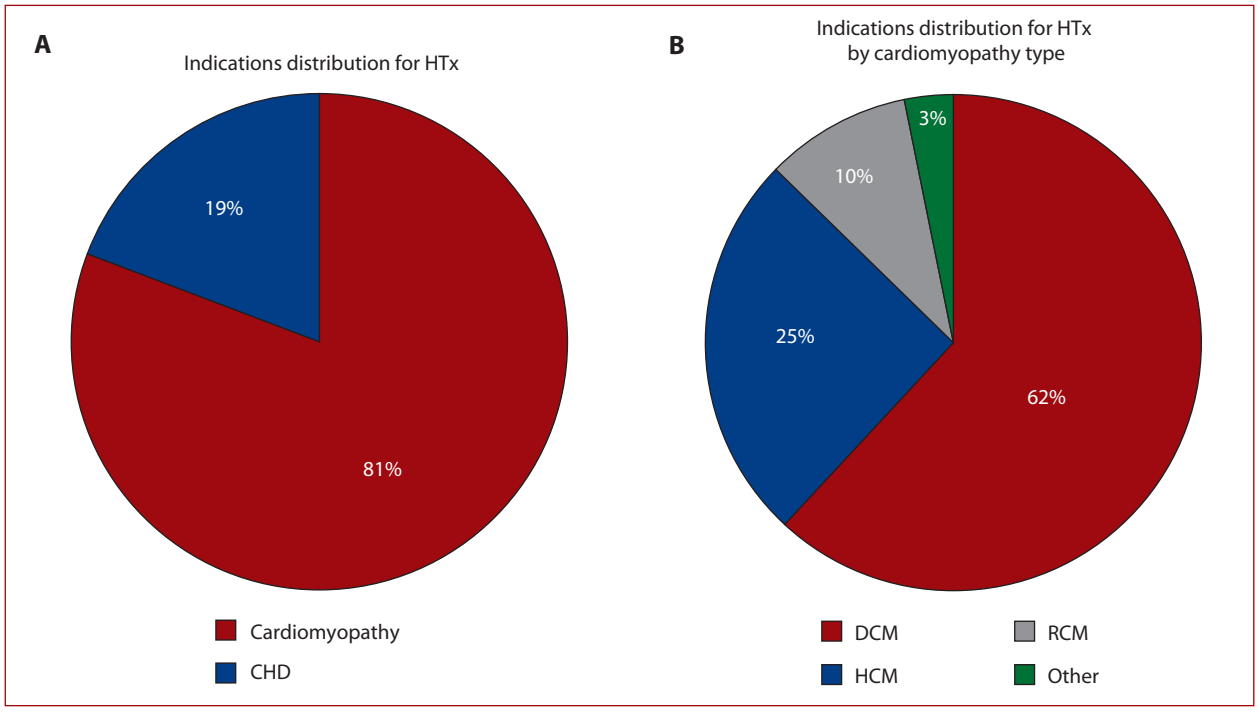

Figure 1. Indications for heart transplants in the Silesian Center for Heart Diseases in Zabrze

Abbreviations: DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HTx, heart transplantation; RCM, restrictive cardiomyopathy; CHD, congenital heart defect

curve, and the number of HTx performed were presented in Table 4 and Figures 1–4.

In 2010, the program of mechanical circulatory support (MCS) in children was initiated in Silesian Center for Heart Diseases in patients diagnosed with severe HF. Up to date, 45 implantations with MSC have been performed with the use of the extracorporeal pulsatile systems produced in Poland (POLCAS, currently ReligaHeart EXT — 2 implantations) or Germany (Berlin Heart EXCOR — 40 implantations). There were also three implantations with the completely implantable heart assist system (Berlin Heart INCOR). MSC was used as a bridge to transplantation in 20 patients (18%) including 2 from another Center. One- and 5-year survival was 92.6% each, and there was no difference in survival between the two groups ($P = 0.11$).

DISCUSSION

Advances in surgical and anesthetic techniques, new immunosuppressive drugs, and thus new post-transplantation protocols, have a significant impact on the survival time of pediatric patients after heart transplantation. The observed survival times of our study group, in different periods, are comparable to those from the most experienced foreign centers. Mean survival time for children who underwent

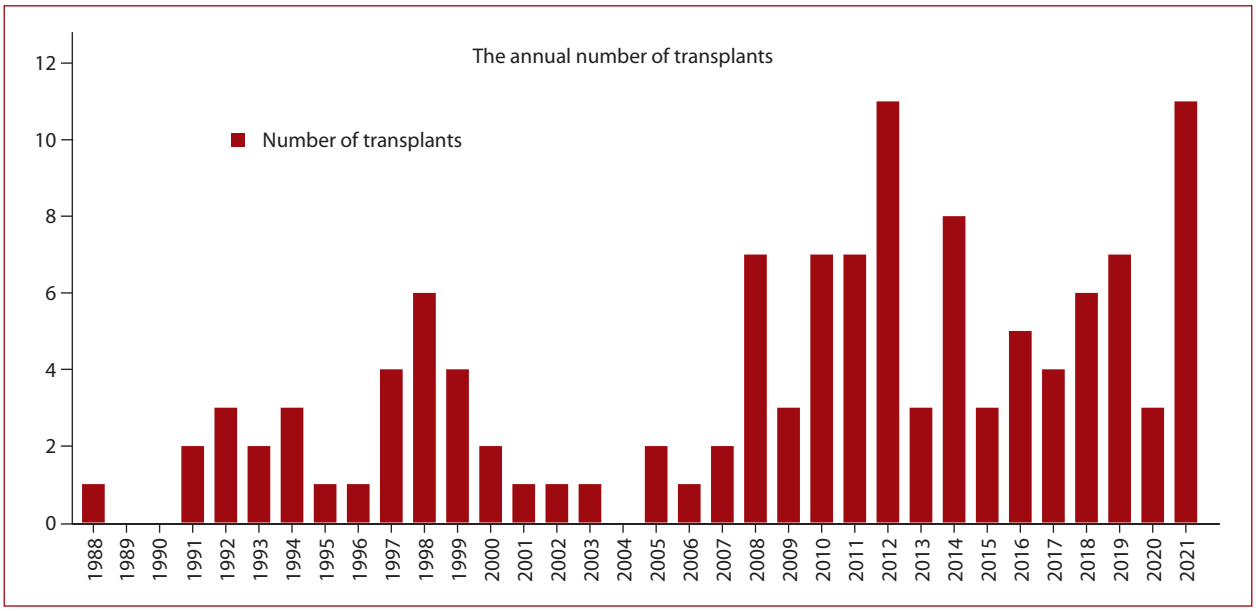

Figure 2. Number of pediatric heart transplants in the Silesian Center for Heart Diseases in Zabrze by year

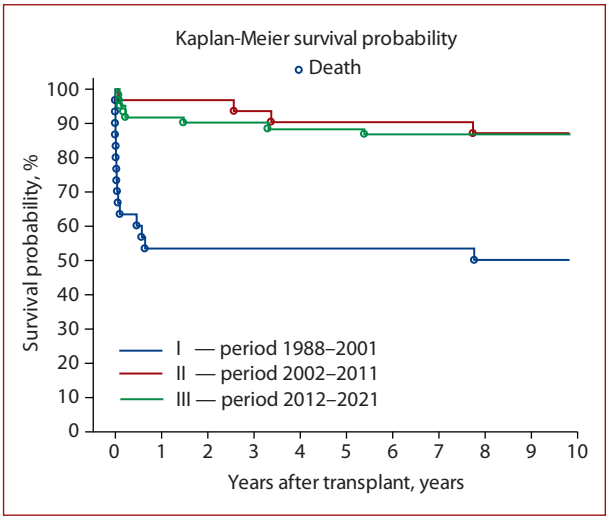

Figure 3. Kaplan-Meier survival curve after pediatric heart transplant in the Silesian Center for Heart Diseases in Zabrze. I 1988–2001; II 2002–2011; III 2012–2021

HTx at the age <1 year of age was 20.1 (SD, 0.8) years; at the age 1–5 years was 17.2 (SD, 7.1); at the age 6–10 years was 13.9 (SD, 1.8), and at the age 11–17 years was 12.4 (SD, 6.8) years [11]. One-, 5-, and 10-year survival rates were slightly better in the group of patients with cardiomyopathy, compared to patients with congenital heart disease as an indication for HTx (91.5% vs. 79.0%, 80.4% vs. 70% and 76.2% vs. 66.1%, respectively) [11, 12]. In the observed group, the survival rate was: 89.3% vs. 85.2%; 87.5% vs. 76.7%, and 84.2% vs. 62.7%, respectively. The population of children supported with MSC before HTx also increased. In this group of patients, there was a survival rate difference depending on the type of MCS. A longer survival time was observed in the group of patients on pulsatile extracorporeal ventricular assist devices (VAD) or total artificial hearts (TAH) in comparison to the group in which extracorporeal membrane oxygenation (ECMO) was used before HTx (1-year survival, respectively, 91.7% vs. 66.1%). In pediatric patients who underwent HTx after MCS in SCCS (n = 20; 18%), 1- and 5-year survival rates were 93.7% with no statistical significance (P >0.05). The immunosuppressive induction protocol with the use of steroids and calcineurin inhibitors also had an impact on long-term survival. The occurrence of episodes of rejection significantly affected long-term survival although 1-year survival of patients who had experienced heart rejection versus patients who had not was comparable (81.6% vs. 89.8%); the 5- and 10-year survival rates were significantly different: 70.1% vs. 79.3%, respectively. In 8.1% to 21.4% of patients, the first episode of rejection occurred in the first year after transplantation [11, 12]. In almost 15% of patients, the treated rejection occurred in the first year after HTx, less frequently in patients who did not receive any induction and TAC had been used as immunosuppressive therapy regardless of age. In recipients with TAC treatment and no induction, rejection occurred in 14.6% of patients compared to the group with TAC treatment and induction, CyA treatment and induction, and CyA treatment and no induction (17.7%, 26.0%, and 26.9%, respectively) [11, 12]. In our study group rejection episodes requiring additional medical treatment occurred more frequently than in the ISHLT registry database. In the group of patients without MSC before HTx, rejection was confirmed in 33.3% of patients compared to the group with MCS — 38.5%. The difference was not significant (P = 0.74).

The development of CAV affected approximately 16% of infants who had HTx, 26% of children at the age 1–5, 27% at the age 6–10, and 37% at the age 11-17. The risk of CAV depends not on the type of induction and immunosuppressive protocols used, but on the donor's age, the recipient's weight, and the need for retransplantation.

The higher risk of CAV affects patients with higher levels of circulating antibodies (PRA-panel reactive antibody) at the time of transplantation [11, 12]. The diagnosis of CAV reduces 1- and 3-year survival to 66%–77% and 52%–60%, respectively.

Cytomegalovirus (CMV) reinfection after HTx is associated with increased morbidity and mortality in solid organ recipients. CMV reinfection has been shown to play a role in graft failure, acute rejection, development of CAV, and PTLD [12, 18]. It occurs in the first two months after HTx, mostly in seronegative CMV recipients who receive a seropositive donor's organ. In our study group, CMV reinfection occurred in 2.45% (n = 3) of patients transplanted between 2008 and 2021, despite using prophylactic antiviral treatment with intravenous and oral valganciclovir for up to 100 days after HTx. Another posttransplant complication is malignant disease, especially in pediatric recipients. Lymphomas originating from B-lymphocytes associated with Epstein-Barr virus (EBV) reinfection are the most frequently occurring malignancies. The risk of developing malignancies increases with time after HTx: 1.6%; 4.7%, and 9.7% in years 1, 5, and 10, respectively. Fifteen years after HTx, neoplastic proliferative lesions occur in as many as 17% of patients [11, 12]. In the study group, PTLD occurred in 3 (2.45%) patients, two of whom died (1.64%).

CONCLUSION

Cardiac transplantation in both adults and children remains the main method of treatment of end-stage heart failure despite the development of artificial circulatory techniques, using both pulsatile and continuous flow pumps. Our results at both early and long-term posttransplant periods, are comparable to those obtained in the most experienced foreign centers. An inadequate number of pediatric donors remains a problem, which is related not only to local conditions but mainly to lack of awarness of benefits of transplantation in society. In comparison to countries with smaller populations, such as the Czech Republic or Croatia, the organ donation rate in Poland remains low, amounting to 14.6 donors per 1 million inhabitants, and varies among regions. In 2017, there were 24.7 donors per 1 million inhabitants in West Pomerania in Poland. In the same period, there were only 5.2 donors per 1 million inhabitants in the Podkarpackie Region. In Croatia, the donation rate is 33.0 donors per 1 million inhabitants, in the Czech Republic there are 25.5 donors per 1 million inhabitants, and in the best functioning donation system in Spain, the rate is 46.9 donors per 1 million inhabitants [19]. The low rate of donations in Poland continues to be of concern to national institutions, including Poltransplant, and is the main topic of not only social campaigns but also development programs for healthcare professionals.

In conclusion, heart transplantation is an effective treatment method for heart failure but still requires further research, especially in the area of early and noninvasive diagnosis of acute allograft rejection that influences long-term outcomes. EMB remains the gold standard for the diagnosis of rejection in adults, but it is not performed in small children. There are publications on the important possible role of cardiovascular magnetic resonance (CMR) to support acute cardiac allograft rejection as an alternative to EBM [20], but the pediatric recipient population is still subject to technical limitations. Small children do not cooperate during the procedure, especially in breath holding, and they must be deeply anesthetized and often intubated. If the CMR procedure was simplified and shortened, there would be a possibility to implement the standard protocol for evaluation in the pediatric population. But still the role of CMR remains to be confirmed in prospective multicenter studies.

Article information

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Association between the visceral adiposity index and the coronary artery calcification score and atherosclerotic plaque morphology

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ABSTRACT

Background: The relationship between the visceral adipose index (VAI), a surrogate marker of visceral adipose tissue dysfunction, and coronary atherosclerotic plaque (CAP) morphology remains unclear.

Aims: This study aimed to investigate the relationships between the VAI and the coronary artery calcification (CAC) score and CAP morphology in asymptomatic patients.

Methods: We retrospectively assessed 782 patients between January 2012 and January 2020. CAC scores were determined at the threshold of 130 Hounsfield units according to the Agatston technique using 64-slice computed tomography. Patients were assigned to groups with no plaque (NP), fatty plaque (FP), calcified plaque (CP), and mixed plaque (MP).

Results: The median VAI levels were significantly different in each group (NP: 1.2 vs. FP: 1.7 vs. CP: 2.3 vs. MP: 2.8; P <0.001). An increased VAI level was an independent predictor of the CAC score. The threshold value of the VAI exhibited a gradual increase in predicting CAP morphology. VAI threshold values were >1.6 for the FP group (vs. the NP group), >2.1 for the CP group (vs. the FP group), and >2.6 for the MP group (vs. the CP group).

Conclusion: High VAI levels independently predict an increased CAC score and CAP morphology. The VAI exhibits superior diagnostic performance in distinguishing the presence and morphology of CAP in asymptomatic patients and offers gradual cut-off values. Therefore, the VAI may be a potential screening tool for risk stratification and diagnosing CAP morphology in patients with suspected coronary artery disease.

Key words: atherosclerosis, coronary artery calcium score, coronary artery disease, visceral adiposity index

INTRODUCTION

Atherosclerosis is an inflammatory process that begins as fatty streaks on the arterial wall and continues with the progression of plaque and complex lesions into the arterial lumen. Plaque rupture is associated with acute cardiovascular events such as thrombosis, myocardial infarction, and stroke [1]. This causes a significant global carotid atherosclerosis burden that increases with age [2]. Therefore, there is a need to identify inexpensive, accessible, and practical tools for preventing and managing carotid atherosclerosis and reducing the disease burden.

Coronary artery calcification (CAC), which is an important indicator of coronary atherosclerotic plaque (CAP) burden, is a pathognomonic finding of atherosclerosis and cardiovascular events [3]. Coronary artery calcification scores improve risk stratification when they are added to coronary computed tomography (CT) angiography results or the Framingham Risk Score [4]. Furthermore, CAC scores and CAP morphology are essential indicators of cardiovascular events and outcomes [5]. Visceral adipose tissue (VAT) plays a vital role in the development and morphology of CAP [6]. It can exacerbate the inflammatory response, trigger insulin resistance, and accelerate atherosclerosis [7]. However, imaging modalities such as multi-slice CT that allow for evaluation of CAP burden and morphology

WHAT'S NEW?

The findings of this study show that the visceral adipose index (VAI) as a surrogate for visceral adipose tissue dysfunction is associated with the coronary artery calcification (CAC) score and coronary atherosclerotic plaque (CAP) morphology. Increased VAI levels were found to be independent predictors of increased CAC scores and CAP morphology. The VAI exhibits superior diagnostic performance in distinguishing the presence and morphology of CAP in asymptomatic patients and offers gradual cut-off values. Therefore, the VAI may be a potential screening tool for risk stratification and CAP morphology in patients with suspected coronary artery disease.

and VAT are costly, carry radiation risks, and are not accessible in some hospitals [8].

Increasing evidence indicates that VAT is associated with atherogenic dyslipidemia, characterized by decreased high-density lipoprotein cholesterol (HDL-C) and increased triglycerides [9]. The visceral adiposity index (VAI), derived from anthropometric and atherogenic parameters, is a simple proxy for visceral fat function confirmed by abdominal magnetic resonance imaging findings [10]. In addition, the VAI has been suggested as an important predictor of atherosclerosis [11]. Limited studies have reported a positive association between VAI levels and CAC scores [12–14], consistent with VAT studies [8, 15]. The VAI can be a powerful tool in the assessment of CAP burden. However, the relationship between the VAI and plaque morphology remains unclear. Therefore, this study was undertaken to investigate the relationships between the VAI and the CAC score and CAP morphology in asymptomatic patients.

METHODS

Patient selection

A total of 4 126 patients with suspected coronary artery disease (CAD) who were referred for multi-detector CT coronary angiography from a cardiac center between January 2012 and January 2020 were assessed retrospectively. The study was designed in compliance with the revised Declaration of Helsinki (2013, Brazil), followed all relevant ethics protocols, and was approved by the local ethics committee (no: E1-22-3009). The need for informed consent was waived by the local ethics committee due to the study's retrospective design.

A previous study reported a positive correlation between VAI and CAC scores ($r = 0.242$; $P < 0.001$) in asymptomatic patients who underwent cardiac CT [13]. Based on the correlation coefficient between VAI and CAC scores in this study, the sample size was calculated as a minimum of 175 patients using two-sided testing, 5% alpha error probability, and 90% power with G*Power v3.1 software [16]. The sample size formula was as follows: $N = ([Z_\alpha + Z_\beta] / C)^2 + 3$ [17], where the standard normal deviation for $\alpha = Z_\alpha = 1.96$, the standard normal deviation for $\beta = Z\beta = 1.28$, and the correlation coefficient (C) for small correlation=0.244 [18]. C was calculated as follows: $C = 0.5 \times \ln[(1 + r) / (1 - r)] = 0.244$, where $r = 0.242$.

Inclusion criteria were asymptomatic patients with cardiovascular risk profiles based on conventional risk factors such as smoking, hypertension, diabetes mellitus, and dyslipidemia. Exclusion criteria were a history of CAD, acute coronary syndrome, heart failure, rheumatic diseases, asthma, pulmonary embolism, inflammatory disease, acute and chronic kidney disease, peripheral artery disease, chronic obstructive pulmonary disease, cerebrovascular disease, liver disease, and cancer. After the exclusion process, 782 patients were included in the study. The indication for CT in asymptomatic patients was based on evaluation of the CAC score for cardiovascular risk assessment [19]. The 10-year cardiovascular disease risk score was calculated using the Systematic Coronary Risk Estimation (SCORE) system (http://www.heartscore.org), which includes age, sex, smoking, systolic blood pressure, and lipid levels. Patients with diabetes mellitus are not included in the SCORE system because they have very high cardiovascular risk [19].

All patients' demographic, laboratory, and coronary angiography data were obtained from the hospital's electronic information system and patient files. Blood pressure of >140/90 mm Hg in repeated measurements or the use of antihypertensive drugs was defined as hypertension and a fasting plasma glucose level of ≥126 mg/dl or the use of antidiabetic drugs was defined as diabetes mellitus. Dyslipidemia was defined as current use of lipid-lowering agents or a triglyceride level of >150 mg/dl, low-density lipoprotein cholesterol (LDL-C) level of >100 mg/dl, and low HDL-C (<40 mg/dl for men, <50 mg/dl for women) [20].

Laboratory measurements

Blood samples of all patients were taken in the morning after patients had fasted before coronary angiography. Complete blood counts and lipid panels were measured using a Beckman Coulter LH 780 device (Mervue, Galway, Ireland). Thus, the levels of hemoglobin (photometrically), platelet count (impedance method), high-sensitivity C-reactive protein (hs-CRP) (immunoturbidimetric method), triglycerides and total cholesterol (enzymatic colorimetric method), and HDL-C (homogeneous enzymatic colorimetric method) were determined. LDL-C levels were calculated using the Friedewald formula.

The VAI was calculated with a sex-specific equation that included measurements of body mass index (BMI) and waist circumference where lipid levels were in mmol/l [10].

For Males:

$$VAI = \frac{\text{Waist circumference}}{39.68 + (1.88 \times \text{BMI})} \times \frac{\text{Triglycerides}}{1.03} \times \frac{1.31}{\text{HDL} - \text{C}}$$

For Females:

$$VAI = \frac{\text{Waist circumference}}{36.58 + (1.89 \times \text{BMI})} \times \frac{\text{Triglycerides}}{0.81} \times \frac{1.52}{\text{HDL} - \text{C}}$$

Coronary artery calcification assessment

An oral beta-blocker agent (40 mg propranolol) was given to patients with heart rates of >75 beats/min 1 hour before the procedure. All images were acquired by 64 multi-slice CT (Toshiba Aquilion system, Tokyo, Japan) with a rotation time of 400 mm and a 1 mm reconstruction device able to descend to 0.5 sections. An automatic dose modulation system was used in the examinations and hearts were scanned in a craniocaudal direction from the carina to the apex. Imaging was performed by electrocardiogram (ECG) gating with 120 peak kilovoltage, 300 milliampere seconds, 3 mm section thickness, and 200–270 mm field of view (FOV) . All images were transferred to a workstation for CAC scoring and evaluated with a Toshiba Aqua 4.1 instrument (Otawara, Japan). CAC scores were calculated considering the 130 Hounsfield units threshold according to the Agatston technique [21]. The CAC score was categorized as zero, minimal (1–10), mild (11–100), moderate (101–400), or severe (>400) [22]. The classification of CAP was based on a previously reported modified American Heart Association classification. Accordingly, the coronary system was separated into 16 distinct segments based on original axial images, thin slices, maximum intensity projections, and cross-sectional reconstructions orthogonal to the long axis of each coronary segment (0.75 mm in thickness) [23]. One coronary plaque per segment was selected upon determining the number and significance of atherosclerotic coronary segments for all patients. CAP in each segment was classified as (1) zero-plaque or none (NP); (2) calcified plaque (CP) (higher CT intensity than the contrast-enhanced coronary lumen); (3) non-calcified plaque (non-CP) (lower CT intensity than the contrast-enhanced coronary lumen); or (4) mixed plaque (MP) (plaque containing calcified and non-calcified components). According to the presence of plaque, the patients were assigned to two groups – those with and without atherosclerosis.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, US). The normality distribution of numerical data was evaluated with the Kolmogorov-Smirnov test. Normally distributed variables were presented as mean with standard deviation (SD), and non-normally distributed variables were presented as median with quartiles (IQR). For comparisons between groups, Student's t-test, Mann-Whitney U test, one-way analysis of variance (ANOVA; post-hoc: Bonferroni test), or Kruskal-Wallis H test (post-hoc: Dunn's test) was used according to normality distributions. Categorical variables were expressed as numbers and percentages, and comparisons between groups were evaluated with the χ^2 and Fisher's exact tests. Bonferroni adjustment was used in post-hoc analyses of the R × C contingency table. Spearman correlation analysis was used for the relationship between CAC scores and VAI levels. Linear regression analysis with the backward method was used for independent predictors of CAP burden and logarithmic transformation was applied to numerical variables that did not show normal distribution before analysis. Logistic regression analysis with the backward Wald method was performed to identify any possible independent predictors of atherosclerosis and plaque morphology. Medications were not included in the regression model because of the high collinearity between medication and comorbid conditions in the regression analyses. To evaluate the diagnostic performance of the VAI, the area under the curve (AUC) was calculated in the receiver operating characteristic (ROC) curve analysis and the cut-off values were determined according to the Youden index method. *P*-value <0.05 was considered statistically significant.

RESULTS

A total of 782 patients were analyzed in the study, including 281 (35.9%) females and 501 males (64.1%) at mean (SD) age of 51.7 (7.2) years. The median CAC score was 0 (range = 0-3759), and 9% (n = 70) of the patients had minimal CAC scores, 15.1% (n = 118) had mild CAC scores, 8.2% (n = 64) had moderate CAC scores, and 3.3% (n = 26) had severe CAC scores. CAP was not detected in most of the patients (64.5%). The rates of patients with NP were 49.9% (n = 390), 14.6% for only fatty plaque (FP) (n = 114), 17% for only CP (n = 135), and 18.3% for MP (n = 143). Accordingly, the prevalence of atherosclerosis was 50.1% (n = 392). The mean age (52.8 vs. 50.4 years; *P* <0.001), ratios of female sex (51% vs. 20.8%; *P* <0.001), smoking (48.5% vs. 36.9%; *P* <0.001), diabetes mellitus (32.7% vs. 22.3%; *P* = 0.001), hypertension (52.0% vs. 40.0%; *P* = 0.001), and median VAI levels (2.3 vs. 1.2; *P* < 0.001) were higher in patients with atherosclerosis compared to those without. Distributions of demographic and clinical findings according to the presence of atherosclerosis are shown in Table 1.

The mean age was similar in the FP and NP groups and lower in those groups compared to other morphology groups. The mean age was also similar in the CP and MP groups. The proportion of female patients was lower in the NP group and higher in the MP group (NP: 20.8% vs. Only FP: 36.8% vs. Only CP: 49.6% vs. MP: 63.6%; *P* <0.001). The rate of smoking was lower in the NP group while it was similar in other morphology groups (NP: 36.9% vs. Only FP: 47.4% vs. Only CP: 48.1% vs. MP: 49.1%; *P* = 0.01). The rate of diabetes mellitus did not differ significantly in the only CP and MP groups, while it was higher compared to the other groups (NP: 22.3% vs. Only FP: 25.4% vs. Only CP: 37.8% vs. MP: 33.6%; *P* = 0.002). The hypertension rate was

Table 1. Distribution of demographic and laboratory findings

Variables	All population (n = 782)	Atherosclerosis		*P*-value
		No (n = 390)	Yes (n = 392)	
Age, years	51.7 (7.2)	50.4 (6.5)	52.8 (7.5)	<0.001
Female sex, n (%)	281 (35.9)	81 (20.8)	200 (51.0)	<0.001
BMI, kg/m^2	26.2 (3.4)	25.8 (3.5)	26.5 (3.4)	0.004
WC, cm	95.4 (7.7)	93.4 (7.9)	97.1 (6.9)	<0.001
Active smoking, n (%)	334 (42.7)	144 (36.9)	190 (48.5)	<0.001
Diabetes mellitus, n (%)	215 (27.5)	87 (22.3)	128 (32.7)	0.001
Hypertension, n (%)	360 (46.0)	156 (40.0)	204 (52.0)	0.001
Dyslipidemia, n (%)	424 (54.2)	159 (40.8)	257 (65.6)	<0.001
Laboratory findings				
Hemoglobin, g/dl	13.5 (1.4)	13.4 (1.3)	13.6 (1.5)	0.06
Neutrophil count, ×10^3/µl	3.9 (3.3–5.0)	3.6 (3.0–4.4)	4.4 (3.6–5.4)	<0.001
Platelet count, ×10^3/µl	257.1 (61.0)	257.6 (59.5)	256.5 (62.6)	0.80
Lymphocyte count, ×10^3/µl	2.6 (0.7)	2.7 (0.7)	2.5 (0.7)	<0.001
Monocyte count, ×10^3/µl	0.6 (0.2)	0.5 (0.1)	0.7 (0.2)	<0.001
HDL-cholesterol, mmol/l	1.3 (0.3)	1.4 (0.3)	1.2 (0.3)	<0.001
LDL-cholesterol, mmol/l	3.4 (1.0)	3.3 (0.9)	3.5 (1.1)	0.005
Triglycerides, mmol/l	1.5 (1.1–1.9)	1.3 (0.9–1.6)	1.7 (1.3–2.4)	<0.001
Hs-CRP, mg/l	0.8 (0.3–1.1)	0.3 (0.1–0.5)	0.8 (0.4–1.3)	<0.001
VAI	1.5 (1.2–2.2)	1.2 (0.9–1.5)	2.3 (1.7–3.2)	<0.001
Medications, n (%)				
Statins	407 (52.0)	157 (40.3)	250 (63.8)	<0.001
Acetylsalicylic acid	127 (16.2)	55 (14.1)	72 (18.4)	0.11
Beta-blockers	120 (15.3)	52 (13.3)	68 (17.3)	0.12
ACEi/ARBs	353 (45.1)	153 (39.2)	200 (51.0)	0.001
Metformin	183 (23.4)	83 (21.3)	100 (25.5)	0.16
DPP4i	122 (15.6)	53 (13.6)	69 (17.6)	0.12
Sulfonylurea	114 (14.7)	44 (11.3)	56 (14.3)	0.21
SGLT-2i	93 (11.9)	43 (11.0)	52 (13.3)	0.34
Insulin	140 (17.9)	61 (15.6)	79 (20.2)	0.10

Numerical variables were shown as mean (SD) or median (interquartile range [IQR]). Categorical variables were shown as number (%)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; β, regression coefficients; BMI, body mass index; CACS, coronary artery calcium score; CAP, coronary atherosclerotic plaque; CI, confidence interval; DPP4i, dipeptidyl peptidase 4 inhibitors; HDL, high-density lipoprotein, hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; SE, standard error; SGLT2i, sodium-glucose transport protein 2 inhibitors; VAI, visceral adiposity index; WC, waist circumference

higher in the MP group while it did not differ significantly between the other groups (NP: 40.0% vs. Only FP: 47.4% vs. Only CP: 45.2% vs. MP: 62.2%; $P = 0.001$). The median CAC score was higher in the MP group than in the CP group (MP: 50 vs. Only CP: 25; $P < 0.001$). Except for hemoglobin and platelet count, laboratory parameters showed significant differences in CAP morphology. The median VAI levels were significantly different in each group (NP: 1.2 vs. FP: 1.7 vs. CP: 2.3 vs. MP: 2.8; $P < 0.001$) (Figure 1, Table 2).

There were positive correlations between VAI levels and CAC scores in the whole population (r = 0.576; $P < 0.001$), male patients (r = 0.562; $P < 0.001$), female patients (r = 0.543; $P < 0.001$) (Supplementary material, *Table S1*), the only CP group (r = 0.478; $P < 0.001$), and the MP group (r = 0.512; $P < 0.001$). Based on categorized CAC scores, VAI levels were increased from the normal group to the severe group (Figure 1). Increased VAI levels were independent predictors of CAC scores (Table 3). Accordingly, it was determined that a 1-unit increase in log (VAI) level increased the CAC score by 1.83-fold independently of other risk factors.

Multivariable logistic regression models to predict the presence of atherosclerosis and CAP morphology are presented in Supplementary material, *Tables S2–S5*. Increased VAI levels were independent predictors of the presence of atherosclerosis in the whole population (vs. NP group) (odds ratio [OR], 20.72; $P < 0.001$), the only FP group (vs. NP group) (OR, 6.25; $P < 0.001$), the only CP group (vs. only FP group) (OR, 2.98; $P < 0.001$), and the MP group (vs. only CP group) (OR, 2.01; $P < 0.001$) (Table 4).

The threshold value of VAI for predicting the presence of atherosclerosis (vs. NP group) was > 1.6 (AUC, 0.898; sensitivity, 83.1%; specificity, 90.9%) (Figure 2A, Table 4). The threshold value exhibited a gradual increase in predicting CAP morphology (Table 4). Accordingly, the threshold value of the VAI was >1.6 for the only FP group (vs. NP group) (AUC, 0.825; sensitivity, 69.8%; specificity, 87.6%) (Figure 2B), > 2.1 for the only CP group (vs. only FP group) (AUC, 0.764; sensitivity, 63.8%; specificity, 85.1%) (Figure 2C), and > 2.6 for the MP group (vs. only CP group) (AUC, 0.712; sensitivity, 65.6%; specificity, 63.4%) (Figure 2D).

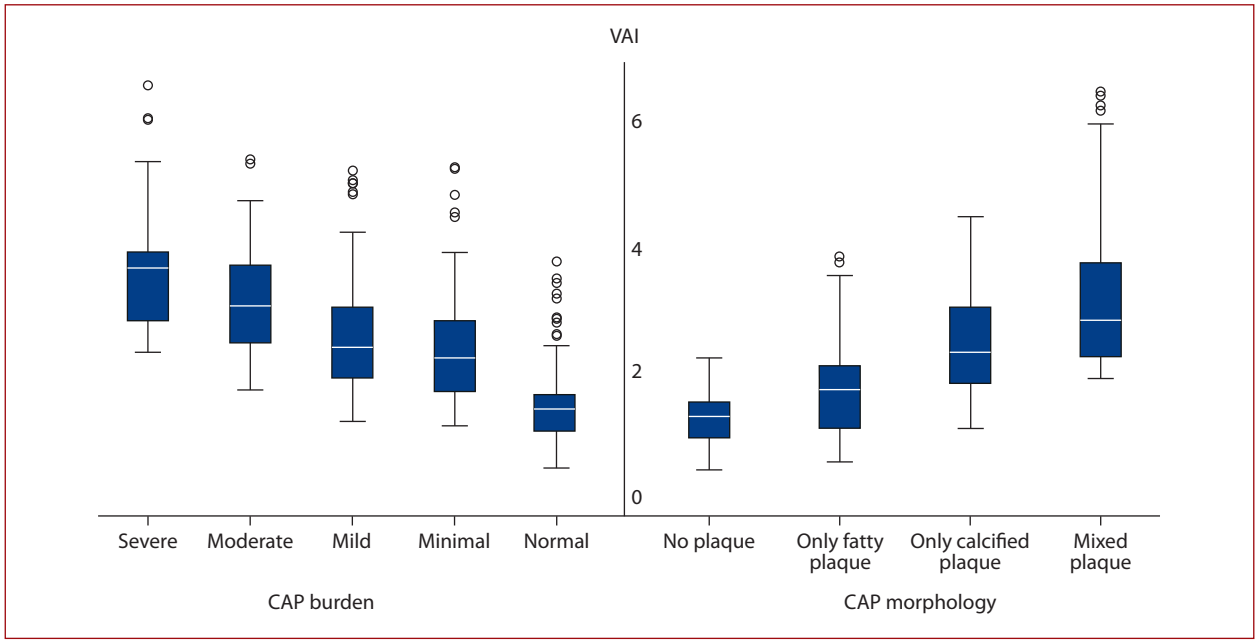

Figure 1. Box and whisker plots of VAI distribution by categorized CAC score and CAP morphology. Data are presented as median (interquartile range [IQR]). Outliers are shown in circles

Abbreviations: CAC, coronary artery calcification; CAP, coronary atherosclerotic plaque

Table 2. Factors associated with CAP morphology

Variables	No plaque (n = 390)	CAP morphology			*P*-value
		Only fatty plaque (n = 114)	Only calcified plaque (n = 135)	Mixed plaque (n = 143)	
Age, years	50.4 (6.5)	50.8 (7.4)	53.3 (7.0)[a, b]	54.0 (7.3)[a, b]	<0.001
Female sex, n (%)	81 (20.8)	42 (36.8)[a, c, d]	67 (49.6)[a, b, d]	91 (63.6)[a–c]	<0.001
BMI, kg/m^2	25.8 (3.5)[b, c, d]	26.3 (2.9)	26.4 (3.3)	26.9 (3.6)	0.002
WC, cm	93.4 (7.9)[b, c, d]	98.2 (4.5)	96.3 (7.2)	96.8 (8.1)	<0.001
Active smoking, n (%)	144 (36.9)[b, c, d]	54 (47.4)	65 (48.1)	71 (49.1)	0.01
Diabetes mellitus, n (%)	87 (22.3)	29 (25.4)	51 (37.8)[a, b]	48 (33.6)[a, b]	0.002
Hypertension, n (%)	156 (40.0)	54 (47.4)	61 (45.2)	89 (62.2)[a–c]	<0.001
Dyslipidemia, n (%)	159 (40.8)	59 (51.8)[a, c, d]	88 (65.2)[a, b, d]	110 (76.9)[a–c]	<0.001
Laboratory findings					
Hemoglobin, g/dl	13.4 (1.3)	13.5 (1.5)	13.6 (1.5)	13.7 (1.6)	0.16
Neutrophil count, ×10^3/µl	3.6 (3.0–4.4)	4.2 (3.5–5.1)[a, c, d]	4.6 (3.7–5.9)[a, b]	4.6 (3.8–5.7)[a, b]	<0.001
Platelet count, ×10^3/µl	257.6 (59.5)	256.6 (63.1)	255.9 (59.3)	257 (65.7)	0.99
Lymphocyte count, ×10^3/µl	2.7 (0.7)	2.6 (0.7)	2.4 (0.8)[a, b]	2.4 (0.7)[a, b]	<0.001
Monocyte count, ×10^3/µl	0.5 (0.1)	0.6 (0.2)	0.7 (0.2)[a, b]	0.7 (0.2)[a, b]	<0.001
HDL-cholesterol, mmol/l	1.4 (0.3)	1.2 (0.3)[a, d]	1.2 (0.2)[a, d]	1.0 (0.2)[a–c]	<0.001
LDL-cholesterol, mmol/l	3.3 (0.9)	3.5 (0.9)[a, d]	3.5 (1.1)[a, d]	3.8 (1.0)[a–c]	0.03
Triglycerides, mmol/l	1.3 (0.9–1.6)	1.3 (0.9–1.8)	1.7 (1.4–2.4)[a, b, d]	2.2 (1.6–2.7)[a–c]	<0.001
Hs-CRP, mg/l	0.3 (0.1–0.5)	0.6 (0.3–1.1)[a, c, d]	1.0 (0.8–1.7)[a, b, d]	1.8 (1.6–2.4)[a–c]	<0.001
VAI	1.2 (0.9–1.5)	1.7 (1.1–2.1)[a, c, d]	2.3 (1.8–3.0)[a, b, d]	2.8 (2.1–3.8)[a–c]	<0.001
Medication, n (%)					
Statins	157 (40.3)	55 (48.2)	86 (63.7)[a, b, d]	109 (76.2)[a, b, c]	<0.001
Acetylsalicylic acid	55 (14.1)	19 (16.7)	25 (18.5)	28 (19.6)	0.36
Beta-blockers	52 (13.3)	18 (15.8)	23 (17.0)	27 (18.9)	0.38
ACEi/ARBs	153 (39.2)	51 (44.7)	60 (44.4)	89 (62.2)[a, b, c]	<0.001
Metformin	83 (21.3)	22 (19.3)	37 (27.4)	41 (28.7)	0.14
DPP4i	53 (13.6)	18 (15.8)	24 (17.8)	27 (18.9)	0.41
Sulfonylurea	44 (11.3)	14 (12.3)	20 (14.8)	22 (15.4)	0.51
SGLT-2i	43 (11.0)	14 (12.3)	18 (13.3)	20 (14.0)	0.75
Insulin	61 (15.6)	21 (18.4)	27 (20.2)	31 (21.7)	0.35

Numerical variables were shown as mean (SD) or median (interquartile range [IQR]). Categorical variables were shown as number (%)
[a]*P* <0.05 vs. no plaque group. [b]*P* <0.05 vs. Only fatty plaque group. [c]*P* <0.05 vs. Only calcified plaque group. [d]*P* <0.05 vs. Mixed plaque group

Abbreviations: see Table 1

Table 3. Independent predictors of CAP burden

Variables	Univariable regression				Multivariable regression			
	β	95% CI		*P*-value	β	95% CI		*P*-value
		Lower	Upper			Lower	Upper	
Age, years	0.03	0.02	0.04	<0.001	0.03	0.02	0.03	<0.001
Female sex	0.55	0.43	0.68	<0.001	–	–	–	–
BMI	0.02	0.00	0.04	0.04	–	–	–	–
WC	0.02	0.01	0.02	<0.001	–	–	–	–
Active smoking	0.15	0.03	0.28	0.02	0.12	0.02	0.22	0.04
Diabetes mellitus	0.29	0.15	0.43	<0.001	0.13	0.02	0.24	0.02
Hypertension	0.28	0.15	0.40	<0.001	–	–	–	–
Dyslipidemia	0.44	0.32	0.56	<0.001	–	–	–	–
Hemoglobin	0.04	0.00	0.09	0.08	–	–	–	–
Neutrophil count	1.74	1.31	2.17	<0.001	–	–	–	–
Platelet count	0.01	–0.01	0.02	0.92	–	–	–	–
Lymphocyte count	0.08	–0.01	0.17	0.08	–	–	–	–
Monocyte count	0.02	0.01	0.02	<0.001	0.01	0.01	0.02	<0.001
HDL-cholesterol	–0.98	–1.19	–0.78	<0.001	–	–	–	–
LDL-cholesterol	0.05	0.02	0.08	0.02	–	–	–	–
Triglycerides	2.18	1.87	2.49	<0.001	–	–	–	–
Hs-CRP	2.24	1.62	2.86	<0.001	–	–	–	–
VAI	2.32	2.12	2.53	<0.001	1.83	1.61	2.05	<0.001
					Adjusted R^2 = 0.479; *P* <0.001			

Before linear regression analysis, logarithmic transformation was applied to CAC score, neutrophil, triglyceride, hs-CRP and VAI variables

Abbreviations: see Table 1

Table 4. Predictive value of VAI in atherosclerosis and CAP morphology

VAI	OR	95% CI		*P*-value	ROC curve analysis			
		Lower	Upper		AUC	Sensitivity	Specificity	Threshold value
Atherosclerosis								
Crude	26.56	16.09	43.84	<0.001	0.898	83.1%	90.9%	>1.6
Multivariable	20.72	12.03	35.68	<0.001				
Only FP (vs. NP)								
Crude	7.88	4.60	13.51	<0.001	0.825	69.8%	87.6%	>1.6
Multivariable	6.25	3.39	11.53	<0.001				
Only CP (vs. Only FP)								
Crude	3.16	2.14	4.66	<0.001	0.764	63.8%	85.1%	> 2.1
Multivariable	2.98	1.97	4.52	<0.001				
Mixed plaque (vs. Only CP)								
Crude	2.05	1.55	2.71	<0.001	0.712	65.6%	63.4%	>2.6
Multivariable	2.01	1.50	2.69	<0.001				

Abbreviations: AUC, area under the curve; CI, confidence interval; CP, calcified plaque; FP, fatty plaque; NP, non-plaque; OR, odds ratio; ROC, receiver operating characteristic; VAI, visceral adiposity index

The CAC score was 0 for 411 (95.4%) patients with VAI levels below 1.6. No CAP was detected in 358 of these patients. The remaining 53 patients had only FP. Accordingly, for 358 patients who had VAI levels of 1.6 and below, constituting 45.8% of the population, the CAC score was 0 and CAP was negative.

DISCUSSION

This study of asymptomatic patients without known CAD has demonstrated that high VAI levels, reflecting VAT dysfunction, were significantly associated with higher CAC scores and the presence of CAP. Moreover, this association was independent of the effects of other cardiovascular risk factors. This work has also provided new findings confirming that the VAI as a surrogate for VAT dysfunction is associated with CAP morphology. Thresholds of the VAI in distinguishing the presence and morphology of CAP offer different implications that may allow using it as a potential screening tool for the risk stratification of patients with suspected CAD.

High BMI or obesity plays a vital role in the development or acceleration of atherosclerosis by mediating some mechanisms such as abnormal lipid profiles, insulin resistance, and systemic inflammation. However, there is also evidence that obesity does not show a linear relationship with cardiovascular events after disease onset or that it presents

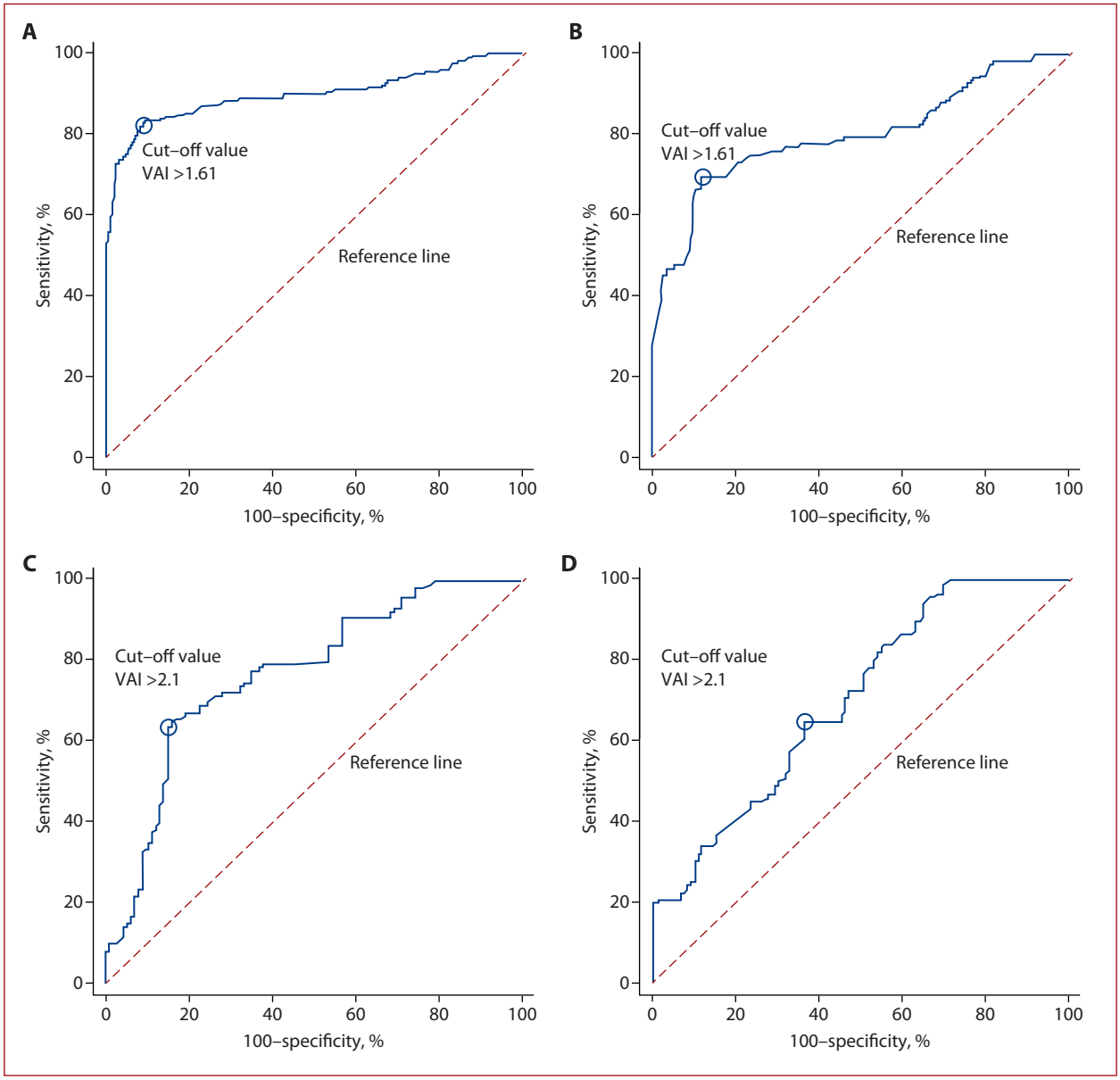

Figure 2. Diagnostic performance assessment of VAI in predicting presence and morphology of CAP. **A.** Presence of atherosclerosis vs. non-CAP. **B.** Only fatty plaque vs. non-CAP. **C.** Only calcified plaque vs. Only fatty plaque. **D.** Mixed plaque vs. Only calcified plaque

Abbreviations: VAI, visceral adipose index; other — see Figure 1

a potential protective effect in coexistence with cardiovascular disease [24]. These contradictions cause the so-called obesity paradox. Furthermore, an increased BMI level is associated with increased risk of atherosclerosis while not all patients who develop atherosclerosis are obese [25]. However, increasing evidence indicates that VAT is responsible for mechanisms mediated by obesity [26]. The VAI is an important surrogate marker of VAT and includes several parameters associated with VAT dysfunction. Furthermore, it has been reported that the VAI is a better predictor of cardiovascular events than its components [21, 27].

In asymptomatic patients with suspected CAD, the presence of atherosclerosis was associated with higher VAI and hs-CRP levels, and these were correlated with increased CAC scores. CAC, found in coronary arteries before the development of clinically significant narrowness, is an essential predictor of subclinical atherosclerosis [3]. Our results are consistent with previous studies that reported positive correlations between VAI levels and CAC scores [12–14]. This may be because, in addition to the effects of high triglycerides and low HDL-C in the development of atherosclerosis, VAT dysfunction can accelerate atherosclerosis by affecting adipokine production, insulin sensitivity, and inflammatory responses including nuclear factor kappa B activation and cytokine expression [7]. These mechanisms are also closely related to the progression of atherosclerotic lesions in addition to macrophage accumulation and play essential roles in plaque morphology [28]. Therefore, the VAI acts as a potential marker for CAD. A 1-unit increase in the VAI raised the probability of

atherosclerosis by 20.7-fold, independently of other risk factors, and a threshold value of >1.6 detected atherosclerosis with high diagnostic performance.

A cohort study of Chinese patients without increased carotid intima-media thickness and carotid plaque reported that increased VAI levels were an independent predictor of increased risk of carotid plaque [29]. To our knowledge, this is the first study to examine the relationship between the VAI and CAP morphology. The highest VAI levels were observed in the MP group, followed by the CP and FP groups. Furthermore, the VAI was found to be a common predictor of CAP morphology regardless of the patient's age, sex, and comorbid conditions, and it exhibited superior diagnostic performance. A retrospective study reported that higher VAT area tertiles were associated with a higher prevalence of CP in patients without diabetes mellitus. In contrast, there was no difference between tertiles among patients with diabetes mellitus. This difference was associated with a hypothesis that oxidative stress resulting from advanced glycation end products and hyperglycemia in patients with diabetes might significantly affect CAP morphology, thereby reducing the effect of VAT area [30]. Several studies have suggested that an increase in epicardial adipose tissue (EAT) is associated with MP and non-CP [31, 32]. EAT as part of VAT was shown to be an independent predictor of CAP burden [33]. Another study reported an increased prevalence of non-CP in patients with high EAT volume [34]. A study evaluating 565 consecutive patients with proven or suspected CAD showed that high VAT levels were associated with non-CP in men and CP in women. However, it was reported that VAT levels were more strongly associated with non-CP in the whole population [6]. Although the current literature offers conflicting results for EAT and VAT in CAP morphology, our results are partially consistent with those of previous VAT studies.

VAI levels were associated with CAP burden regardless of sex. In addition, it was positively correlated with the CAC score in cases of both MP and CP. Patients with MP also had higher CAC, hs-CRP, and triglycerides levels and lower HDL levels compared to patients with CP. Extensive VAT or its dysfunction may result in worse lipid profiles due to its atherogenic effects [9]. A recent study reported that low HDL-C levels were important predictors of the napkin-ring sign for high-risk coronary plaque despite statin therapy [35]. This is consistent with the lower HDL-C levels observed in MP or only CP patients with higher rates of statin use. In the formation of FP, macrophages consume cholesterol and turn into foam cells. This initiates an inflammatory response. In the later stages of atherosclerosis, the plaque becomes rich in calcium and can accumulate more dead foam cells and other debris, exacerbating the inflammatory response [28].

The VAI was an independent predictor of all CAP morphologies. Furthermore, the VAI yielded gradually increasing thresholds for distinguishing among CAP morphologies. More importantly, in the case of a CAC score of 0, it was found that the VAI discriminated between CAP being normal or non-CP. The prevalence of non-CP in asymptomatic patients has been reported to be between 4% and 38% while approximately 1% of patients with CAC scores of 0 were diagnosed with acute coronary syndrome [36–38]. The prevalence of FP was 14.6%, and a 1-unit increase in the VAI raised the probability of FP by 6.25-fold independently of traditional risk factors. The current findings have indicated that the majority of patients with VAI levels below the threshold of 1.6 should not be subjected to radiation exposure or unnecessary angiography. In asymptomatic cases, gradually increasing VAI threshold values may play a role in patients' risk stratification and treatment strategies such as lifestyle modification and pharmacological interventions. However, VAI levels may differ by ethnicity [39]. Therefore, the role of the VAI in plaque morphology warrants further investigation.

Limitations of the study

This study has some significant limitations. First, it had a single-center retrospective design. Second, patients were not separated by ethnicity. In addition, the distribution of CV risk factors such as smoking may differ in different populations [40]. Third, the VAT and EAT levels of the patients were not evaluated; considering the limited studies in the relevant literature, these parameters could be more descriptive in CAP morphology. Fourth, adipocytokine and pro-inflammatory cytokine levels were not measured. These parameters could better reflect the inflammatory milieu. Another significant limitation is the exclusion of patients with a history of CAD. This study does not fully reflect the CAD cohort as it investigated asymptomatic patients. Finally, calcium volume was not measured. Data from the Multi-Ethnic Study of Atherosclerosis (MESA) registries suggest that calcium volume may be a superior parameter compared to Agatston CAC [4, 41].

CONCLUSIONS

In asymptomatic patients, high VAI levels independently predict increased CAC score and CAP morphology. The VAI exhibits superior diagnostic performance in distinguishing the presence and morphology of CAP in patients with suspected CAD, and it offers gradual cut-off values. Therefore, the VAI may be a potential screening tool for risk stratification and CAP morphology in patients with suspected CAD.

Supplementary material

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

Article information

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Predictors of long-term prognosis based on clinical status and measurements obtained in heart failure patients after 9-week hybrid comprehensive telerehabilitation: A subanalysis of the TELEREH-HF randomized clinical trial

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ABSTRACT

Background: Assessing prognosis in heart failure (HF) is of major importance.

Aims: The study aimed to define predictors influencing long-term cardiovascular mortality or HF hospitalization ("composite outcome") based on clinical status and measurements obtained after a 9-week hybrid comprehensive telerehabilitation (HCTR) program.

Methods: This analysis is based on the TELEREH-HF (TELEREHabilitation in Heart Failure) multicenter randomized trial that enrolled 850 HF patients (left ventricular ejection fraction [LVEF] ≤40%). Patients were randomized 1:1 to 9-week HCTR plus usual care (experimental arm) or usual care only (control arm) and followed for median (interquartile range [IQR]) 24 (20–24) months for development of the composite outcome.

Results: Over 12–24 months of follow-up, 108 (28.1%) patients experienced the composite outcome. The predictors of our composite outcome were: nonischemic etiology of HF, diabetes, higher serum level of N-terminal prohormone of brain natriuretic peptide, creatinine, and high-sensitivity C-reactive protein; low carbon dioxide output at peak exercise; high minute ventilation and breathing frequency at maximum effort in cardiopulmonary exercise tests; increase in delta of average heart rate in 24-hour Holter ECG monitoring, lower LVEF, and patients' non-adherence to HCTR. The model discrimination C-index was 0.795 and decreased to 0.755 on validation conducted in the control sample which was not used in derivation. The 2-year risk of the composite outcome was 48% in the top tertile versus 5% in the bottom tertile of the developed risk score.

Conclusion: Risk factors collected at the end of the 9-week telerehabilitation period performed well in stratifying patients based on their 2-year risk of the composite outcome. Patients in the top tertile had an almost ten-fold higher risk compared to patients in the bottom tertile. Treatment adherence, but not peak VO_2 or quality of life, was significantly associated with the outcome.

Key words: heart failure, prognosis, risk stratification, telerehabilitation

WHAT'S NEW?

This is the first risk stratification model for clinically stable heart failure patients based on demographic data, baseline characteristics, clinical status, and measurements obtained after 9-week hybrid comprehensive telerehabilitation including exercise training. This risk stratification model indicated that treatment adherence is the best predictor of long-term prognosis in heart failure patients.

INTRODUCTION

Heart failure (HF) is a major cause of cardiovascular (CV) mortality and hospitalization [1–4]. Despite progress in pharmacological and non-pharmacological treatment, the prognosis for HF patients remains poor [3, 4]. The ESC-HF (European Society of Cardiology-Heart Failure) pilot survey reported that 12-month all-cause mortality rates for hospitalized and ambulatory clinically stable HF patients were 17% and 7%, respectively, and the 12-month hospitalization rates were 44% and 32%, respectively [4]. Moreover, re-hospitalization affects half of HF patients within 6 months after discharge [3]. Although most HF patients are treated in accordance with current guidelines, the expected benefits are not always achieved by all patients [5–7]. Therefore, many risk stratification models have been developed to identify high-risk patients who need more aggressive treatment and more frequent control visits in follow-up [8–16]. Unfortunately, the clinical value of risk prediction models for HF prognosis and outcomes is limited. This is due to several factors, including the fact that some models were developed before the era of treatment guidelines [13–16]. Moreover, published data showed that it is easier to predict mortality than HF hospitalization [1]. This may be partially explained by patient-related factors that can determine the prognosis itself. Re-hospitalization rates might depend on the quality of care and organization of healthcare in a particular country.

Little is known about the association between comprehensive assessments and measurements obtained after cardiac rehabilitation of HF patients and their influence on prognosis and the need for re-hospitalization. Most previous studies developed risk stratification models based on HF patients hospitalized for exacerbation of clinical status or HF patients who participated in clinical research assessment of administered drug treatment [8–16]. Only one study reported a risk stratification model based on HF patients who were referred for the cardiac rehabilitation program [2].

The recently completed TELEREH-HF (TELEREHabilitation in Heart Failure) trial demonstrated that 9-week hybrid comprehensive telerehabilitation (HCTR) significantly improves physical capacity and quality of life (QoL) in patients with HF compared to usual care (UC) [17]. However, HCTR had no significant impact on mortality and hospitalization rates in a long-term follow-up (i.e., 12–24 months) after the intervention was completed [17]. In this context the questions arose: is it possible to translate the short-term improvement in physical capacity and QoL into the improvement in long-term prognosis? Is it possible to select a subgroup of HF patients with a good versus poor long-term prognosis based on risk factors collected at the end of the telerehabilitation period? Therefore, this study aimed to define predictors influencing long-term CV mortality or HF hospitalization based on clinical status and measurements obtained after the 9-week HCTR program.

METHODS

The design and main results of the TELEREH-HF study have been published elsewhere [17–21]. The TELEREH-HF trial was a randomized (1:1), multi-center (5 centers in Poland), prospective, open-label, parallel-group, controlled study (Clinical Trials.gov NCT 02523560), which compared HCTR plus UC with UC alone in 850 clinically stable HF patients (New York Heart Association [NYHA] class I, II, or III) with left ventricular ejection fraction (LVEF) ≤40% after hospitalization for worsening HF within 6 months before randomization. Patients were randomized between June 8, 2015, and June 28, 2017. The detailed TELEREH-HF inclusion and exclusion criteria were previously published elsewhere [17, 18].

The HCTR intervention was comprehensive and encompassed telecare, tailored home-based telerehabilitation, and remote monitoring of cardiovascular implantable electronic devices. Patients in the HCTR group underwent a 9-week HCTR program consisting of an initial stage (1 week) in the hospital and a basic stage (8 weeks) of HCTR performed at home, five times weekly. Patients underwent endurance aerobic training based on Nordic walking, respiratory muscle training, and light resistance and strength training. A detailed description of the medical team composition, equipment for telemonitoring, and intervention has been published elsewhere [17, 18].

The study was guided by good clinical practice and in accordance with the Declaration of Helsinki and the regulations applicable in Poland. The trial protocol was approved by the local ethics committee (IK-NP-0021-85/1402/13). Each patient provided written informed consent [17, 18].

All patients underwent the following assessments at entry and after completing the 9-week program: clinical examinations (including NYHA class assessment), lab tests (blood count, serum creatinine, electrolytes [natrium, potassium], glycemia, N-terminal prohormone of brain natriuretic peptide [NT-proBNP], high-sensitivity C-reactive protein [hs-CRP], aspartate aminotransferase, alanine aminotransferase, thyroid stimulating hormone [TSH], international normalized ratio [INR], urinalysis), echocardiography,

six-minute walk test (6MWT), cardiopulmonary exercise test (CPET), 24-hour Holter ECG monitoring, psychological assessment, and HCTR adherence evaluation. Patients were followed for 12–24 months after the intervention/observation was completed to collect data on mortality and hospitalization. Mortality data were collected during follow-up for a maximum of 24 months with a maximum of two check-up visits within the 12 and 24 months following the end of the preliminary 9-week HCTR and the follow-up period in the UC group. The follow-up was also conducted in the form of a telephone conversation with the patients and/or family members on a monthly basis to accurately collect mortality and hospitalization data.

Echocardiography

Two-dimensional echocardiography was performed using standard parasternal, apical, and subcostal views. LVEF was calculated from conventional apical two-chamber and four-chamber images using the biplane Simpson technique.

Six-minute walk test

The 6MWT was conducted using a standardized protocol after taking usual medications. Patients were required to perform a six-minute shuttle walk test with markers placed at 25 m.

Cardiopulmonary exercise test

The symptom-limited CPET on a treadmill according to a ramp protocol and the ESC guidelines was performed using a Schiller MTM-1500 med [22, 23]. Oxygen consumption (VO_2) was measured continuously using breath-by-breath analysis. The peak VO_2 value was presented per kilogram of body mass per minute (ml/kg/min). Maximal exercise was defined as the respiratory exchange ratio (RER) ≥1.

24-hour Holter ECG monitoring

For 24-hour Holter ECG monitoring, we used a 12-channel Holter digital recorder Lifecard CF, Del Mar Reynolds Medical UK/US. Twenty-four-hour Holter recordings were assessed using the Pathfinder SL analysis system and Spacelabs Healthcare. Rigorous quality control was performed on all Holter ECG studies by trained physicians in one center dedicated to Holter analysis.

Psychological assessment

Health-related quality of life assessment. The Medical Outcome Survey Short Form 36 Questionnaire (SF-36) was used to assess QoL. The SF-36 consists of two major domains (physical and mental QoL) and various subscales [24]. Higher scores indicate a better QoL.

Depression assessment. The Beck Depression Inventory II (BDI-II) — a 23-item questionnaire, was administered to assess patients' self-reported depression symptoms. In general terms, BDI II scores range from 0 to 63, and the lower the score, the better patients' emotional condition. Patients with BDI II scores ≥14 were considered affected by depression [25].

Assessment of HCTR efficacy

Response to HCTR was assessed by changes — delta (Δ) in all evaluated parameters as a result of comparing measurements from the beginning and the end of the program (0 vs. 9 weeks).

Assessment of HCTR adherence

Fully adherent patients were those who adhered to both the number of prescribed training sessions and duration of the prescribed cycle in at least 80%; the rest was classified as partially adherent or non-adherent [17, 18].

Statistical analysis

Our primary analysis focused on patients randomized to the HCTR group, with the control arm used as a validation sample. Quantitative variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate, and categorical variables were expressed as counts and percentages. Missing data were imputed with the median. The distribution of continuous variables was tested for normality with the Kolmogorov-Smirnov test. The study groups were compared using the χ^2 test of independence (unless the number of expected events is fewer than 5, in which case Fisher's exact test was used) for categorical variables and two independent t-tests or Wilcoxon rank-sum tests for continuous data, as appropriate. The primary outcome for this analysis was HF hospitalization or CV mortality. Follow-up time was calculated from the end of the 9-week HCTR program to the final visit at the study end (maximum follow-up of 24 months) or the time when the first event occurred. Patients who were lost during the follow-up were censored at the time of the last contact. Cox proportional hazards regression was used to identify predictors significantly associated with the primary outcome. Candidate predictors are listed in Table 1. All variables with significant prognostic impact in univariate analysis ($P \leq 0.10$) were included in the multivariable model. Then a backward selection was used to create the final model (model I; adjusted for age and sex). Model II was developed after forcing three other common predictors to Model I. The linear predictor obtained in the final Cox proportional hazards regression model was calculated as the risk score. The proportionality of hazards was verified using the weighted Schoenfeld residuals. Model discrimination was assessed using Harrell's Concordance Statistics (C-index). We first assessed discrimination on the development sample (HCTR) and then applied final Model I to the control arm (not used in model development) as a validation sample. Kaplan-Meier curves were constructed and log-rank tests with Tukey-Kramer correction for multiple comparisons were calculated summarizing the relationship between the tertiles of the risk score and survival. First, the risk score was calculated for each

Table 1. Baseline characteristics of the HCTR group depending on event occurrence; and candidate predictor variables for event (cardiovascular death or heart failure hospitalization)

Baseline	HCTR group with event (n = 108)	HCTR group without event (n = 276)	*P*-value
Male sex, n (%)	94 (87.0)	250 (90.6)	0.31
Age, years, mean (SD)	63.1 (11.3)	61.6 (10.6)	0.20
BMI, kg/m^2, mean (SD)	28.9 (5.1)	28.9 (5.1)	0.99
LVEF, %, mean (SD)	28.5 (7.1)	32.0 (6.6)	<0.001
Duration of heart failure, years, median (IQR)	8.0 (3.3–13.7)	5.1 (1.4–10.0)	0.001
Etiology of heart failure, n (%)			
Ischemic, n (%)	62 (57.4)	189 (68.5)	0.04
Non ischemic, n (%)	46 (42.6)	87 (31.5)	
Past medical history, n (%)			
Atrial fibrillation or atrial flutter, n (%)	29 (26.8)	44 (15.9)	0.01
Hypertension, n (%)	54 (50.0)	174 (63.0)	0.02
Stroke, n (%)	9 (8.3)	14 (5.1)	0.23
Diabetes mellitus, n (%)	48 (44.4)	82 (29.7)	0.006
Chronic kidney disease, n (%)	39 (36.1)	31 (11.2)	<0.001
Hyperlipidemia, n (%)	55 (49.5)	135 (48.9)	0.72
Implantable devices, n (%)			
Cardiovascular implantable electronic device, n (%)	91 (84.3)	214 (77.5)	0.14
Implantable cardioverter-defibrilator, n (%)	51 (47.2)	139 (50.4)	0.12
Cardiac resynchronization therapy (CRT-P/CRT-D), n (%)	39 (36.1)	73 (26.4)	
Lab parameters			
NT-proBNP, pmol/l, median (IQR)	1946 (843–813)	669 (261–1307)	<0.001
NT-proBNP in patients with sinus rhythm, pmol/l, median (IQR)	1349 (865–2172)	536 (231–1114)	<0.001
NT-proBNP in patients with atrial fibrillation or atrial flutter, pmol/l, median (IQR)	2419 (1342–4300)	1349 (865–2172)	0.01
Cardiopulmonary exercise test			
pVO_2, ml/kg/min, mean (SD)	14.3 (4.4)	18.2 (5.6)	<0.001
Minute ventillation at peak effort, l/min, mean (SD)	43.6 (14.4)	51.7 (19.0)	<0.001
Breathing frequency at peak effort, /min, mean (SD)	29.5 (6.4)	29.3 (6.3)	0.81
Pharmacotherapy, n (%) the number of patients taking the drug given in parentheses			
β-blocker, n (%)	104 (96.3)	265 (96.0)	>0.99
Bisoprolol (n = 39, n = 120), dose (mg), median (IQR)	5 (5–10)	5 (5–10)	0.55
Carvedilol (n = 31, n = 66), dose (mg), median (IQR)	25 (12.5–50)	25 (12.5–50)	0.85
Metoprolol (n = 21, n = 59), dose (mg), median (IQR)	100 (100–175)	100 (50–175)	0.36
Nebivolol (n = 11, n = 19), dose (mg), median (IQR)	5 (2.5–5)	5 (2.5–5)	0.82
Atenolol, Betaxolol, (n=2, n=1)			
ACEIs/ARBs, n (%)	100 (92.6)	258 (93.5)	0.76
ACEIs, n (%)	86 (79.6)	220 (79.7)	0.99
Ramipril (n = 68, n = 182), dose (mg), median (IQR)	2.5 (2.5–5)	5 (2.5–5)	0.06
Perindopril (n = 10, n = 16), dose (mg), median (IQR)	5 (5–5)	5 (5–5)	0.97
Enalapril (n = 2, n = 6), dose (mg), median (IQR)	20 (10–30)	20 (15–40)	0.73
Cilazapril, Lisinopril, Trandolapril (n = 6, n = 16)			
ARBs n (%)	14 (13.0)	38 (13.8)	0.84
Losartan (n = 5, n = 15), dose (mg), median (IQR)	50 (50–50)	50 (50–50)	0.70
Candesartan (n = 5, n = 6), dose (mg), median (IQR)	8 (4–8)	12 (8–32)	0.12
Valsartan (n = 4, n = 8), dose (mg), median (IQR)	80 (60–120)	80 (80–160)	0.58
Telmisartan (n = 0, n = 9), dose (mg), median (IQR)		80 (40–80)	
Ivabradine, n (%)	7 (6.5)	21 (7.6)	0.70
Ivabradine dose (mg), median (IQR)	7.5 (5–10)	10 (7.5–10)	0.14
Aldosterone antagonists, n (%)	95 (88.0)	228 (82.6)	0.20
Eplerenone (n = 59, n = 153), dose (mg), median (IQR)	25 (25–50)	25 (25–50)	0.01
Spironolactone (n = 36, n = 75), dose (mg), median (IQR)	25 (25–25)	25 (25–25)	0.61
After 9 weeks of HCTR			
Functional status by NYHA class, n (%)			
I	17 (15.7)	81 (29.3)	<0.001
II	65 (60.2)	169 (61.2)	
III	26 (24.1)	26 (9.4)	
Clinical finding, n (%)			
Lower limb swelling, n (%)	13 (12.0)	17 (6.2)	0.054
Anamnesis, n (%)			
Active smoking, n (%)	6 (5.6)	18 (6.5)	0.72
Alcohol abuse, n (%)	2 (1.8)	9 (3.3)	0.73

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Table 1 (cont.). Baseline characteristics of the HCTR group depending on event occurrence; and candidate predictor variables for event (cardiovascular death or heart failure hospitalization)

Baseline	HCTR group with event (n = 108)	HCTR group without event (n = 276)	*P*-value
Lab parameters			
Sodium, mmol/l, mean (SD)	140.3 (2.9)	140.7 (2.7)	0.14
Potassium, mmol/l, mean (SD)	4.47 (0.47)	4.52 (0.43)	0.33
Hemoglobin, g/dl, mean (SD)	13.8 (1.5)	14.3 (1.3)	0.005
eGFR, ml/min/1.73 m^2, mean (SD)	56.8 (18.3)	72.3 (20.6)	<0.001
NT-proBNP, pg/ml, median (IQR)	1958 (987–3660)	698 (257–1204)	<0.001
Creatinine, mg/dl, median (IQR)	1.34 (1.12–1.79)	1.05 (0.90–1.22)	0.06
Hs-CRP, mg/dl, median (IQR)	2.50 (1.32–4.90)	1.60 (0.90–3.01)	<0.001
SBP, mm Hg, mean (SD)	116.9 (21.9)	122.9 (17.9)	0.002
DBP, mm Hg, mean (SD)	72.2 (10.4)	75.5 (10.6)	0.006
Six-minute walk test			
Distance, m, mean (SD)	424 (101)	475 (99.5)	<0.001
Cardiopulmonary exercise test			
Exercise time, s, mean (SD)	357 (149)	474 (187)	<0.001
Maximal heart rate, bpm, mean (SD)	116 (22)	124 (22)	<0.001
Sinus rhythm, bpm, mean (SD)	114 (20.5)	123 (20.7)	0.002
Atrial fibrillation or atrial flutter, bpm, mean (SD)	120 (25.2)	132 (25.0)	0.045
$pVCO_2$, ml/kg/min, mean (SD)	1.27 (0.46)	1.71 (0.71)	<0.001
Minute ventillation at rest, l/min, mean (SD)	13.8 (5.5)	13.3 (5.3)	0.40
Minute ventillation at peak effort, l/min, mean (SD)	47.8 (15.1)	54.6 (20.0)	<0.001
Breathing frequency at rest, /min, mean (SD)	19.7 (5.4)	19.0 (4.6)	0.19
Breathing frequency at peak effort, /min, mean (SD)	31.2 (6.3)	30.0 (6.2)	0.09
RER, mean (SD)	0.98 (0.13)	0.99 (0.12)	0.24
VE/VO_2 slope, mean (SD)	33.4 (13.3)	29.6 (8.8)	0.007
VE/VCO_2 slope, mean (SD)	33.3 (11.4)	29.3 (8.8)	0.001
Echocardiography			
LVsD, mm, mean (SD)	57.2 (10.2)	52.6 (9.6)	<0.001
LVdD, mm, mean (SD)	66.2 (8.7)	62.3 (8.5)	<0.001
LVsV, ml, mean (SD)	166.1 (76.1)	136.3 (65.5)	<0.001
LVdV, ml, mean (SD)	227.1 (87.5)	197.6 (81.1)	0.002
LVEF (%), mean (SD)	29.7 (7.8)	34.1 (7.4)	<0.001
24-hour ECG Holter monitoring			
Average heart rate, bpm, mean (SD)	69.9 (8.7)	68.3 (8.0)	0.09
Sinus rhythm, bpm, mean (SD)	68.2 (7.7)	67.2 (7.5)	0.31
Atrial fibrillation or atrial flutter, bpm, mean (SD)	74.5 (10.0)	74.0 (8.6)	0.83
Maximal heart rate, bpm, mean (SD)	102.4 (16.3)	103.7 (16.6)	
0.51 Sinus rhythm, bpm, mean (SD)	100.8 (16.0)	102.2 (15.1)	0.48
Atrial fibrillation or atrial flutter, bpm, mean (SD)	106.8 (17.1)	111.3 (22.3)	0.36
Minimal heart rate, bpm, mean (SD)	59.7 (9.4)	56.9 (9.0)	0.006
Sinus rhythm, bpm, mean (SD)	57.8 (7.8)	55.6 (7.8)	0.03
Atrial fibrillation or atrial flutter, bpm) mean (SD)	65.0 (11.5)	63.1 (13.0)	0.53
Quality of life			
SF-36, score, mean (SD)	88.4 (13.1)	93.1 (12.1)	<0.001
BDI-II, score, mean (SD)	10.2 (6.8)	8.6 (6.2)	0.03
Changes 0–9 week			
Lab parameters			
Sodium, mmol/l, mean (SD)	–0.12 (2.93)	0.03 (2.81)	0.63
Potassium, mmol/l, mean (SD)	0.01 (0.41)	0.04 (0.45)	0.46
Hemoglobin, g/dl, mean (SD)	0.04 (1.00)	0.00 (1.3)	0.75
eGFR, ml/min/1.73 m^2, mean (SD)	0.12 (11.2)	1.16 (13.73)	0.49
Creatinine, mg/dl, median (IQR)	0.01 (–0.08–0.16)	0.00 (–0.10– 0.09)	0.06
NT-proBNP, pg/ml, median (IQR)	–32.5 (–517–421)	–7.7 (–196–136)	0.43
Hs-CRP, mg/dl, median (IQR)	–0.19 (–1.46 to –1.1)	–0.15 (–0.85–0.41)	0.82
Clinical finding			
Improvement in NYHA class, n (%)	23 (21.3)	65 (23.5)	0.61
No change in NYHA class, n (%)	75 (69.4)	193 (69.9)	
Worsening of NYHA class, n (%)	10 (9.3)	18 (6.5)	
SBP, mm Hg, mean (SD)	–0.78 (17.4)	–1.11 (17.7)	0.87
DBP, mm Hg, mean (SD)	–0.04 (11.0)	–1.12 (11.4)	0.40

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Table 1 (cont.). Baseline characteristics of the HCTR group depending on event occurrence and candidate predictor variables for event (cardiovascular death or heart failure hospitalization)

Baseline	HCTR group with event (n = 108)	HCTR group without event (n = 276)	*P*-value
Six-minute walk test			
Distance, m, mean (SD)	39.3 (69.2)	31.2 (52.3)	0.24
Cardiopulmonary exercise test			
Exercise time, sec, mean (SD)	40.0 (80.1)	53.5 (89.6)	0.17
Maximal heart rate, bpm, mean (SD)	4.45 (22.8)	0.99 (19.93)	0.14
pVO_2, ml/kg/min, mean (SD)	0.89 (2.96)	1.20 (3.31)	0.40
pVO_2 % pred, %, mean (SD)	3.58 (12.0)	3.66 (12.66)	0.96
$pVCO_2$, ml/kg/min, mean (SD)	0.10 (0.31)	20.13 (0.35)	0.53
RER, mean (SD)	0.03 (0.12)	0.02 (0.14)	0.50
Minute ventillation at rest, l/min, mean (SD)	0.73 (4.28)	0.46 (4.30)	0.58
Minute ventillation at peak effort, l/min, mean (SD)	4.15 (10.2)	2.96 (12.9)	0.34
Breathing frequency at rest, /min, mean (SD)	0.78 (4.51)	0.32 (4.49)	0.37
Breathing frequency at peak effort, /min, mean (SD)	1.74 (4.90)	0.71 (5.14)	0.07
24-hour ECG Holter monitoring			
Average heart rate, bpm, mean (SD)	0.35 (6.31)	–0.99 (6.23)	0.06
Minimal heart rate, bpm, mean (SD)	–0.04 (5.50)	–0.14 (5.84)	0.87
Maximal heart rate, bpm, mean (SD)	4.59 (16.5)	1.29 (14.8)	0.06
Baseline presence of nsVT, 9-week absence of nsVT, n (%)	11 (10.4)	32 (11.8)	0.69
LVsD, mm Hg, mean (SD)	–0.29 (4.50)	–0.87 (5.45)	0.33
LVDd, mm Hg, mean (SD)	–0.36 (4.35)	–0.90 (4.92)	0.32
LVsV, mm Hg, mean (SD)	–11.0 (48.1)	–7.42 (38.6)	0.44
LVdV, mm Hg, mean (SD)	–8.3 (60.1)	–2.78 (47.5)	0.39
LVEF, %, mean (SD)	1.12 (3.80)	2.13 (3.94)	0.02
SF-36, score, mean (SD)	1.63 (11.0)	2.00 (9.41)	0.76
Adherence to HCTR, n (%)	93 (86.1)	253 (91.7)	0.10

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BDI-II, Beck Depression Inventory; BF, breathing frequency; BMI, body mass index; CRT-D, cardiac resynchronization therapy and cardioverter- defibrillator; CRT-P, cardiac resynchronization therapy with peacemaker function; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HCTR, hybrid comprehensive telerehabilitation; HR, heart rate; hs-CRP, high-sensitivity C-reactive protein; LVDd, left ventricular diastolic diameter; LVEF, left ventricular ejection Fraction; LVSd, left ventricular systolic diameter; LVdV, left ventricular diastolic volume; LVsV, left ventricular systolic volume; nsVT, nonsustained ventricular tachycardia; NT-proBNT, N-terminal fragments of B-type natiuretic peptide; NYHA, New York Heart Association, $pVCO_2$, carbon dioxide output at peak exercise; pVO_2, oxygen uptake at peak exercise; pVO_2% pred, percentage of predicted peak oxygen uptake; RER, respiratory exchange ratio; SBP, systolic blood pressure; SF-36, Short Form 36 Health Survey Questionnaire; VE/VCO_2-slope, slope of the relationship between minute ventilation and carbon dioxide output; VE/VO_2-slope, slope of the relationship between minute ventilation and oxygen uptake; VE, minute ventilation at peak exercise

patient, next the patients were assigned into 3 groups according to the value of terciles of the risk score, and finally the probabilities of surviving without a composite endpoint in these 3 groups were estimated and compared with the Kaplan-Meier method. In all analyses, the tests were two-sided, and the level of significance was set at 0.05. The statistical analysis was performed using SAS version 9.4 (SAS Inc., NC, US).

RESULTS

Of the 850 randomized patients, 425 were assigned to HCTR and 425 to UC. Twenty-seven patients did not participate in the HCTR program due to technical difficulties with operating the telerehabilitation set (21), new onset of comorbidities (4), and return to work (2) [17]. Finally, 384 patients were included in the present analysis. Over 12–24 months of follow-up (median [IQR], 24 [20–24] months), 27 (7%) patients died of cardiovascular causes, 95 (24.7%) experienced HF hospitalization, and 108 (28.1%) experienced the composite endpoint. The baseline characteristics of the entire primary study sample (HCTR group) and composite event status are presented as Supplementary material.

Association between baseline predictors and the composite outcome

The predictors of higher CV mortality or HF hospitalization retained after backward elimination are presented in Table 2 and included the following variables collected at the end of the 9-week telerehabilitation period: nonischemic etiology of HF, diabetes, higher serum level of NT-proBNP, creatinine and hs-CRP; low carbon dioxide output at peak exercise, lower LVEF, high minute ventilation, and high breathing frequency at maximum effort in the CPET. Moreover, an increase in the average heart rate in 24-hour ECG Holter monitoring between week 0 and week 9 achieved statistical significance. Finally, non-adherence to HCTR more than doubled the risk of the primary composite outcome.

Notably, despite improving during the 9-week telerehabilitation period, peak VO2 at the end of the 9-week program was not significantly associated with the primary composite outcome (Table 2). The same was true for the SF-36 and BDI-II.

The final model's discrimination C-index was 0.795 (95% CI, 0.754–0.836). When validated in the control sample which was not used in derivation, the C-index decreased

Table 2. Predictors of cardiovascular-mortality and heart failure hospitalization within 2 years (multivariable Cox proportional hazards model)

	Model I, Harrell's Concordance Statistics (C-index) = 0.795		Model II, Harrell's Concordance Statistics (C-index) = 0.798	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age, years	0.982 (0.960–1.004)	0.10	0.981 (0.959–1.004)	0.10
Sex, male	1.311 (0.655–2.625)	0.44	1.334 (0.662–2.689)	0.42
Non-ischemic etiology of heart failure	2.043 (1.316–3.173)	0.001	2.073 (1.329–3.231)	0.001
Diabetes mellitus	1.564 (1.030–2.373)	0.04	1.530 (1.003–2.335)	0.048
NT-proBNP 9 week	1.105 (1.027–1.189)	0.007	1.102 (1.023–1.187)	0.01
Creatinine 9 week	3.038 (2.040–4.523)	<0.001	2.987 (1.975–4.518)	<0.001
Hs-CRP 9 week	1.036 (1.005–1.068)	0.02	1.039 (1.007–1.072)	0.02
$pVCO_2$ 9 week	0.088 (0.036–0.216)	<0.001	0.090 (0.029–0.281)	<0.001
VE 9 week	1.057 (1.027–1.088)	<0.001	1.056 (1.025–1.088)	<0.001
BF 9 week	1.034 (1.002–1.068)	0.04	1.035 (1.002–1.069)	0.04
LVEF 9 week	0.973 (0.948–0.999)	0.04	0.973 (0.948–0.999)	0.04
Average heart rate in HM 9 week, baseline	1.051 (1.019–1.084)	0.001	1.050 (1.018–1.082)	0.002
Adherence to HCTR	0.415 (0.231–0.743)	0.003	0.405 (0.225–0.730)	0.003
pVO_2 9 week	—	—	1.005 (0.932–1.083)	0.91
SF-36 (score) 9 week	—	—	0.992 (0.973–1.011)	0.39
BDI-II (score) 9 week	—	—	1.001 (0.966–1.036)	0.97

Abbreviations: NT-proBNP, N-terminal fragments of B-type natiuretic peptide; hs-CRP, high-sensitivity C-reactive protein; $pVCO_2$, carbon dioxide output at peak exertion; VE, minute ventilation at peak exercise; BF, breathing frequency; LVEF, left ventricular ejection fraction; HR, hazard ratio; HM, 24-h ECG Holter monitoring; pVO_2 oxygen uptake at peak exertion; SF-36, Short Form 36 Health Survey Questionnaire; BDI-II, Beck Depression Inventory

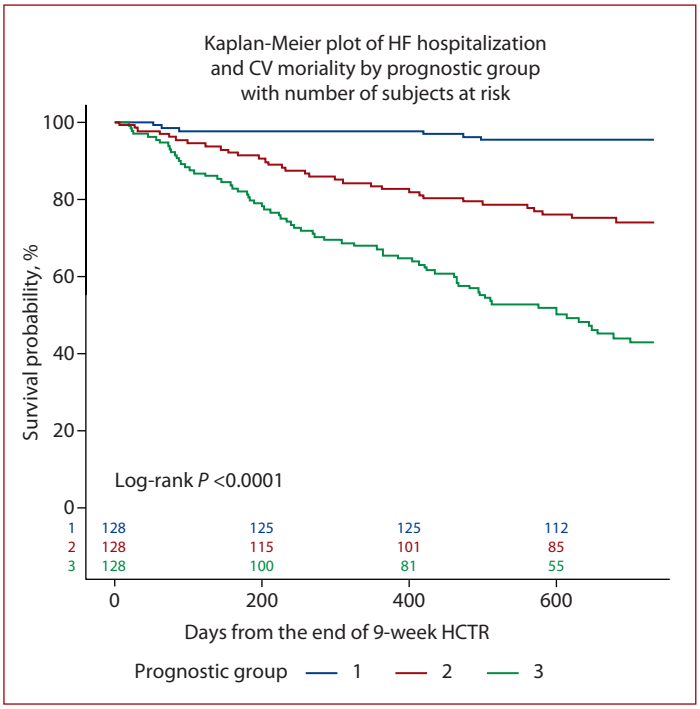

Figure 1. Kaplan-Meier plot, survival of the three prognostic group: good prognosis — risk score <0.0; moderate prognosis — risk score from 0.0 to 1.1; poor prognosis — risk score >1.1

to 0.755 (95% CI, 0.708–0.802). The baseline characteristics of the UC sample are presented in the Supplementary material.

Risk stratification

When the model-based risk of the composite event was stratified into tertiles, we observed substantial separation of the observed 2-year risk of CV mortality or hospitalization. Figure 1 shows the Kaplan-Meier curves for the three ranges of model-based risk: (1) good prognosis (risk score <0.0): 2-year risk of outcome 95% CI, 0.047 (0.010–0.084); (2) moderate prognosis (risk score from 0.0 to 1.1): 2-year risk of outcome 95% CI, 0.260 (0.182–0.338); (3) poor prognosis (risk score >1.1): 2-year risk of outcome 95% CI, 0.481 (0.395–0.567).

DISCUSSION

This analysis from the TELEREH-HF randomized controlled trial database was the basis for the development of the risk stratification model for CV mortality or HF hospitalization occurrence based on the comprehensive noninvasive assessment of HF patients who completed the 9-week

HCTR program. To our knowledge, this is the first risk stratification model for clinically stable HF patients based not only on demographic data and baseline characteristics but also on measurements obtained after 9-week HCTR and response to exercise training assessed by changes (delta [Δ]) in parameters as a result of comparing values from the beginning and the end of the telerehabilitation program.

Based on our data, the score indicated that each of the following factors had independent predictive power: patients' non-adherence to HCTR, nonischemic etiology of HF, diabetes, lower LVEF, higher serum level of NT-proBNP, creatinine and hs-CRP; low peak VCO_2, high VE, and high BF at maximum effort in the CPET and an increase in difference (Δ) in the average heart rate in 24-hour-ECG Holter monitoring between baseline and after 9-week HCTR examinations.

It should be emphasized that in our model, patients fully adherent to HCTR were associated with more than twice lower risk of CV death and HF hospitalization. This is in line with a published meta-analysis of controlled trials by Ruppar et al., who demonstrated that among HF patients, intervention to improve medication adherence has a significant impact on decreasing readmissions and reducing mortality [26]. Hybrid telerehabilitation is a comprehensive procedure that supports adherence to both medical treatment and exercise training. Moreover, daily contact with the telemonitoring center helped patients to develop healthy habits for the future.

The nonischemic etiology of HF was associated with our composite endpoint. This result is in contrast with data from the Seattle Heart Failure Model, which indicated that ischemic etiology with other predictors (NYHA class, diuretic dose, LVEF, systolic blood pressure, sodium, hemoglobin, percent lymphocytes, uric acid, and cholesterol) had independent predictive power [13, 14]. However, results from the DANISH study (Danish Study to Assess the Efficacy of ICDs in Patients with Non-Ischemic Systolic Heart Failure on Mortality) reported that for many patients with dilated cardiomyopathy, ICDs do not increase longevity, which indicates that this subgroup of patients had a high risk of CV death [27]. Our analysis confirms these findings. This may be related to myocardial fibrosis as a substrate for malignant ventricular arrhythmias, specific genetic mutations affecting arrhythmic risk, nonhomogeneous etiology, and the naturally aggressive course of the disease in some cases [27].

Comorbidities are of great importance in the stratification of CV risk. In our model diabetes was associated with higher risk of CV mortality or HF hospitalization in long-term follow-up. However, hypertension, stroke, chronic kidney disease, and hyperlipidemia were not predictive of prognosis and readmissions. Diabetes is a common comorbidity and ranges from 10% to 30% in HF with reduced LVEF. Additionally, it has a significant negative impact on prognosis [28]. Moreover, diabetic patients more frequently suffered from HF. According to the Swedish Heart Failure Registry, in patients with HF and diabetes, mortality was 37% [29]. In the REACH (Reduction of Atherothrombosis for Continued Health) Registry, diabetes was associated with a 33% greater risk of HF hospitalization, moreover, the presence of HF at baseline was independently associated with CV death and hospitalization for HF [30]. Diabetes was also the predictor of fatal outcomes in the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trial [12]. In the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) model, diabetes in older age and with lower LVEF were the most prognostic variables predicting either the composite endpoint of CV death or HF hospitalization, or all-cause mortality [15]. Diabetes was associated with a doubling of risk of either death or the composite outcome when insulin-treated, and a 50% increase in the risk of non-insulin-treated diabetes [15]. In our model, diabetes increased the risk of a composite endpoint one and a half times. In the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) model, like in ours, the presence of hyperlipidemia was not predictive of post-discharge mortality in HF patients [11]. In contrast to our results, reactive airway disease, depression, and liver disease were associated with higher risk of post-discharge mortality.

LVEF is generally considered a strong predictor of poor prognosis, which was confirmed in the Seattle HF, CHARM, and CORONA models as well as in our model [12–15].

Only a few models incorporated biochemical data and biomarkers for risk stratification. This is due, *inter alia*, to the fact that when the CHARM and Seattle models were developed, biomarkers were not routinely used [13–15].

Renal function is an important predictor of prognosis. In our model, the serum creatinine level was a strong predictor of outcome. This result is consistent with the CORONA model [12]. The plasma concentration of NT-proBNP level is commonly used as an initial test in the diagnosis of HF [5, 6]. In the CORONA model, NT-proBNP was the most important prognostic variable for each outcome (CV, HF, sudden cardiac death; CV, HF hospitalization; all-cause mortality or HF hospitalization as well as atherothrombotic and coronary endpoint), which is in line with our results in terms of predicting CV mortality or HF hospitalization [12]. It is worth noticing that although NT-proBNP may be considered to reflect cardiac and renal function, both creatinine and LVEF remained in the final models of CORONA and TELEREH-HF. Many inflammatory markers are elevated in HF. In our model, hs-CRP was a significant predictor of the composite outcome. Meanwhile, in the CORONA model, hs-CRP was an independent predictor of the atherothrombotic endpoint [12].

Data from CPETs are commonly used to determine the prognosis in HF patients. Keteyian et al. evaluated multiple CPET-derived variables for their association with prognosis in patients with HF with reduced LVEF. This analysis showed that the relationship for all variables, except for the RER, was highly significant [31]. Published data indicated that

peak VO_2, percent predictive VO_2, CPET duration, and the VE/VCO_2 slope have the strongest ability to predict prognosis in HF patients [31, 32]. In the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise TraiNing) risk stratification model, the most important predictor for the composite of death or all-cause hospitalization endpoint was exercise duration in the CPET [2]. In our model breathing frequency (BF), maximal minute ventilation (VE), and carbon dioxide production (VCO_2) during the CPET were stronger predictors of CV death or HF hospitalization than peak VO_2 and VE/VCO_2 slope. This led to these two last variables not being included in the final multivariable model. Advanced HF is associated with an increase in VE (due to increased dead space ventilation) and an increase in VCO_2 relative to VO_2 (because of bicarbonate buffering of lactic acid), in line with our results. Therefore, the association between BF, VE, CO_2, and VE/VCO_2 is very strong and supports these findings.

Another variable that affects prognosis is heart rate. Published data reported an association between increased heart rate over time and cardiovascular and all-cause mortality [32]. This was confirmed in our analysis, where an increase in difference (Δ) in the average heart rate in 24-hour ECG Holter monitoring between baseline and after 9-week HCTR examinations was a predictor of poor prognosis. Similarly, in the CHARM and CORONA studies, heart rate was included in the risk stratification models [12, 15].

It is worth noting that the TELEREH-HF population included a fairly homogeneous group of stable patients with HF with reduced LVEF treated in accordance with the current guidelines (which was included in the study inclusion/exclusion criteria). Ninety-six percent of patients were treated with β-blockers, 93% with an ACEI or ARB, 82% with aldosterone antagonists; 79% had CIEDs and 62% ICDs. Similarly, patients enrolled in the HF-ACTION study were treated according to evidence-based therapy (95% of them took β-blockers, 74% used ACEI, and 40% had an ICD). The determinants of higher mortality in the HF-ACTION trial were male sex, lower body mass index (BMI), higher serum urea nitrogen, and shorter CPET duration. The corresponding C-index was 0.73, suggesting a moderately good capacity of the model to indicate patients at greater risk of death [2]. For the second predictive model of the primary composite endpoint of death or hospitalization from any cause, the same variables were included with one exception — the Kansas City Cardiomyopathy Questionnaire symptom stability statement score was incorporated instead of BMI [2]. The defined models from the HF-ACTION are not consistent with ours. However, the models deal with different aspects of prognosis: in the HF-ACTION death or hospitalization from any cause vs. CV mortality or HF hospitalization in the TELEREH-HF study.

In the context of published data, it is worth noting the good C-index of our model (0.795 in development, 0.755 in the validation sample), especially given that the study was randomized. According to the results of the study by Ouwerkerk et al. "Cohort and prospective studies produced higher C-statistics than models on the basis of data of randomized trial" [1]. The reason for the lower C-statistic in the other randomized controlled trials may be that these studies were not primarily created for the development of the risk stratification model, and the population was more homogenous due to preselection according to inclusion and exclusion criteria.

Identifying a strong model for predicting both prognosis and rehospitalization should allow for more personalized treatment and holistic management of HF patients who completed the home-based telerehabilitation program. This is in line with the current recommendations that support multidisciplinary tailored management of HF patients to maintain short-term improvement after hospitalization or other interventions such as cardiac rehabilitation [5, 6].

Strengths and limitations

The TELEREH-HF model refers to a homogeneous population of HF patients with reduced LVEF ≤40% treated according to the current standards, which, on the one hand, is an advantage and, on the other hand, a limitation, as the results may not be simply translated into other populations, e.g., HF with preserved LVEF, different racial or ethnic groups. The advantage of this analysis is the comprehensive patient evaluation based on noninvasive examinations recommended by the guidelines and achievable in HF and cardiac rehabilitation departments [5, 6]. Notably, our model did not take into account the socioeconomic status of patients, which may also affect prognosis.

The presented results refer only to the Polish population, where diagnostic, treatment options, and the organization of healthcare differ in comparison to other European countries [33]. Moreover, the use of new therapies in HF changes the prognosis of current HF patients in Poland and other countries, which might affect the presented results from the perspective of 2023 and current clinical practice.

CONCLUSION

Based on data from the TELEREH-HF randomized trial, we were able to show that it is possible to use risk factors collected at the end of the 9-week telerehabilitation period to stratify patients based on their 2-year risk of CV mortality or HF hospitalization. In our model, patients in the top tertile had an almost ten-fold higher risk compared to patients in the bottom tertile. Treatment adherence, but not peak VO_2 or quality of life, was significantly associated with the outcome.

Supplementary material

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

Article information

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Positive left atrial remodeling in patients with paroxysmal atrial fibrillation after a successful radiofrequency pulmonary vein isolation

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ABSTRACT

Background: A potential relationship between the initial left atrial (LA) echocardiographic parameters and LA remodeling after pulmonary vein isolation using (PVI) radiofrequency energy energy with effectiveness of this treatment was discussed.

Aim: We aimed to determine the relationship between initial and post-follow-up transthoracic echocardiography-derived predictors of successful PVI in patients with paroxysmal atrial fibrillation (AF).

Methods: Eighty patients with paroxysmal AF (aged 58 [interquartile range, IQR, 50–63] years; male, 50 [62.5%]), hospitalized for the first PVI procedure were included. Before and after a minimum of 6 months of follow-up, clinical and echocardiographic evaluations were performed. LA morphological parameters (diameter, volumes, and other detailed LA parameters), as well as LA peak segmental and global longitudinal strains (PLS) and LA wall strain synchrony were assessed.

Results: In the whole group after the follow-up period, patients presented higher mean LA $Vol_{conduit}$. Patients with no AF recurrences had lower post-PVI LA volumes, higher LA ejection fraction, and LA expansion index when compared to the patients after ineffective PVI. Patients who maintained sinus rhythm after the PVI procedure were characterized by higher initial segmental strains: LA $PLS_{basal\text{-}inferior}$ and $PLS_{apical\text{-}septal}$, as well as higher LA wall strain dispersion over time.

Conclusions: Some echocardiographic parameters related to LA morphology improve after successful PVI treatment. LA strains and wall strain dispersion over time are not related to LA remodeling after a successful PVI procedure. However, the baseline LA standard and novel echocardiographic parameters cannot be used for remote evaluation of the effectiveness of the PVI procedure.

Key words: atrial fibrillation, left atrium, pulmonary vein isolation, strain

INTRODUCTION

Atrial fibrillation (AF) is a common supraventricular arrhythmia resulting mainly from progressive unfavorable remodeling of the left atrium (LA). Additionally, in the course of AF, the negative electrical and structural remodeling of LA is consolidated and intensified at the same time [1, 2]. LA remodeling is therefore a complex process, simply defined as a change in LA size and function. The observed structural changes in the LA do not always correlate with the changes observed during myocardial electrical remodeling in patients with recurrent AF [3]. It was found that LA dysfunction assessed using the 2-dimensional speckle-tracking echocardiography (STE) method may precede visible structural changes in the atria, also in potentially healthy individuals [4–6].

The complete isolation of pulmonary veins by linear lesions around their antrum is currently recognized as the most effective method of AF treatment, which is reflected in the growing number of procedures performed also in Poland [7, 8]. Actually, in the light of the latest 2020 European Society of Cardiology

WHAT'S NEW?

Our study aimed to determine the relationship between initial and post-follow-up standard and novel echocardiographic parameters of left atrial (LA) morphology and function and the effectiveness of pulmonary vein isolation (PVI) with radiofrequency energy) in patients with paroxysmal atrial fibrillation (AF). The presented study is unique in terms of the comprehensiveness of the detailed echocardiographic assessment of the LA (both morphology and deformations — segmental and global) in the entire study group. Although some of the echocardiographic parameters describing the morphology of the LA improve after a successful PVI procedure, there is still no single parameter to clearly define the possibility of recurrence of arrhythmia after PVI. Echocardiographic evaluation should be complex, using various available imaging techniques and potentially useful parameters to evaluate the morphology and function of heart chambers. Our observations might also be useful in daily clinical practice and turn out to be of interest to a large group of physicians and investigators focused on AF, especially in connection with long-term effectiveness of ablation treatment and detailed echocardiographic examination.

(ESC) guidelines on the treatment of AF, several randomized controlled trials and observational studies, pulmonary vein isolation (PVI) with radiofrequency (RF) energy or cryoballoon ablation are comparable methods of AF treatment in terms of effectiveness and possible complications, mostly as the first procedure [8, 9].

The pre-procedural echocardiographic assessment, taking into account both the LA morphology (analysis of dimensions and volume: passive, active, and phase) and LA function (analysis of global and segmental strains), may help assess the relationship between the effectiveness of the PVI procedure and early LA dysfunction in the group of patients with paroxysmal AF [10–13]. In turn, the post-procedural assessment will contribute to a more complete understanding of LA remodeling processes depending on maintaining sinus rhythm.

This study aimed to determine the influence of initial and post-follow-up transthoracic echocardiography-derived predictors of successful PVI in patients with paroxysmal AF undergoing the ablation procedure for the first time.

METHODS

We enrolled in the study eighty patients with diagnosed paroxysmal non-valvular AF who were hospitalized in the Department of Cardiology between 2013 and 2017 to have their first PVI procedure.

The standard inclusion criteria were: documented paroxysmal symptomatic non-valvular AF (European Heart Rhythm Association [EHRA] scale, IIb–III) despite the optimal treatment and qualification for PVI, adequate anticoagulant therapy before admission, maintaining sinus rhythm during hospitalization, preserved left ventricular systolic function (LVEF ≥50%), written informed consent, and >18 years of age.

We excluded patients with a history of any artery pathology (stenosis defined as arterial stenosis ≥50% in the NASCET [14], vasculitis or dissection), connective tissue disease, a history of stroke or transient ischemic attack (TIA) in the past, structural heart disease (cardiomyopathies, significant valvular heart disease), states associated with hypercoagulability or a predisposition to systemic embolism, a history of PVI in the past, pregnancy, refusal to participate, acute kidney disease, chronic kidney disease with glomerular filtration rate (GFR) <30 ml/min/1.73 m^2.

Written informed consent was obtained from each patient. The study protocol was approved by the Bioethical Committee of the Medical University of Silesia and performed according to the ethical guidelines of the 1975 Declaration of Helsinki.

The study group was evaluated during hospitalization before the procedure and after the follow-up period. In the current study, up to 6 months after the ablation procedure, a telephone conversation was conducted with the patient to assess the arrhythmia sensation and the pharmacotherapy used. Due to assessing multiple endpoints, clinical evaluation was performed after a minimum of 6 months to a maximum of 12 months after PVI. This time is necessary, among other things, for full healing of damaged tissue after PVI with RF energy. On the other hand, it was necessary due to the technical requirements of 7-day Holter electrocardiogram (ECG) monitoring in each patient and other examinations resulting from the multi-endpoint study design.

On admission, we collected from each subject a detailed medical history that included the current course of the disease, the main symptoms (assessed with the EHRA classification), concomitant diseases (including coronary artery disease, type 2 diabetes mellitus, arterial hypertension, hyperlipidemia, peripheral artery disease), a familial history of arrhythmia, current pharmacotherapy (especially compliance with oral anticoagulants) and tobacco smoking. We also collected physical examination parameters: weight, height, body mass index (BMI), and body surface area (BSA). Before the ablation procedure, each patient underwent in-hospital Holter ECG monitoring (24 hours) as well as transthoracic and transesophageal echocardiography.

After a minimum of 6 months of follow-up period transthoracic echocardiography and Holter ECG home monitoring (7 days) were performed in all subjects. Furthermore, medical history, including possible recurrence of arrhythmia and pharmacotherapy was taken.

Holter ECG monitoring

Holter ECG recordings were made using Lifecard CF recorders, and the recordings were assessed using the Del Mar Reynolds Sentinel system (Sentinel, Spacelabs Healthcare, Snoqualmie, WA, US). The registration was made during the day immediately preceding the PVI procedure. Registration after the follow-up period was carried out at least 7 months after the procedure using the 7-day option with ECG recording at home. An episode of AF was considered to be arrhythmia lasting >30 seconds. Two episodes of AF at the same time separated by sinus rhythm lasting <30 seconds were considered as one episode.

Transthoracic and transesophageal echocardiography

On admission, ECG-gated transthoracic and transesophageal echocardiography were performed in all patients. An experienced physician took all of the measurements during sinus rhythm, using the same investigation protocol and techniques to reduce inter- and intra-observer variability. The echocardiography examination was performed using VIVID 7 echocardiographic devices — General Healthcare (Chicago, IL, US) equipment with a 2.5 MHz sector ultrasound transducer for transthoracic and a 2–7 MHz for transesophageal echocardiography. The examination results were stored for further analysis.

Evaluation of LA echocardiographic parameters of morphology and function

The $LA_{diameter}$ was measured in the long-axis (LAX) view while all LA volumes were measured in the four-chamber (4CH) apical view.

Assessed LA passive volumes included:

- Pre-atrial contraction LA volume — $LA\ Vol_{preA}$
- Minimal LA volume — $LA\ Vol_{min}$
- Maximal LA volume — $LA\ Vol_{max}$.

Assessed LA active volumes included:

- LA reservoir volume — $LA\ Vol_{reservoir}$
- LA conduit volume — $LA\ Vol_{conduit}$
- LA passive emptying volume — $LA\ Vol_{passive\ emptying}$
- LA contractile volume — $LA\ Vol_{contractile}$.

Other parameters were calculated from the volumes of passive and active LA:

- LA ejection fraction — LA EF;
- LA expansion index LA — $LA_{expansion\ index}$
- LA active emptying fraction — $LA_{active\ empt\ frac}$;
- LA passive emptying fraction — $LA_{passive\ empt\ frac}$.

Previously recorded echocardiographic images in the DICOM (Digital Imaging and Communications in Medicine) format were analyzed using an external workstation equipped with the EchoPAC PC Dimension software (version 7.1.2 by General Electric Healthcare), enabling semi-automatic deformation analysis.

Grayscale imaging for two-chamber (2CH) and 4CH projections was obtained with a frame rate of 60–80 Hz per second. The line along the endocardium was manually drawn starting at the endocardial border of the mitral ring and along the endocardial-lumen boundary of the LA excluding the pulmonary veins to the opposite side of the mitral ring. An additional epicardium line was automatically generated by the software, creating a region of interest (ROI). After manually adjusting the ROI shape, in both the 4CH and 2CH projections, the software split the LA into six segments and generated longitudinal strain curves. In the curve analysis, point zero was considered to be the beginning of the P-wave timing [15, 16]. During LA systolic phase, segmental and global longitudinal peak LA strains were assessed.

Maximum LA peak longitudinal strain (LA PLS) corresponding to LA segments and maximum LA global PLS (LA PGLS), were measured in the LA contraction phase in 2CH (Figure 1) and 4CH (Figure 2) views:

- Basal for the inferior wall (basal-inferior) — $LA\ PLS_{bas\text{-}inf\ 2CH}$;
- Medial for the inferior wall (medial-inferior) — $LA\ PLS_{med\text{-}inf\ 2CH}$;
- Apical for the inferior wall (apical-inferior) — $LA\ PLS_{api\text{-}inf\ 2CH}$;
- Basal for the anterior wall (basal-anterior) — $LA\ PLS_{bas\text{-}ant\ 2CH}$;
- Medial for the anterior wall (medial-anterior) — $LA\ PLS_{med\text{-}ant\ 2CH}$;
- Apical for the anterior wall (apical-anterior) — $LA\ PLS_{api\text{-}ant\ 2CH}$;
- Global for all segments — $LA\ PGLS_{2CH}$;
- Basal for the lateral wall (basal-lateral) — $LA\ PLS_{bas\text{-}lat\ 4CH}$;

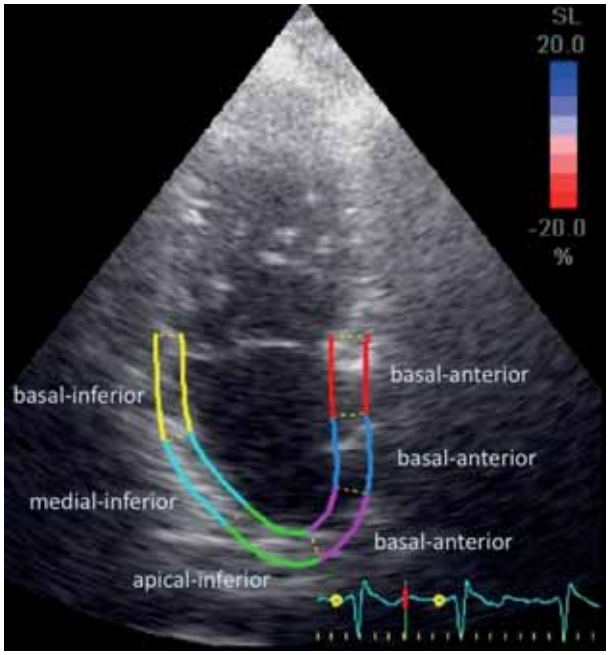

Figure 1. Division of the LA into segments corresponding to strains in the 2CH view

Abbreviations: LA, left atrium; 2CH, two-chamber

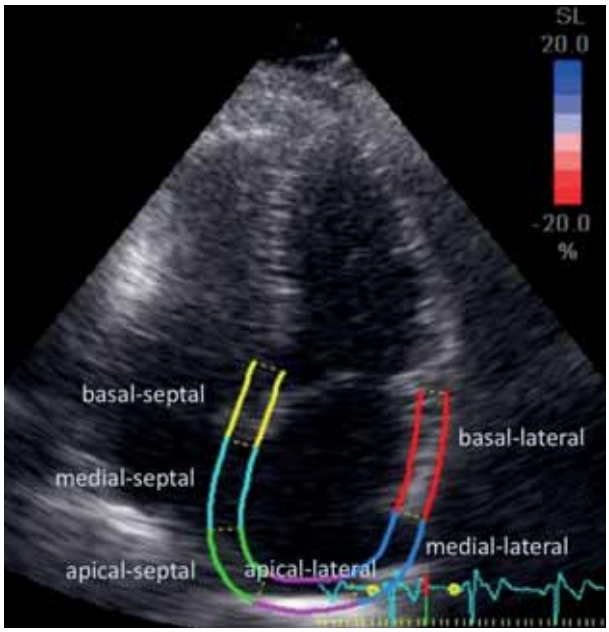

Figure 2. Division of the LA into segments corresponding to strains in 4CH view

Abbreviations: LA, left atrium; 4CH, four-chamber

- Medial for the lateral wall (medial-lateral) — LA $PLS_{med\text{-}lat\ 4CH}$
- Apical for the lateral wall (apical-lateral) — LA $PLS_{api\text{-}lat\ 4CH}$
- Basal for the septal wall (basal-septal) — LA $PLS_{bas\text{-}sept\ 4CH}$
- Medial for the septal wall (medial-septal) — LA $PLS_{med\text{-}sept\ 4CH}$
- Apical for the septal wall (apical-septal) — LA $PLS_{api\text{-}sept\ 4CH}$
- Global for all segments — LA $PGLS_{4CH}$.

In addition, the LA segmental wall strain dispersion in time (ms) (LA synchrony) in the 2CH and 4CH views was assessed and defined as the difference between the earliest and the latest maximum longitudinal LA strains for individual segments.

PVI procedure

At the beginning of the PVI procedure, rotational LA angiography was performed. Then, after a transseptal puncture, 3-dimensional electro-anatomical mapping was performed using the CARTO®3 system (Biosense Webster, Diamond Bar, CA, US). PVI was obtained by RF radiofrequency ablation with a ThermoCool® SmartTouch® SF catheter (Biosense Webster, Diamond Bar, CA, US). The procedure was performed using a Lasso electrode (Biosense Webster, Diamond Bar, CA, US) or Achieve (Medtronic, MN, US).

Immediately after the transseptal puncture, all patients received continuous infusion of unfractionated heparin (2000 IU/h) (preceded by an intravenous bolus of unfractionated heparin [100 IU/kg]) to obtain activated clotting time (ACT) above 300 seconds.

Statistical analysis

Statistical analysis was performed using STATISTICA software (version 13.1 PL). All data were collected in a Microsoft Office Excel spreadsheet (version 2016 PL). A *P*-value of less than 0.05 was considered to indicate statistical significance. Results for continuous variables were presented as mean with standard deviation for normal distributions or median with interquartile range (IQR) for non-normal distributions. The normality of the distribution of continuous variables was verified with the Shapiro-Wilk test. Ordinal variables in the Tables are shown as absolute numbers and percentages. Depending on the distribution of variables, for pre- and post-PVI comparisons, parametric (t-test for dependent variables) and non-parametric (Wilcoxon matched-pairs signed-rank test) tests for dependent variables were used. For separate groups (effective/ineffective PVI) parametric (t-test) and non-parametric (Mann-Whitney U test) tests for independent variables were used.

RESULTS

The study group characteristics

The median (IQR) follow-up was 9.9 (7.6–11.8) months. After the follow-up period, the effectiveness of the PVI procedure (sinus rhythm maintenance confirmed by 7-day Holter ECG examination) was confirmed in 53.8% of patients. Table 1 presents the basic parameters characterizing the

Table 1. Characteristics of the study group

	Study group (n = 80)
Demographics	
Age, year, median (IQR)	58 (50–63)
Male sex, n (%)	50 (62.5)
AF duration	
0–5 years, n (%)	37 (46)
5–10 years, n (%)	27 (34)
>10 years, n (%)	16 (20)
Baseline biometric evaluation, mean (SD)	
Height, cm	174.2 (9.2)
Weight, kg	88.3 (15.2)
BMI, kg/m^2	29.1 (4.25)
BSA, m^2	2.06 (0.22)
Functional class and risk scale	
EHRA, score, median (IQR)	3 (2–3)
CHA_2DS_2-VASc score, median (IQR)	2 (1–2.5)
Co-morbidities, n (%)	
Coronary artery disease	15 (19)
Arterial hypertension	56 (70)
Diabetes mellitus	15 (19)
Hyperlipidemia	55 (69)
Obesity	27 (34)
Tobacco smoking, n (%)	
Never	46 (57.5)
In the past	22 (27.5)
Active	12 (15)

Abbreviations: AF, atrial fibrillation; BMI, body mass index; BSA, body mass area

Table 2. LA echocardiographic parameters before PVI procedure and after the observation period

	Parameters	Before (n = 66)	After PVI (n = 66)	*P*-value
LA morphological parameters	$LA_{diameter}$, mm	39.6	—	—
	$LA\ Vol_{preA}$, ml	53 (35–64)	51 (37–66)	0.76
	$LA\ Vol_{min}$, ml	36.5 (25–49)	33 (26–51)	0.57
	$LA\ Vol_{max}$, ml	74.5 (60–103)	72.5 (62–88)	0.15
	$LAVI_{max}$, ml/m^2	36.3 (29.4–49.5)	35.7 (30–45.4)	0.16
	$LA\ Vol_{reservoir}$, ml	38 (32–49)	37 (32–44)	0.21
	$LA\ Vol_{conduit}$, ml	25.4 (15.1)	30.1 (13.3)	0.01
	$LA\ Vol_{passive\ emptying}$, ml	21 (16–35)	20 (15–26)	0.05
	$LA\ Vol_{contractile}$, ml	14.5 (8–20)	16 (11–22)	0.56
	LAEF, %	52 (46–58)	54 (44–59)	0.33
	$LA_{expansion\ index}$	1.17 (0.48)	1.15 (0.46)	0.75
	$LA_{active\ empt\ frac}$, %	31 (17–38)	33 (26–39)	0.63
	$LA_{passive\ empt\ frac}$, %	32 (13)	30 (12)	0.3
LA strains and LA wall strain dispersion	$LA\ PLS_{bas-inf\ 2CH}$, %	–17.5 (–21.8 to –13.4)	–19.4 (–22.3 to –13)	0.32
	$LA\ PLS_{med-inf\ 2CH}$, %	–15.2 (–18 to –11.8)	–14.6 (–18.3 to –11.5)	0.64
	$LA\ PLS_{api-inf\ 2CH}$, %	–10.9 (–14.3 to –6.4)	–10.1 (–12.6 to –6.8)	0.25
	$LA\ PLS_{bas-ant\ 2CH}$, %	–14.6 (–19.5 to –9.8)	–14.7 (–19.4 to –10.3)	0.97
	$LA\ PLS_{med-ant\ 2CH}$, %	–11.6 (–17.1 to –7)	–13.1 (–16.7 to –8.6)	0.83
	$LA\ PLS_{api-ant\ 2CH}$, %	–10.7 (–16.3 to –6.3)	–10.2 (–14.1 to –6.1)	0.12
	$LA\ PGLS_{2CH}$, %	–12.8 (4.7)	–12.4 (3.8)	0.53
	LA wall strain $dispersion_{2CH}$, ms	98.5 (45–182)	97 (63–164)	0.17
	$LA\ PLS_{bas-lat\ 4CH}$, %	–14.2 (–19 to –9.1)	–16.9 (–19.7 to –12.4)	0.26
	$LA\ PLS_{med-lat\ 4CH}$, %	–11.6 (–16.6 to –8.6)	–12.6 (–17.3 to –9.8)	0.8
	$LA\ PLS_{api-lat\ 4CH}$, %	–10.1 (–14.2 to –5.6)	–10.7 (–14.2 to –7)	0.92
	$LA\ PLS_{bas-sept\ 4CH}$, %	–14.1 (–18 to –10.6)	–16.8 (–19.9 to –14.5)	0.5
	$LA\ PLS_{med-sept\ 4CH}$, %	–14.7 (–18.1 to –9.9)	–15.6 (–19 to –11.8)	0.87
	$LA\ PLS_{api-sept\ 4CH}$, %	–11.6 (–16.3 to –7)	–12.4 (–17.9 to –7)	0.57
	$LA\ PGLS_{4CH}$, %	–12 (4.8)	–12.7 (4.3)	0.37
	LA wall strain $dispersion_{4CH}$, ms	101.5 (44–177)	97 (49–165.5)	0.35

Results are given as the mean with standard deviation (SD) for normal distributions or the median with interquartile range (IQR) for non-normal distributions

Abbreviations: api-ant, apical-anterior; api-inf, apical-inferior; api-lat, apical-lateral; api-sept, apical-septal; bas-ant, basal-anterior; bas-inf, basal-inferior; bas-lat, basal-lateral; bas-sept, basal-septal; empt frac, emptying fraction; LA, left atrium; PGLS, maximum left atrial peak global longitudinal strain; PLS, maximum left atrial peak longitudinal strain; max, maximal; min, minimal; med-ant, medial-anterior; med-inf, medial-inferior; med-lat, medial-basal; med-sept, medial-septal; RF, radiofrequency pulmonary vein isolation; preA, preatrial; PVI, pulmonary vein isolation with RF energy; TTE, transthoracic echocardiography; Vol, volume; 2CH, two-chamber view; 4CH, four-chamber view

study group. Patent foramen ovale was found in 23 patients (28.2%) while patients with LA appendage thrombus were excluded from the study.

Echocardiographic evaluation before the PVI procedure and after the follow-up period

The analyzed LA echocardiographic parameters are summarized in Table 2.

After the follow-up period, patients had statistically significantly higher mean $LA\ Vol_{conduit}$. Moreover, a trend towards the difference in the $LA\ Vol_{passive\ emptying}$ parameter was shown — after the PVI procedure, lower values were obtained as compared to the initial results ($P = 0.05$).

Additionally, in the study group, a difference in left ventricular end-systolic diameter (LV ESD) was demonstrated — lower LV ESD was observed before the PVI procedure compared to the results after the follow-up period (30 [28–33] vs. 32 [29–34]; $P = 0.02$). There were no statistically significant differences between LV ejection fraction (LVEF), other LV dimensions and volumes, as well as LV stroke volume initially and after the follow-up period.

LA echocardiographic parameters and the effectiveness of the PVI procedure

An analysis of the relationship between the pre- and post-PVI procedure echocardiographic parameters and the effectiveness of the procedure (patients with and without AF recurrence after the follow-up period) was performed (Tables 3 and 4).

Patients after successful PVI procedure were characterized by statistically significant higher initial segmental deformations: $LAPLS_{bas-inf\ 2CH}$ and $LAPLS_{api-sept\ 4CH}$, as well as a higher initial LA wall strain dispersion in time in the 2CH view (Table 3). The analysis performed after the follow-up period showed lower $LA\ Vol_{min}$, $LA\ Vol_{max}$, and $LAVI_{max}$, and higher LA EF and $LA_{expansion\ index}$ in patients who underwent successful PVI treatment (Table 4).

DISCUSSION

This article reports partial results of a single-center, non-randomized, prospective study of a population consisting of relatively young patients with a history of paroxysmal, symptomatic AF, without significant structural heart disease, and with a low score obtained in the CHA_2DS_2-VASc

Table 3. Initial LA echocardiographic parameters depending on the effectiveness of the PVI procedure

LA echocardiographic parameters before PVI procedure	Effective PVI (n = 43)	Ineffective PVI (n = 35)	*P*-value
$LA_{diameter,}$ mm	39.4 (4.4)	39.7 (4.1)	0.78
LA $Vol_{preA,}$ ml	51.6 (17.3)	58.2 (24.7)	0.26
LA $Vol_{min,}$ ml	33 (24–48)	40 (30–55)	0.18
LA $Vol_{max,}$ ml	70 (57–96)	82 (67–104)	0.36
$LAVI_{max,}$ ml/m^2	36.9 (9.8)	41.9 (13.6)	0.07
LA $Vol_{reservoir,}$ ml	40.6 (12.9)	39.9 (11.4)	0.83
LA $Vol_{conduit,}$ ml	28 (12–39)	22 (16–32)	0.37
LA $Vol_{passive\ emptying,}$ ml	24 (16–37)	21 (17–34)	1
LA $Vol_{contractile,}$ ml	14.9 (9.2)	14.7 (8.1)	0.95
LA EF, %	54 (47–60)	49 (40–60)	0.15
$LA_{expansion\ index}$	1.16 (0.9–1.5)	0.98 (0.8–1.3)	0.15
$LA_{active\ empt\ frac,}$ %	33 (17–40)	24 (20–40)	0.45
$LA_{passive\ empt\ frac,}$ %	33 (10)	31 (10)	0.6
LA $PLS_{bas–inf\ 2CH,}$ %	–19.4 (4.7)	–15.8 (6.2)	0.02
LA $PLS_{med–inf\ 2CH,}$ %	–15.6 (4.7)	–13 (5.6)	0.06
LA $PLS_{api–inf\ 2CH,}$ %	–10.5 (–14.6– 6.1)	–11.4 (–13.9 to –7)	0.8
LA $PLS_{bas–ant\ 2CH,}$ %	–14.6 (–19.4 to –10.6)	–15.3 (–19.5– 8)	0.8
LA $PLS_{med–ant\ 2CH,}$ %	–11.4 (–17.7 to –8.6)	–11.8 (–15.4 to –6.6)	0.75
LA $PLS_{api–ant\ 2CH,}$ %	–11.7 (7.9)	–11.2 (6)	0.76
LA $PGLS_{2CH,}$ %	–12.4 (5)	–11.8 (4.6)	0.59
LA wall strain $dispersion_{2CH,}$ ms	115 (50–200)	63 (38–147)	0.02
LA $PLS_{bas–lat\ 4CH,}$ %	–13.8 (–18.4 to –8.9)	–14.9 (–21.7 to –9.2)	0.62
LA $PLS_{med–lat\ 4CH,}$ %	–11.6 (–16 to –8.4)	–13.1 (–17 to –9.6)	0.62
LA $PLS_{api–lat\ 4CH,}$ %	–10.3 (–14 to –5.7)	–10.1 (–17.3 to –5.8)	0.78
LA $PLS_{bas–sept\ 4CH,}$ %	–15.5 (5.6)	–14 (6.6)	0.37
LA $PLS_{med–sept\ 4CH,}$ %	–15.9 (–17.9 to –12)	–11.1 (–18.6 to –7.7)	0.05
LA $PLS_{api–sept\ 4CH,}$ %	–13.4 (–16.3 to –9.6)	–8.6 (–13.3 to –6)	0.02
LA $PGLS_{4CH,}$ %	–12 (4.3)	–11 (5.4)	0.45
LA wall strain $dispersion_{4CH,}$ ms	86.5 (32.5–171)	133 (59–179)	0.34

Results are given as the mean with standard deviation (SD) for normal distributions or the median with interquartile range (IQR) for non-normal distributions

Abbreviations: see Table 2

classification who were qualified for their first PVI procedure with RF energy.

In the whole group, after the follow-up period, patients presented statistically significantly higher mean LA $Vol_{conduit}$. In the analysis of LA echocardiographic parameters after the follow-up period, patients with no AF recurrences had statistically significant lower LA volumes (minimal, maximal, and maximal indexed), higher LA ejection fraction and LA expansion index, when compared to the patients after ineffective PVI treatment. Patients who maintained sinus rhythm after the PVI procedure were characterized by statistically significant higher initial segmental strains: LA $PLS_{bas-inf}$ and $PLS_{api-sept}$, as well as higher LA wall strain dispersion in time in the 2CH projection.

In recent years, there has been a growing interest in the use of novel techniques for assessing function of heart chambers in clinical practice, in this case, LA strains. More and more information about the 2D LA PGLS can be found in the available literature [11, 17–19]. However, the assessment of deformation of individual LA segments may provide valuable information about the risk of arrhythmia, a detailed assessment of potential wall fibrosis/weakening that takes into account LA symmetric and asymmetric remodeling, an additional assessment of cardioembolic risk, or an evaluation of the effectiveness in a time of a sinus rhythm recovery procedures. In this study, in the analysis of the pre-procedural LA PLS, both global and segmental, two initial segmental strains that had a statistically significant impact on the effectiveness after the follow-up period were identified. The lower (better) values for pre-procedural LA $PLS_{bas-inf}$ assessed in the 2CH view and LA $PLS_{api-sept}$ in the 4CH view were associated with the maintenance of a sinus rhythm after follow-up. Moreover, statistical significance was obtained for the LA wall strain dispersion in time — initially, greater LA dyssynchrony was observed in patients in whom PVI treatment turned out to be effective in time. These results seem to be random.

PVI procedure is currently considered to be the most effective therapy to restore sinus rhythm in AF patients. In this study, patients who maintained sinus rhythm after a successful first-time PVI procedure were characterized by LA-positive remodeling. In the study group, after the follow-up period, a significant reduction in the LA volumes — minimum, maximum, and maximum indexed to BSA – was observed. These results are consistent with the published meta-analysis by Augustine Njoku et al. [12] of twenty-one studies (3822 subjects), where patients with AF recurrence after PVI treatment had a higher mean LA

Table 4. LA echocardiographic parameters after follow-up period depending on the effectiveness of the PVI procedure

LA echocardiographic parameters after follow–up period	Effective PVI (n = 43)	Ineffective PVI (n = 35)	*P*-value
LA Vol_{preA}, ml	47.5 (37–57)	55 (37–78)	0.27
LA Vol_{min}, ml	30 (25–43)	45 (27–61)	0.02
LA Vol_{max}, ml	72.6 (18.8)	84.1 (20.8)	0.02
$LAVI_{max}$, ml/m^2	34.5 (7)	41.4 (13)	<0.001
LA $Vol_{reservoir}$, ml	38 (33–46)	35.5 (28.5–41)	0.22
LA $Vol_{conduit}$, ml	29.9 (14.6)	31.3 (13.5)	0.7
LA $Vol_{passive\ emptying}$, ml	22.2 (9.8)	19.1 (6.4)	0.14
LA $Vol_{contractile}$, ml	16 (11–19)	14 (11–24)	0.97
LA EF, %	57 (49–60)	46 (38–56)	0.002
$LA_{expansion\ index}$	1.3 (0.4)	0.9 (0.45)	0.004
$LA_{active\ empt\ frac}$, %	30 (10)	30 (10)	0.4
$LA_{passive\ empt\ frac}$, %	30 (13)	30 (10)	0.14
$LA_{passive\ empt\ frac}$, %	33 (10)	31 (10)	0.6
LA $PLS_{bas–inf\ 2CH}$, %	–19.7 (–23.5 to –12.5)	–19.4 (–21.8 to –15.5)	0.84
LA $PLS_{med–inf\ 2CH}$, %	–15.6 (–18.4 to –11.5)	–14.1 (–17.5 to –11.2)	0.62
LA $PLS_{api–inf\ 2CH}$, %	–10.1 (–12.5 to –4.8)	–9.7 (–12.7 to –7.9)	0.47
LA $PLS_{bas–ant\ 2CH}$, %	–15.6 (–20.1 to –11.1)	–12.9 (–18.4 to –9.6)	0.41
LA $PLS_{med–ant\ 2CH}$, %	–13.6 (5.3)	–12.1 (5.6)	0.3
LA $PLS_{api–ant\ 2CH}$, %	–11 (–13.3 to –7.2)	–9.1 (–15.5 to –6)	0.94
LA $PGLS_{2CH}$, %	–12.2 (3.5)	–12.1 (4)	0.3
LA wall strain $dispersion_{2CH}$, ms	100 (56–154)	89 (67–198)	0.76
LA $PLS_{bas–lat\ 4CH}$, %	–17.2 (–19.7 to –11.5)	–16.4 (–19.7 to –13.7)	0.36
LA $PLS_{med–lat\ 4CH}$, %	–12.4 (–19.7 to –9.8)	–13.2 (–16.9 to –8.6)	0.87
LA $PLS_{api–lat\ 4CH}$, %	–10.3 (–16.6 to –6.8)	–11.5 (–12.9 to –7.1)	0.85
LA $PLS_{bas–sept\ 4CH}$, %	–16.3 (–19.1 to –13.6)	–18 (–21.4 to –15.6)	0.07
LA $PLS_{med–sept\ 4CH}$, %	–15.3 (–18 to –10.8)	–16.1 (–20 to –12)	0.29
$PLS_{api–sept\ 4CH}$, %	–12.8 (–17.7 to –7.4)	–12.3 (–18.2 to –6.2)	0.75
LA $PGLS_{4CH}$, %	–12.6 (4.6)	–13.6 (4.8)	0.4
LA wall strain $dispersion_{4CH}$, ms	105 (70–167)	87 (32–164)	0.38

Results are given as the mean with standard deviation (SD) for normal distributions or the median with interquartile range (IQR) for non-normal distributions

Abbreviations: see Table 2

volume/LA volume indexed to BSA when compared to patients without AF recurrence.

On the other hand, in our study no statistically significant difference in the $LAVI_{max}$ was found, assessed in the whole group before and after PVI treatment, without taking into account the effectiveness of the procedure. That parameter is commonly considered to be prognostic for AF recurrences [12]. However, in the available literature, there is a cut-off point of $LAVI_{max}$ <34.4 ml/m^2 that is associated with the best AF ablation outcome [20, 21], while Shin et al. [22] found that $LAVI_{max}$ of 34 ml/m^2 showed sensitivity of 70% and specificity of 91% in predicting AF recurrence. In the current study patients in whom PVI proved to be effective in the follow-up period had a lower mean value of the $LAVI_{max}$ parameter when compared to the patients with AF recurrences – assessed before the PVI procedure (the mean [SD] 36.9 [9.8] ml vs. 41.9 [13.6] ml; trend towards statistical significance — *P*=0.07) and after the PVI procedure (34.5 [7] ml vs. 41.4 [13] ml; *P* <0.001).

At the same time, in patients without post-PVI AF recurrence, an improvement in LA function measured by an increase in $LA_{expansion\ index}$ and thus higher LA EF were observed. A lower median of LA $Vol_{passive\ emptying}$ after PVI (trend towards significance) was also noted, compared to the results obtained before the procedure. This demonstrates positive LA remodeling in these patients, which, in turn, may favor the continued maintenance of sinus rhythm in the future. It is puzzling that there is no coincident improvement in LA function as measured by the evaluation of LA global and segmental strains and LA wall strain synchrony. It should be noted, however, that the study population included selected, relatively young patients with an initially non-sustained form of atrial arrhythmia, not burdened with significant cardiovascular diseases. Perhaps they did not have significant LA dysfunction at baseline, and the lack of statistical variability in the post-procedural evaluation should be treated as a success, together with the absence of complications related to the procedure itself, e.g. narrowing of the pulmonary veins or complications following a transseptal puncture.

There are several studies indicating that LA strain has a higher predictive value than LA size obtained in conventional echocardiography [13, 23]. Data published so far, strongly suggest that the longitudinal 2D strains of LA may be useful in predicting AF recurrence after PVI procedures [11, 17, 23–26]. 2D STE analysis enables detection of decreased LA reservoir function in patients with paroxysmal AF even before changes in LA volume

are detected [14], which may be potentially associated with greater sensitivity of the method in detecting and predicting AF recurrence. Mirza et al. [23] showed that regardless of LA enlargement, pre-procedural strain of the LA lateral wall can be considered an independent determinant of AF recurrence after PVI. However, the effectiveness of the treatment was assessed 18 months after the procedure, using TomTec software, which differs significantly from the methodology presented in the current study. On the other hand, in the work of Hammerstingl et al. [13], independent predictors of AF recurrence after the PVI procedure were global LA strains obtained in the 2CH and 4CH views and regional LA septal wall strain. Those researchers also used TomTec software to analyze STE in 76 patients with paroxysmal and 27 patients with persistent AF, as well as in a 30-person control group. Similarly, as in our study, the effectiveness of the PVI procedure was assessed after a minimum of 6 months of follow-up.

Recently, there has been an increase in data on new cardiac visualization techniques assessing LA volumes and strains using 3D techniques. What is more, it turns out that these techniques are potentially more accurate in patients with AF and surpass the 2D visualizations widely used so far [27–29]. For example, in a group of 348 patients with symptomatic paroxysmal or persistent AF, Montserrat et al. [30] showed that none of the echocardiographic parameters considered, including LAVI, was associated with AF recurrence after the PVI procedure. Only volumetric assessment of LA with 3D rotational angiography showed in a multivariate analysis that LAVI is the only independent predictor for AF recurrence. Measuring LA volume with this method may be superior to transthoracic echocardiography (TTE) assessment and AF history in predicting arrhythmia recurrence after PVI. There are also reports showing that LA strain determined by 3D STE is a novel and better predictor of AF recurrence after PVI than LA strain determined by 2D STE or other known predictors [27]. These new 3D techniques were not evaluated in the present study, and though less common in routine echocardiographic assessment, they may help to assess more accurately LA morphology and function.

One should certainly bear in mind that there is no single parameter to clearly define the possibility of arrhythmia recurrence after PVI. Echocardiographic assessment should be complex, using various available imaging techniques and potentially useful parameters to assess the morphology and function of the heart chambers, which may help improve prediction of the success of rhythm-control strategy in AF [31].

Limitations

The analyzed group was relatively small, and the statistical power of this study is limited. The conclusions should be used in relation to the population of relatively young patients with a history of paroxysmal, symptomatic AF, without significant structural heart disease, and with a low score obtained in the CHA_2DS_2-Vasc classification who underwent their first-time PVI procedure with RF energy. A larger study population could influence other relationships, especially in the case of parameters where only a trend toward statistical significance was achieved. On the other hand, the size of the group in the presented study did not differ significantly from other studies on related topics. An additional study limitation is associated with the absence of a control group. At the time of the study, no software was available to evaluate LA strains, and there were no guidelines for evaluating LA strains in patients during AF. Additionally, a significant limitation of the presented work is the lack of LV deformation analysis, all the more so since the LV EF change significantly influenced the effectiveness of the PVI procedure.

We are aware of data gaps. Around 20% of the first described population was not included in some of the analyses, which reduces the size of the analyzed population. We showed population numbers that are slightly different from the general population numbers because in each major test missing data were eliminated casewise.

CONCLUSIONS

Some echocardiographic parameters related to LA morphology improve after successful PVI treatment, which may be associated with positive LA remodeling. LA strains and wall strain dispersion in time are not related to LA remodeling after a successful PVI procedure.

The baseline, standard and novel, LA echocardiographic parameters cannot be used for remote evaluation of the effectiveness of the PVI procedure. Further research is needed in this area, especially taking into account the limitations of our study.

Article information

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Stepwise relationship between delay in percutaneous coronary intervention and long-term mortality in patients with non-ST-segment elevation myocardial infarction

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ABSTRACT

Background: Current guidelines recommend coronary catheterization in patients with non-ST-segment elevation myocardial infarction (NSTEMI) within 24 hours of hospital admission. However, whether there is a stepwise relationship between the time to percutaneous coronary intervention (PCI) and long-term mortality in patients with NSTEMI treated invasively within 24 hours of admission has not been established yet.

Aims: The study aimed to evaluate the association between door-to-PCI time and all-cause mortality at 12 and 36 months in NSTEMI patients presenting directly to a PCI-capable center who underwent PCI within the first 24 hours of hospitalization.

Methods: We analyzed data of patients hospitalized for NSTEMI between 2007–2019, included in the nationwide registry of acute coronary syndromes. Patients were stratified into twelve groups based on 2-hour intervals of door-to-PCI time. The mortality rates of patients within those groups were adjusted for 33 confounding variables by the propensity score weighting method using overlap weights.

Results: A total of 37 589 patients were included in the study. The median age of included patients was 66.7 (interquartile range [IQR], 59.0–75.8) years; 66.7% were male, and the median GRACE (Global Registry of Acute Coronary Events) score was 115 (98–133). There were increased 12-month and 36-month mortality rates in consecutive groups of patients stratified by 2-hour door-to-PCI time intervals. After adjustment for patient characteristics, there was a significant positive correlation between the time to PCI and the mortality rates ($r_s = 0.61$; $P = 0.04$ and $r_s = 0.65$; $P = 0.02$ for 12-month and 36-month mortality, respectively).

Conclusions: The longer the door-to-PCI time, the higher were 12-month and 36-month all-cause mortality rates in NSTEMI patients.

Key words: coronary revascularization, early invasive strategy, non-ST-segment elevation myocardial infarction, percutaneous coronary intervention

WHAT'S NEW?

According to the most recent guidelines on the management of acute coronary syndromes without ST-segment elevation, in non-very high-risk patients with non-ST-segment elevation myocardial infarction (NSTEMI), coronary angiography with the intent to perform revascularization should be performed within 24 hours of hospital admission. However, since the previous studies used different, somewhat arbitrary, definitions of very early invasive strategies, there are few data on whether there is a stepwise relationship between the time to percutaneous coronary intervention (PCI) and the long-term mortality rate in patients with NSTEMI undergoing coronary revascularization within 24 hours of admission. Therefore, we aimed to evaluate the relationship between door-to-PCI time and long-term mortality in 37 589 patients with NSTEMI, included in the nationwide registry of acute coronary syndromes. After adjusting for 33 clinically relevant variables, we found that the longer the door-to-PCI time, the higher were 12-month and 36-month all-cause mortality rates.

INTRODUCTION

The routine invasive strategy has been shown to be superior to the optimal medical management strategy in patients with non-ST-segment elevation myocardial infarction (NSTEMI). However, the optimal timing of coronary revascularization has not been established yet. The current guidelines on non-ST-segment elevation acute coronary syndromes (NSTE-ACS) recommend coronary angiography with the intent to perform revascularization within 24 hours from hospital admission in NSTEMI patients, except for very-high risk patients, who should undergo coronary catheterization within 2 hours [1].

Currently, no evidence supports the routine immediate invasive strategy in all patients with NSTE-ACS. Unlike NSTEMI, unstable angina does not lead directly to myocardial injury; therefore, the benefits of very early revascularization might be less pronounced in those patients [2]. Although it is pathophysiologically plausible that more rapid (within 24 hours) revascularization in NSTEMI patients is associated with a mortality rate reduction, it has not been proven in randomized clinical trials [3]. However, in the largest randomized clinical trials comparing different timing strategies in NSTE-ACS patients, the calculation of the time to coronary angiography was based on the randomization time, complicating the interpretation of the results [1]. Moreover, in most of these studies, the proportion of patients who underwent coronary revascularization was lower than 70% [4, 5].

This study aimed to evaluate whether there is a stepwise association between door-to-PCI time and long-term mortality in a cohort of NSTEMI patients who were admitted directly to a PCI-capable center and underwent PCI within 24 hours of admission.

METHODS

Patients

We analyzed the data of patients admitted to the hospital for NSTEMI between July 2007 and July 2019, included in a nationwide, prospective registry of acute coronary syndromes (Polish Registry of Acute Coronary Syndromes; PL-ACS). More details regarding PL-ACS have been described previously [6–10]. Briefly, PL-ACS is a clinical registry established in 2003, which was a joint effort of the Silesian Center for Heart Diseases in Zabrze and the Polish Ministry of Health. The goal of the PL-ACS registry is to collect data about clinical characteristics, treatment modalities, and outcomes of patients with acute myocardial infarction or unstable angina in Poland. Data are entered into the database by the attending physician via a web form.

In the current analysis, NSTEMI patients who arrived directly at the PCI-capable center themselves or in an ambulance, and underwent PCI during the index hospitalization, were considered. The exclusion criteria included out-of-hospital cardiac arrest before admission, pulmonary edema or cardiogenic shock on admission, or missing data on these variables, as well as pain-to-admission time longer than 72 hours and admission-to-PCI time longer than 24 hours. Included patients were assigned into twelve groups based on 2-hour intervals of door-to-PCI time. Definitions used in our study are presented in the Supplementary Materials, *Definitions*.

The outcome of interest and follow-up

The outcome of interest in our study was all-cause mortality analyzed at 12 and 36 months. Vital status and exact death dates were obtained from the National Health Fund, the only payer for healthcare services financed from public funds in Poland. Follow-up data were available for 37 585 (99.99%) patients.

Statistical analysis

Continuous variables were presented as median and interquartile range. Categorical variables were presented as percentages. Door-to-PCI time in patients stratified by year of admission was compared using Jonckheere's trend test. The mortality rates in the 12 groups of patients who underwent PCI within 24 hours of hospital admission, stratified by 2-hour intervals, were presented as crude mortality rates and adjusted by the propensity score weighting method using overlap weights to reduce indication bias. Overlap weighting is a novel statistical method based on the propensity score to adjust for differences in characteristics between analyzed groups by assigning, to each patient, weights that are proportional to the probability of that

patient belonging to the opposite treatment group [11, 12]. The propensity scores were obtained using the logistic regression model, which included 33 clinically relevant baseline characteristic variables that might have influenced the decision about catheterization timing. The complete list of these variables is presented in Supplementary material, *Table S1*. Before developing the propensity score model, missing data were imputed using the k-nearest neighbors algorithm. The correlations between the 12-month and 36-month unadjusted and adjusted (by the propensity score weighting method using overlap weights) mortality rates and consecutive 2-hour interval groups (as an ordinal variable) were analyzed using Spearman's rank correlation coefficient and presented graphically using LOESS smoothing function. The level of statistical significance was P <0.05 (two-tailed). R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) and PSweight: An R Package for Propensity Score Weighting Analysis, as well as Statistica version 13.3 (TIBCO Software, CA, US), were applied for computational analyses.

RESULTS

A total of 37 589 NSTEMI patients, who underwent PCI within the first 24 hours of admission, were included. The frequencies and percentages of patients in the groups stratified by 2-hour intervals of door-to-PCI time are shown in Figure 1. The median door-to-PCI time was 2.7 (1.0–7.3) hours and was increasing during the study period in patients stratified by year of admission ($P_{\text{for trend}}$ <0.001) (Figure 2). The median age of patients was 66.7 (IQR, 59.0–75.8), and two-thirds were male (66.7%). The median GRACE (Global Registry of Acute Coronary Events) score was 115 (98–133). Fifty-one percent of patients had multivessel disease on coronary angiography, and in 2% of patients, the left main was an in farct-related artery. Coronary artery bypass grafting (CABG) was performed in 1.0% of patients, and 2.5% were referred for CABG after discharge. The baseline clinical, angiographic, and procedural characteristics and treatment prescribed on hospital discharge are shown in Table 1. The in-hospital mortality rate in the whole study group was 1.7%. The unadjusted 12-month mortality rate varied between 7.1% to 9.2% in the groups of patients who underwent PCI between 2–4 hours and 16–18 hours after admission, respectively (Figure 3A). The minimal unadjusted 36-month mortality rate was observed in the group who underwent PCI between 2–4 hours after admission, and the maximal mortality rate was in patients who received revascularization within 20–22 hours from admission (13.6% and 18.7%, respectively; Figure 4A). After adjustment for clinical and angiographic characteristics, there was a significant positive correlation between consecutive 2-hour-intervals of door-to-PCI time and the 12-month (r_s = 0.61; P = 0.04) as well as 36-month (r_s = 0.65; P = 0.02) mortality rates (Figures 3B and 4B).

DISCUSSION

Our study showed that longer door-to-PCI time in NSTEMI patients who underwent PCI within the first 24 hours from admission was associated with increased adjusted 12-month and 36-month mortality rates. Contrary to

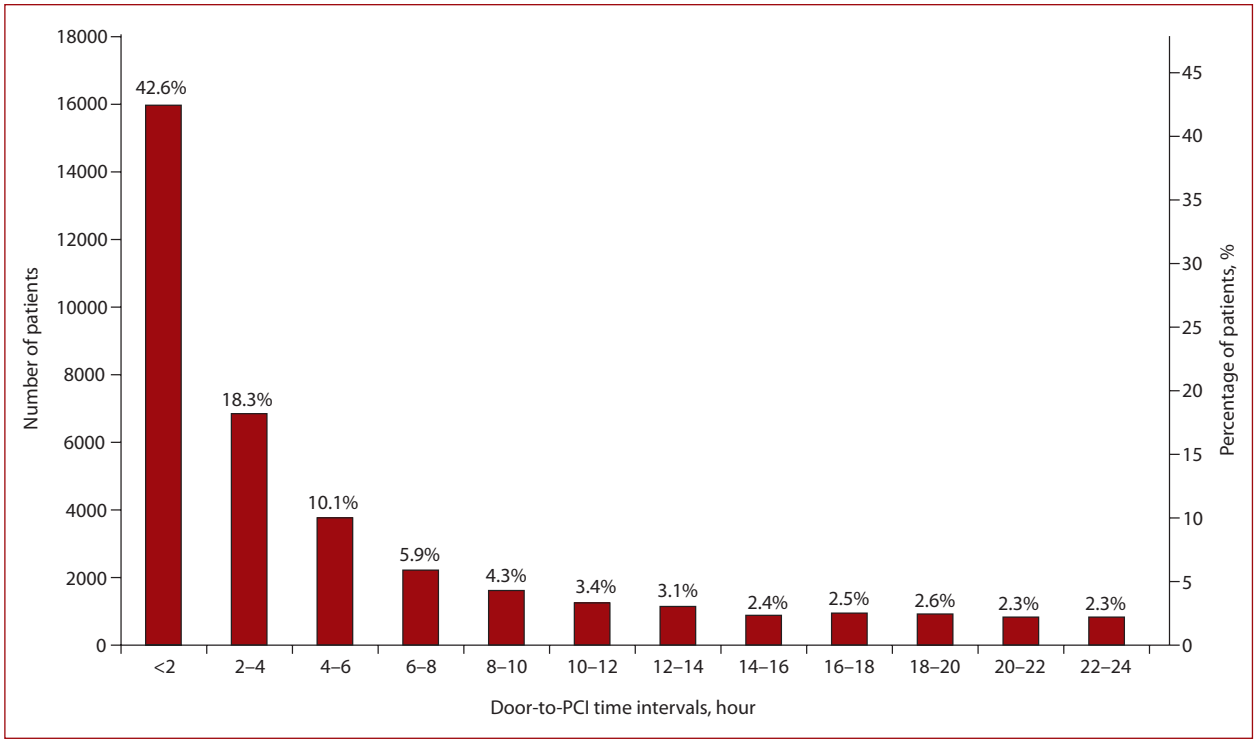

Figure 1. Frequencies and percentages of patients stratified by the door-to-PCI time (hours)

Abbreviation: PCI, percutaneous coronary intervention

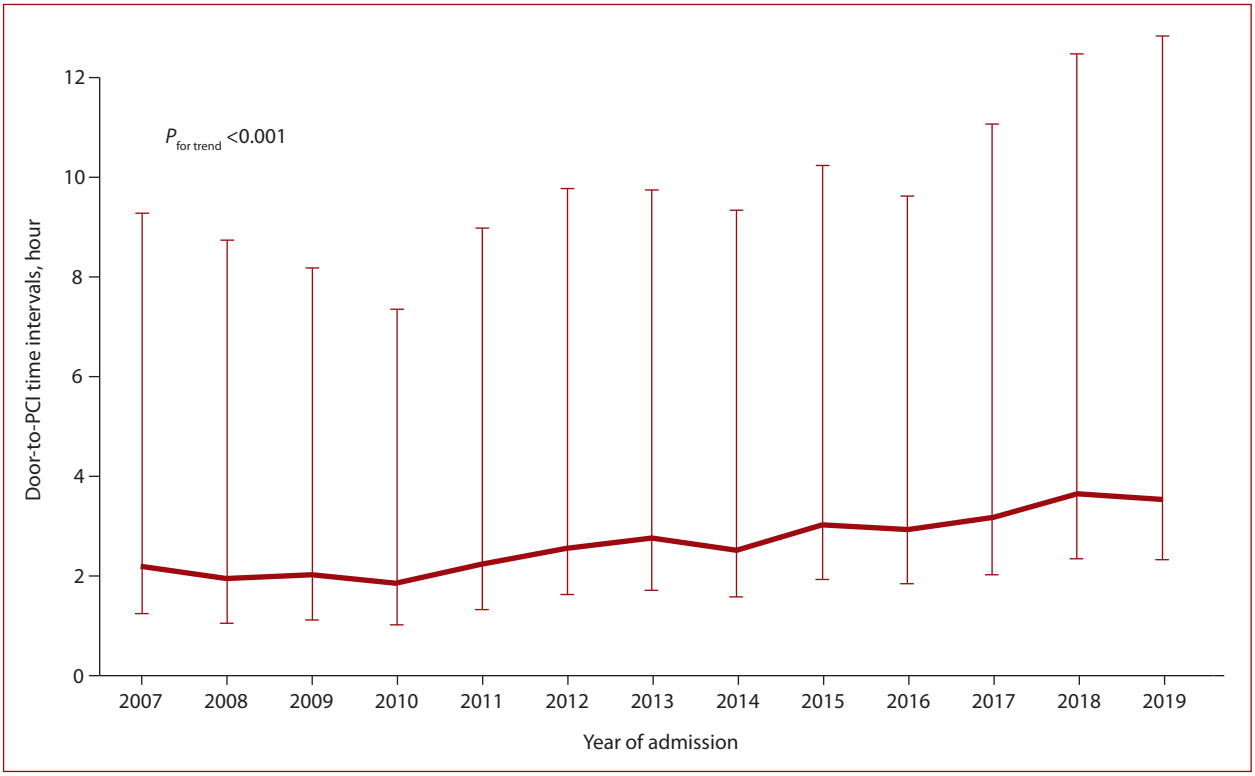

Figure 2. Median (interquartile range) door-to-PCI time (hours) according to a year of admission
Abbreviation: see Figure 1

previous studies, which used different, mostly arbitrarily selected, cut-offs for defining "very early" invasive strategies [13], which limited the clinical applicability of these findings, we showed that increased door-to-PCI time was proportionally associated with increased mortality, i.e., the longer the in-hospital delay in PCI, the higher the mortality rate.

To date, only a few large randomized controlled trials aimed to compare the strategy of immediate or very early invasive coronary angiography with standard treatment in non-high-risk patients with NSTE-ACS. The VERDICT trial (Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography) showed that very early invasive coronary evaluation (within 12 hours) does not improve primary outcome compared with the deferred strategy (within 48 to 72 hours), except for patients with the highest risk according to the GRACE risk score (>140) [5]. On the other hand, the randomized RIDDLE-NSTEMI Study ("Randomized Study of ImmeDiate vs. DeLayEd Invasive Intervention in Patients With Non-ST-segment Elevation Myocardial Infarction") demonstrated that immediate invasive intervention (<2 hours after randomization), as compared to the delayed intervention (2 to 72 hours, median 61 hours), was associated with a lower rate of death or new myocardial infarction at 30 days. It was mainly attributable to a decrease in the new myocardial infarction rate before catheterization in the immediate-intervention group [14]. The aim of a recent clinical trial (Early or Delayed Revascularization for Intermediate and High-Risk Non-ST-Elevation Acute Coronary Syndromes; EARLY) was to compare very early (<2 hours) and delayed (12–72 hours) invasive strategies. In that study, the reduction of the primary endpoint (composite of cardiovascular death and recurrent ischemic events at one month) was observed in the very early invasive strategy group. However, it was driven only by a reduction in recurrent ischemic events [15]. On the other hand, another study (The Leipzig Immediate versus early and late PercutaneouS coronary Intervention triAl in NSTEMI; LIPSIA-NSTEMI Trial) showed no difference in terms of peak creatine kinase myocardial band (CK-MB) level in NSTEMI patients who underwent immediate invasive strategy [16].

Considering that "real-world" patients usually do not experience such long delays as patients in the deferred strategy groups in clinical trials, Mahendiran et al. [17] aimed to compare outcomes of propensity-score matched patients with door-to-catheter times <12 hours and 12–24 hours. They found no difference in one-year major adverse cardiovascular events between these groups. Contrary to that study, our analysis encompassed a significantly larger cohort. Moreover, we used overlap weighting, a novel statistical method that, compared to classic propensity score matching, allows for adjusted comparison of many groups. The advantages of this method are greatest when analyzed groups are initially very different in terms of

Table 1. Clinical characteristics, angiographic findings, treatment, and short- as well as long-term mortality of patients with NSTEMI who underwent PCI within 24 hours of admission.

Variables	All patients (n = 37 589)
Baseline characteristics	
Male sex, n (%)	25 086 (66.7)
Age, years, median (IQR)	66.7 (59.0–75.8)
Hypertension, n (%)	29 228 (77.8)
Hypercholesterolemia, n (%)	17 250 (45.9)
Obesity, n (%)	8 242 (22.4)
Previous stroke, n (%)	1 384 (3.7)
Current smokers, n (%)	10 058 (26.8)
Type 2 diabetes mellitus, n (%)	9 960 (26.5)
Chronic kidney disease, n (%)	2 257 (6.0)
Atrial fibrillation on admission, n (%)	2 009 (5.3)
Previous MI, n (%)	8 912 (23.7)
Previous PCI, n (%)	7 983 (21.2)
Previous CABG, n (%)	2 185 (5.8)
PAD, n (%)	1 795 (4.8)
LVEF <40%, n (%)	4 128 (11.0)
Pain-to-admission time, hours, median (IQR)	5.7 (2.8–12.4)
Killip class II, n (%)	3 980 (10.6)
GRACE Risk Score, median (IQR)	115 (98–133)
Door-to-PCI time, hour, median (IQR)	2.7 (1.0–7.3)
LM — IRA, n (%)	766 (2.0)
MVD, n (%)	6 938 (51.4)
CABG during the index hospitalization, n (%)	380 (1.0)
CABG planned after discharge, n (%)	956 (2.5)
Medical therapy at discharge	
Aspirin, n (%)	34 890 (94.5)
Clopidogrel, n (%)	30 605 (82.9)
Ticagrelor, n (%)	2 462 (6.7)
Prasugrel, n (%)	401 (1.1)
Beta-blocker, n (%)	31 552 (85.5)
ACE-I/ARB, n (%)	30 093 (81.4)
Statin, n (%)	32 784 (88.7)
Outcomes	
In-hospital mortality rate, n (%)	638 (1.7)
12-month mortality rate, n (%)	2 935 (7.8)
36-month mortality rate, n (%)	5 550 (14.8)

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; IRA, infarct-related artery; LM, left main coronary artery; LVEF, left ventricular ejection fraction; MVD, multivessel disease; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention

baseline characteristics, as in the case of patients undergoing very early vs. delayed PCI [11, 12]. Although statistically significant, the association between the longer door-to-PCI time and increased mortality rates presented in our study was moderate, so it might be hardly detectable in the case of a small sample size.

Immediate or very early invasive strategies for NSTE-ACS were also compared to the delayed strategy in several other small randomized trials and observational studies, providing inconclusive results [18–20]. Inconsistent findings of those studies might result from non-negligible differences in timing strategies, definitions, study designs, sample sizes, or endpoints [21]. Moreover, the recent advances in the pharmacological management of NSTE-ACS might reduce the potential benefit of early PCI. Considering that our study took place in the years 2007–2019, utilization of modern guideline-recommended therapies, especially potent $P2Y_{12}$ inhibitors in the study population, was low [22]. However, we included the admission year in the propensity score model to adjust our results for advances in pharmacological therapy over the study period.

Considering the results of this and other studies, it seems that in NSTEMI patients admitted directly to a PCI-capable center, avoiding unnecessary delays to PCI might be beneficial. It is of special importance in the context of increasing in-hospital delays in performing PCI in recent years, observed in our study. However, further randomized clinical trials are necessary to establish whether there is a benefit from this management.

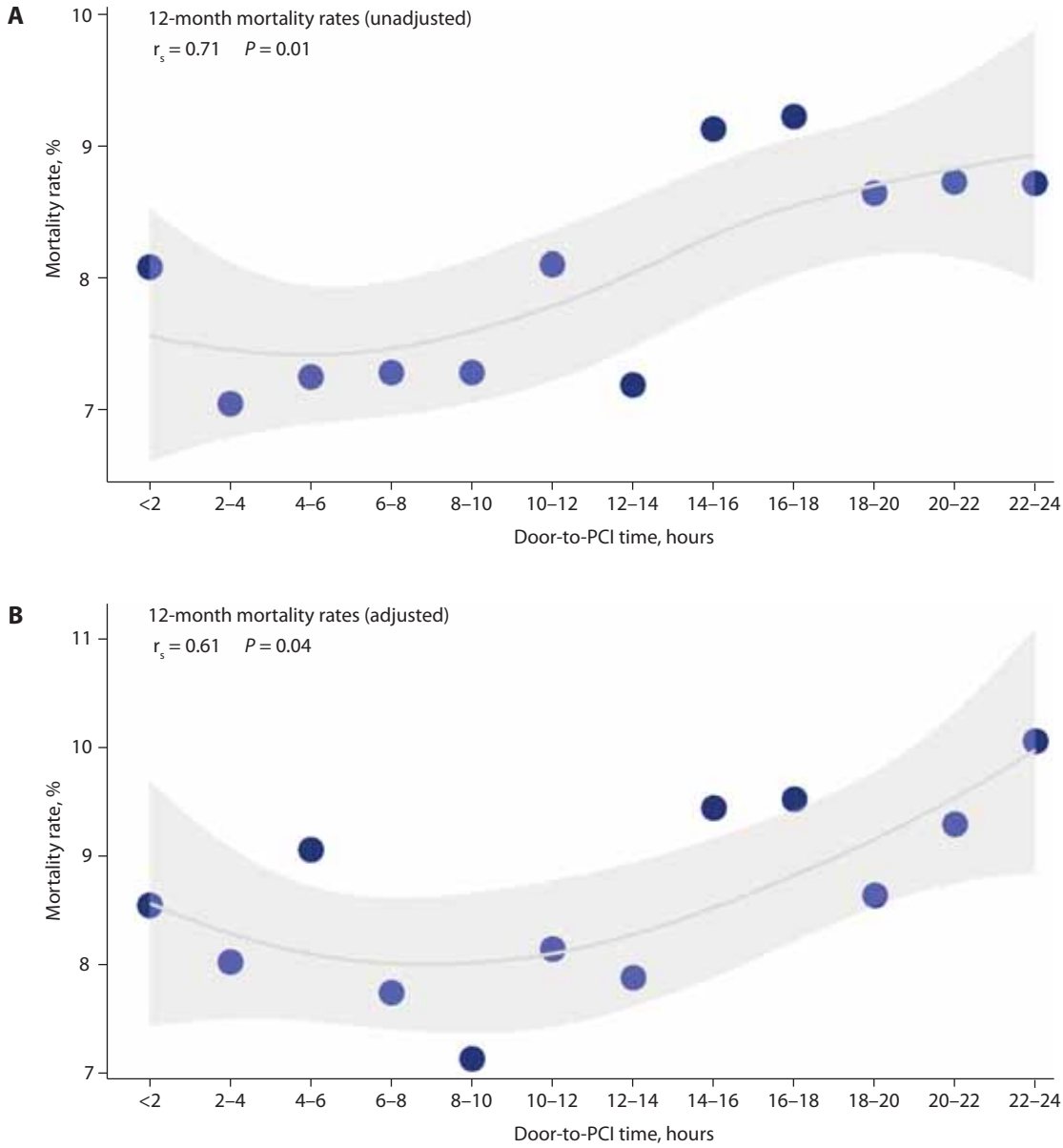

Figure 3. Unadjusted (**A**) and adjusted (**B**) 12-month mortality rates in patients stratified by the door-to-PCI time

Abbreviations: see Figure 1

Study limitations

The main limitation of our study was the observational study design. Therefore, our study could not confirm the causal relationship between time to PCI and mortality. Moreover, information on the cause of death (cardiovascular or non-cardiovascular) or incidence of other adverse events in the follow-up and values of myocardial injury markers were unavailable for the study cohort, so the mechanism of increased all-cause mortality in patients with longer door-to-PCI time remains unclear. In addition, previous studies showed that the outcomes of emergency PCI might be associated with operator volume [23]. However, we could not adjust our analysis results for this potential confounder due to the lack of operator-level data in the PL-ACS registry. Finally, the majority of patients underwent PCI within the first hours following admission, and the median door-to-PCI time was shorter than reported for other countries [17, 24]. The possible explanation might be the inclusion of only patients transported directly to the PCI-capable center because we could not establish other patients' exact admission times. Moreover, obligatory on-site standby rather than having catheterization laboratory staff on call and local clinical practice in Poland may be associated with reduced delay to PCI. Therefore, the results may not fully apply to other healthcare systems.

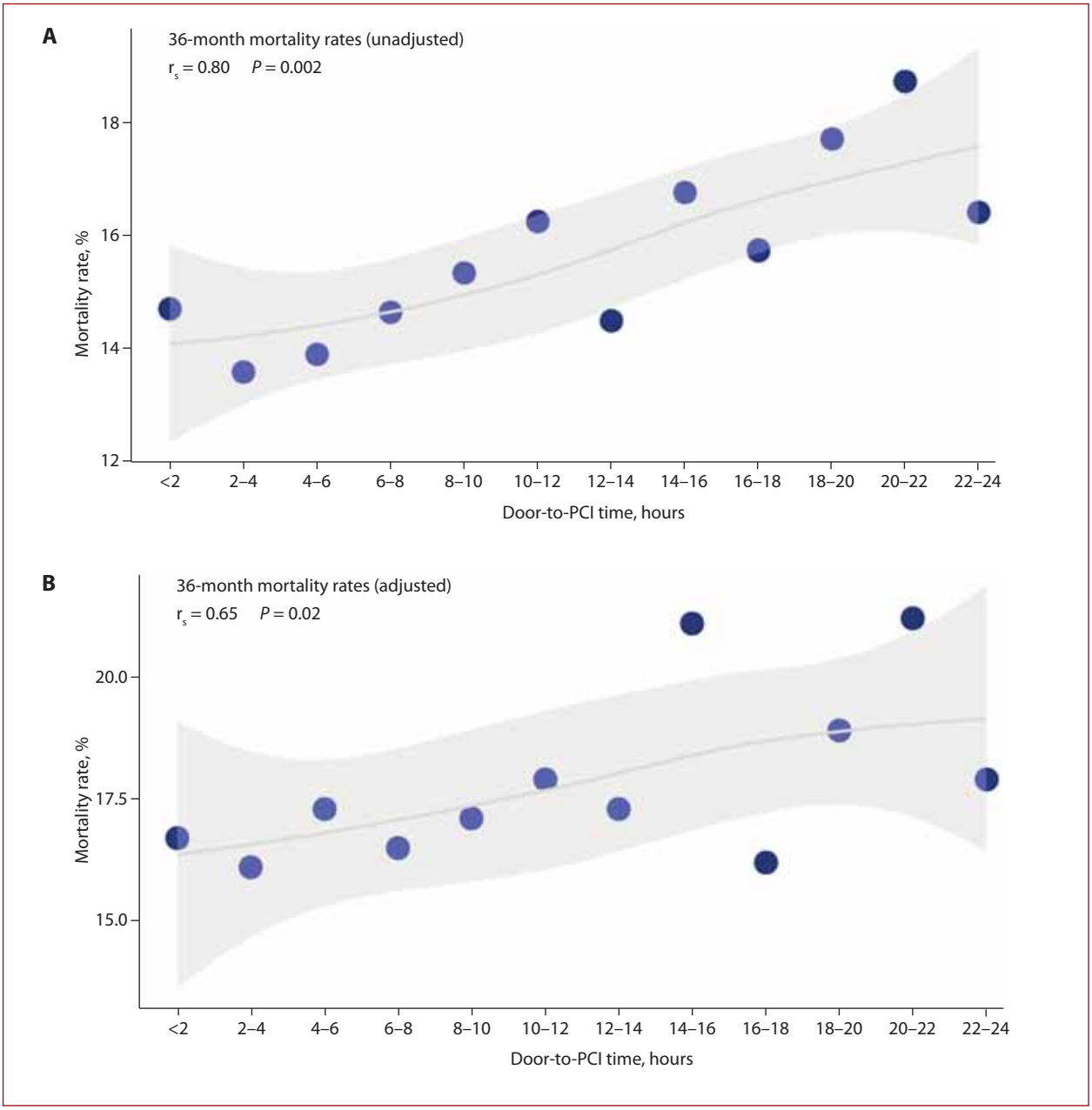

Figure 4. Unadjusted (**A**) and adjusted (**B**) 36-month mortality rates in patients stratified by the door-to-PCI time

Abbreviations: see Figure 1

CONCLUSIONS

After adjustment for clinically relevant confounders, in NSTEMI patients who were admitted directly to the PCI-capable center and underwent PCI within 24 hours from admission, there were higher 12-month and 36-month mortality rates associated with longer door-to-PCI time.

Supplementary material

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

Article information

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The impact of sex on in-hospital and long-term mortality rates in patients undergoing surgical aortic valve replacement: The SAVR and SEX study

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ABSTRACT

Background: Surgical aortic valve replacement (SAVR) is among the most commonly performed valvular surgeries. Despite many previous studies conducted in this setting, the impact of sex on outcomes in patients undergoing SAVR is still unclear.

Aims: This study aimed to define sex differences in short- and long-term mortality in patients undergoing SAVR.

Methods: We analyzed retrospectively all the patients undergoing isolated SAVR from January 2006 to March 2020 in the Department of Cardiovascular Surgery and Transplantology in John Paul II Hospital in Kraków. The primary endpoint was in-hospital and long-term mortality. Secondary endpoints included the duration of hospital stay and perioperative complications. Groups of men and women were compared with regard to the prosthesis type. Propensity score matching was performed to adjust for differences in baseline characteristics.

Results: A total number of 4 510 patients undergoing isolated surgical SAVR were analyzed. A follow-up median (interquartile range [IQR]) was 2120 (1000–3452) days. Females made up 41.55% of the cohort and were older, displayed more non-cardiac comorbidities, and faced a higher operative risk. In both sexes, bioprostheses were more often applied (55.5% vs. 44.5%; P <0.0001). In univariable analysis, sex was not linked to in-hospital mortality (3.7% vs. 3%; P = 0.15) and late mortality rates (23.37% vs. 23.52 %; P = 0.9). Upon adjustment for baseline characteristics (propensity score matching analysis) and considering 5-year survival, a long-term prognosis turned out to be better in women (86.8%) compared to men (82.7%, P = 0.03).

Conclusions: A key finding from this study suggests that female sex was not associated with higher in-hospital and late mortality rates compared to men. Further studies are needed to confirm long-term benefits in women undergoing SAVR.

Key words: mortality, SAVR, sex, TAVI

WHAT'S NEW?

Traditionally, female sex is considered a factor that worsens prognosis after heart surgeries. In this analysis, based on 4 510 patients undergoing isolated aortic valve replacement, in-hospital and late mortality did not differ significantly between men and women. In propensity score matching analysis, 5-year survival in women increased in comparison to men.

INTRODUCTION

Surgical aortic valve replacement (SAVR) is among the most commonly performed heart surgeries and most frequently conducted valvular interventions in Western countries [1]. The obvious indication for SAVR is aortic stenosis (AS), which has equal prevalence in elderly women and men [2]. With the onset of AS symptoms, the prognosis dramatically deteriorates as the disorder is resistant to pharmacological treatment [3]. On the other hand, surgery for AS reduces mortality and symptoms and increases the quality of life in both sexes [4, 5]. Nonetheless, sex differences in outcomes after SAVR are not unequivocally defined because of mixed results of previous studies, with greater evidence of worse prognosis for women [2, 6–11]. Unfavorable outcomes observed in women were explained by smaller anatomical structures rendering the procedure more technically demanding, more frequent frailty syndrome, and more comorbidities increasing the operative risk.

Recently, promising results of transcatheter aortic valve implantation (TAVI) in women were achieved [12, 13]. Nonetheless, the availability of this technique is not yet sufficient to include AS patients; therefore, improving results after the SAVR procedure is still of the utmost importance as surgery remains the gold standard of AS and aortic regurgitation (AR) treatment. This study aimed to assess sex differences in SAVR outcomes.

METHODS

We analyzed all patients undergoing SAVR in a single department of cardiac surgery from January 2006 to March 2020. To rule out the impact of other procedures on subjects undergoing TAVI, patients after annuloplasty and concomitant surgery were excluded. The baseline, clinical, and follow-up data were recorded, including demographic characteristics, concomitant diseases, course of hospitalization with procedural details, and possible complications. Late mortality was assessed with the Polish National PESEL database for the highest accuracy. A decision about the type and model of the prosthesis was made with patients. The primary study endpoints were in-hospital and late mortality. Secondary endpoints included length of hospital stay (LoHS) and periprocedural complications. Propensity score matching was applied for adjustment of baseline differences. All included characteristics are listed in Table 1. The study was conducted in accordance with the Declaration of Helsinki. Due to the retrospective nature of the collected data, patient consent was not required, and the bioethics committee approval was waived.

Study database

Data for this study were collected retrospectively based on the standardized form of the Polish National Database of Cardiac Surgery Procedures ("KROK" registry; www.krok.csioz.gov.pl). The registry is an ongoing, nationwide, multi-institutional record of cardiac surgery procedures in Poland, which was established on the initiative of the Club of Polish Cardiac Surgeons and compiled in cooperation with the Polish Ministry of Health. Centers enrolling patients in the KROK registry are required to transfer the data regarding every cardiac surgery to the central database in the National Center for Healthcare Information Systems at the Ministry of Health.

The data gathered included age, sex, body mass index (BMI), ejection fraction (EF), previous percutaneous coronary intervention (PCI), Canadian Cardiovascular Society (CCS) class, New York Heart Association (NYHA) class, smoking status, diabetes mellitus (DM), arterial hypertension, hypercholesterolemia, asthma, and chronic obstructive pulmonary disease (COPD). The follow-up time was defined as the period to the last observation or death. Data on late mortality were collected from the Polish National PESEL database to achieve the highest possible accuracy.

Based on the KROK registry form, a computer database was built for further statistical analysis.

Missing data in the database

We decided to exclude patients if records of outcomes (i.e., mortality/survivors) were missing. The completeness of each patient record was assessed: records were only analyzed if the percentage of complete data entered was higher than 90%. Records that were lower than 90% were excluded from this analysis. To handle missing data in propensity score matching (PSM), an additional level for the missing values was created for categorical data. In other words, the arbitrary value imputation technique was applied to those parameters. Cases with missing data in continuous parameters were excluded from PSM.

Statistical analysis

Categorical variables were presented as counts and percentages. Continuous variables were expressed as the mean with standard deviation (SD) or the median with the lower and upper quartile (interquartile range [IQR]). Normality was assessed by the Shapiro-Wilk test. Equality of variances was assessed using Levene's test. Differences between groups were compared using the Student's or Welch's t-test depending on the equality of variances for

Table 1. Baseline characteristics after propensity score matching (PSM)

		Men, n = 763	Women, n = 763	*P*-value
Age, years, median (IQR)		67 (58–74)	67 (60–73)	0.73
Body mass index, kg/m^2, median (IQR)		28.2 (25.1–31.5)	28.3 (25.1–32.4)	0.08
Overweight (BMI ≥25 kg/m^2), n (%)		574 (75.2)	577 (75.6)	0.86
Obesity (BMI ≥30 kg/m^2), n (%)		282 (37)	284 (37.2)	0.91
Body surface area, kg/m^2, mean (SD)		2 (0.2)	1.8 (0.2)	<0.001
LVEF, %, median (IQR)		60 (50–65)	60 (50–63)	0.22
AV gradient, mm Hg, median (IQR)		81 (66–96)	86.5 (73–104)	0.56
AR	None, n (%)	94 (12.3)	91 (11.9)	0.98
	Trivial, n (%)	281 (36.8)	279 (36.6)	
	Mild, n (%)	255 (33.4)	256 (33.6)	
	Moderate, n (%)	113 (14.8)	115 (15.1)	
	Severe, n (%)	20 (2.6%)	22 (2.9%)	
Smoking	None, n (%)	605 (79.3)	606 (79.4)	0.82
	Former, n (%)	107 (14)	101 (13.2)	
	Current, n (%)	51 (6.7)	56 (7.3)	
Last creatinine level, mg/dl, median (IQR)		0.9 (0.8–1.03)	0.8 (0.7–1)	<0.001[a]
CCS	N/A, n (%)	62 (8.1)	54 (7.1)	0.86
	I, n (%)	289 (37.9)	294 (38.5)	
	II, n (%)	344 (45.1)	341 (44.7)	
	III, n (%)	63 (8.3)	69 (9)	
	IV, n (%)	5 (0.7)	5 (0.7)	
NYHA	N/A, n (%)	62 (8.1)	54 (7.1)	0.96
	I, n (%)	142 (18.6)	138 (18.1)	
	II, n (%)	374 (49)	370 (48.5)	
	III, n (%)	208 (27.2)	212 (27.8)	
	IV, n (%)	30 (3.9)	34 (4.5)	
Prior MI, n (%)		57 (7.5)	62 (8.13)	0.63
Prior PCI, n (%)		26 (7.8)	32 (9.5)	0.82
Diabetes mellitus, n (%)		171 (22.4)	166 (21.8)	0.76
IDDM, n (%)		72 (9.4)	74 (9.7)	0.86
COPD	None, n (%)	611 (80.1)	615 (80.6)	0.56
	Treated, n (%)	150 (19.7)	148 (19.4)	
	Non-treated/untreated, n (%)	2 (0.3)	0 (0)	
Hypertension, n (%)		645(84.5)	637 (83.5)	0.57
Dyslipidemia, n (%)		290 (38)	280 (36.7)	0.61
EuroSCORE II, median (IQR)		0.9 (0.7–1.4)	1.1 (0.9–1.5)	<0.001[a]

Abbreviations: see Table 4

normally distributed variables. The Mann-Whitney U test was used for non-normally distributed continuous variables or ordinal variables. Categorical variables were compared by Pearson's χ^2 test or by Fisher's exact test if 20% of the cells had an expected count of less than 5. To evaluate the influence of sex on mortality (overall death), the Cox proportional-hazards model was created and adjusted for baseline covariates (age, prior myocardial infarction, current or former smoking status, DM, sinus rhythm before procedure, planned or emergency/urgent procedure, EuroSCORE II, hyperlipidemia and NYHA class). The multivariable model was fitted in backward stepwise regression with a *P*-value threshold of 0.05 stopping rule. Survival probabilities were presented using the Kaplan-Meier curves and compared with the log-rank test.

To avoid the potential influence of the non-randomized design and reduce bias, a propensity score was calculated using a multivariable logistic regression model with sex considered a dependent variable. The propensity score was calculated based on baseline variables (see Table 1 for details). Covariate balance was assessed using standardized mean differences (SMD) that were less than 5. Pairs of male and female patients were formed using 1:1 caliper matching. A caliper width of 0.07 was used. Unpaired patients were rejected from the analysis. Clinical outcomes (including mortality) for matched samples were compared using McNemar's test (Tables 2 and 3). Additionally, a matched pairs design of the win ratio method was applied for lifetime data [14]. The results of this method are presented on the forest plot (Figure 1).

The level of statistical significance was set at $P < 0.05$. Statistical analyses were performed with JMP®, version 16.2.0 (SAS Institute Inc, Cary, NC, US) and using R, Version 4.1.0 (R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria, 2017, www.r-project.org/).

Table 2. Procedural and clinical outcomes after propensity score matching (PSM)

		Women, n = 763	Men, n = 763	*P*-value
Duration of hospitalization, days, median (IQR)		10 (8–14)	10 (8–14)	0.45
Valve type	Bioprosthesis, n (%)	457 (59.9)	453 (59.4)	0.83
	Mechanical, n (%)	306 (40.1)	310 (40.6)	
Valve diameter, mm, median (IQR)		23 (21–23)	23 (21–23)	0.14
Cardioplegia	Crystalloid, n (%)	469 (61.6)	497 (65.5)	0.11
	Blood, n (%)	293 (38.5)	262 (34.5)	
Re-operation	Re-sternotomy, n (%)	44 (9.4)	36 (7.8)	0.8
	Secondary sternal repair, n (%)	10 (2.2)	6 (1.3)	
Death in operating room, n (%)		1 (0.1)	2 (0.3)	0.56

Continuous variables were expressed as the median with the lower and upper quartile (IQR, interquartile range)

Table 3. In-hospital and late mortality after propensity score matching (McNemar's test)

	Female, n = 763	Male, n = 763	*P*-value
Procedural complications, n (%)	72 (9.5)	82 (10.8)	0.40
In-hospital mortality, n (%)	26 (3.4)	27 (3.5)	0.89
Death (within 1 year), n (%)	48 (6.3)	66 (8.7)	0.08
Death (within 2 years), n (%)	61 (8)	84 (11)	0.046
Death (within 3 years), n (%)	72 (9.4)	97 (12.7)	0.04
Death (within 4 years), n (%)	86 (11.3)	117 (15.3)	0.02
Death (within 5 years), n (%)	101 (13.2)	132 (17.3)	0.03
Overall death, n (%)	161 (21.1)	186 (24.4)	0.12

RESULTS

General characteristics

A total of 5035 consecutive patients undergoing invasive replacement of the aortic valve (AV) were included. Following exclusion, 4510 patients treated with isolated SAVR were analyzed (Supplementary material, *Figure S1*). Men formed 58.5 % of the cohort. Women were older (mean age 67.3 years vs. 61.6 years; P <0.001) and more often overweight or obese (mean body mass index [BMI], 29.2 kg/m^2 vs. 28 kg/m^2; P <0.001) with more non-cardiovascular concomitant diseases. Men were more often smokers (10.6% vs. 4.6%; P <0.001), and they more often suffered from prior MI (11.2% vs. 5.4%; P <0.001). The majority of patients were affected by aortic stenosis (85%). The maximal transvalvular (pressure) gradient was higher in women (89.2 vs. 79.4 mm Hg; P <0.001). Men had more often moderate or severe aortic regurgitation. Symptoms assessed by the NYHA functional classification differed significantly in both groups, with female predominance in class III. The baseline patient characteristics are shown in Table 4.

Procedural outcomes

Except for 4 cases, all procedures were performed with the cardioplegic solution. The procedure was longer in men (214 vs. 208 min; P = 0.002), and they received bigger prostheses (23.7 vs. 21.3 mm; P <0.001). Also, the average time of extracorporeal circulation was longer in men (113.2 vs. 108.7 min; P <0.001). Bioprostheses were chosen more often in both sexes, especially in women (61.6% vs. 51.2%; P <0.001).

Clinical outcomes

A follow-up median (IQR) was 2120 (1000–3452) days, for men 2186 (1000–3568) days, and for women 2042 (1006–3270; P = 0.01) days. The frequency of complications did not differ between sexes (10.75% vs. 11.2%; P = 0.67). Univariate analysis did not show differences between women and men in terms of in-hospital mortality (3.7% vs. 3%; P = 0.15) and late mortality (23.37% vs. 23.52%; P = 0.9) (Table 5). Nonetheless, the propensity score analysis disclosed that after 1-year follow-up, the mortality rate in men was higher and remained so until the last observation period when we used McNemar's test for matched pairs (Table 3). The Kaplan-Meier estimate did not show significant differences between men and women in long-term follow-up (Figure 1). In the win ratio approach, a statistically significant mortality rate difference was observed only at 5 years; however, all analyses show similar win ratio results (Figure 2). At 5-year follow-up, women had 33% more wins over death (win ratio [WR], 1.33; 95% CI, 1.00–1.79; P = 0.048). Additionally, the multivariable Cox regression indicated that male sex was associated with higher risk of death (hazard ratio [HR], 1.22; 95% CI, 1.07–1.39; P = 0.003).

DISCUSSION

The key findings of this study led to the conclusion that women do not have higher in-hospital and long-term mortality than men. Traditionally, female sex was associated

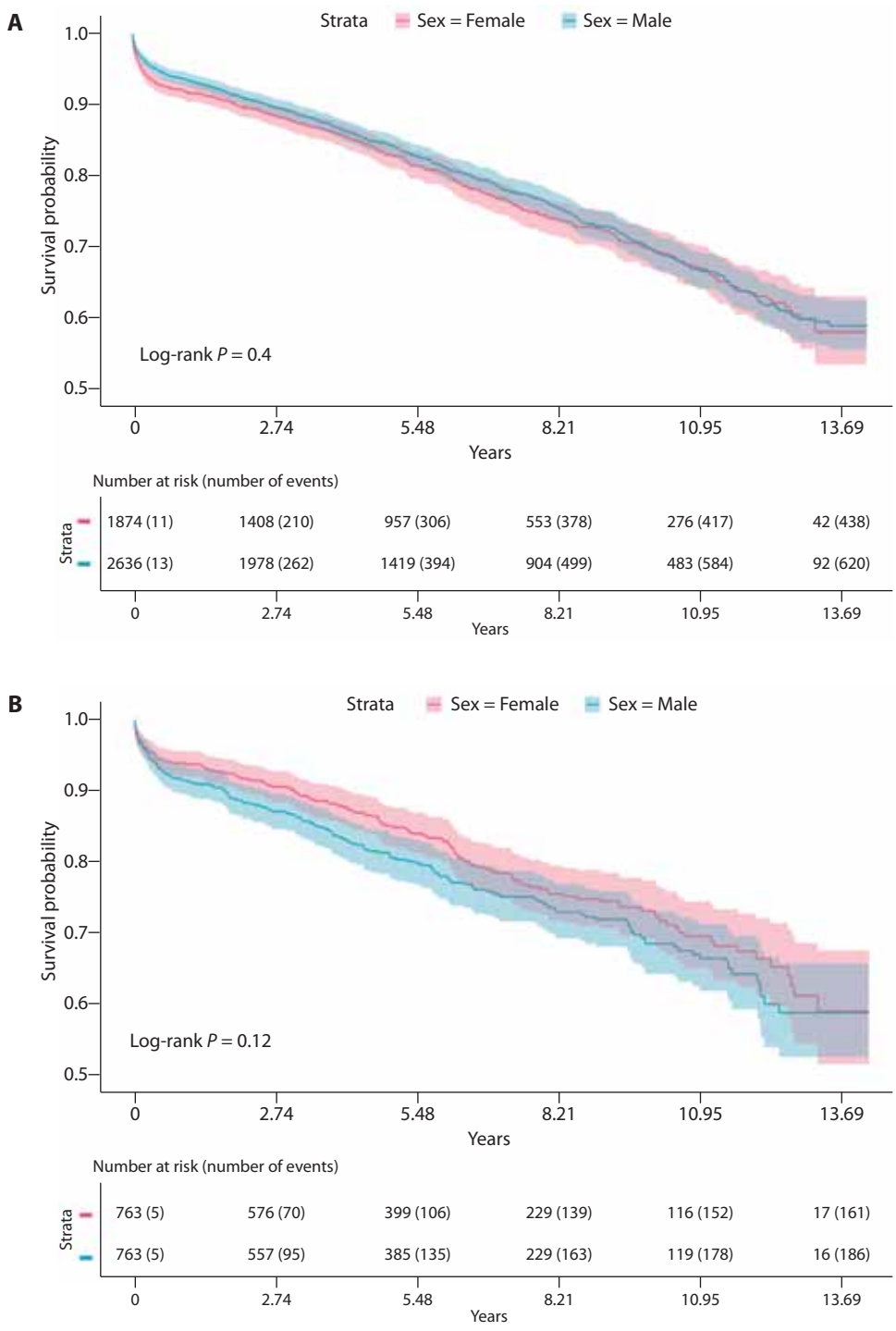

Figure 1. A. Kaplan-Meier curves before propensity score matching (PSM). **B.** Kaplan-Meier curves after PSM
Abbreviations: see Table 3

with worse clinical outcomes after heart surgeries. Female sex is embedded in the Society of Thoracic Surgeons (STS) and EuroSCORE II risk models as a factor worsening prognosis [15]. Nevertheless, it should be pointed out that these scales were designed based on data from coronary artery bypass grafting (CABG) procedures and might not accurately define an operative risk for SAVR.

In previous studies, despite more symptoms, females were treated conservatively for a longer time and were referred for SAVR more rarely; as a consequence, at the time of operation, they presented with worse baseline characteristics [2]. Similarly, in our study, women were older, more often with diabetes, hypertension, and higher operative risk.

Table 4. Baseline characteristics before propensity score matching (PSM)

		Women, n = 1874	Men, n = 2636	Total, n = 4510	*P*-value
Age, years, median (IQR)		69 (62–75)	63 (55–71)	66 (57–73)	<0.001
Body mass index, kg/m^2, median (IQR)		28.8 (25.4–32.5)	27.7 (24.8–30.9)	28.1 (25–31)	<0.001
Overweight (BMI ≥25 kg/m^2), n (%)		1442 (77.2)	1904 (72.7)	3346 (74.6)	0.006
Obesity (BMI ≥30 kg/m^2), n (%)		785 (42.1)	806 (30.8)	1591 (35.5)	<0.001
Body surface area, m^2, median (IQR)		1.8 (1.7–1.9)	2 (1.8–2.1)	1.9 (1.8–2)	<0.001
LVEF, %, median (IQR)		60 (50–65)	55 (45–60)	60 (50–63)	<0.001
AV mean gradient, mm Hg, median (IQR)		86.5 (73–104)	81 (66–96)	84 (70–100)	<0.001
AR	None, n (%)	205 (11)	240 (9.1)	445 (9.9)	<0.001
	Trivial, n (%)	692 (37)	793 (30.2)	1485 (33)	
	Mild, n (%)	649 (34.7)	762 (29)	1411 (31.4)	
	Moderate, n (%)	245 (13.1)	543 (20.7)	788 (17.5)	
	Severe, n (%)	79 (4.2)	287 (10.9)	366 (8.1)	
Smoking	None, n (%)	1604 (85.8)	1878 (71.6)	3482 (77.5)	<0.001
	Former, n (%)	179 (9.6)	469 (17.9)	648 (14.4)	
	Current, n (%)	86 (4.6)	277 (10.6)	363 (8.1)	
Last creatinine level, mg/dl, median (IQR)		0.85 (0.7–1)	0.95 (0.8–1)	0.9 (0.7–1)	<0.001
CCS	N/A, n (%)	144 (7.7)	209 (8)	353 (7.9)	0.77
	I, n (%)	690 (36.9)	962 (36.7)	1652 (36.8)	
	II, n (%)	852 (45.6)	1212 (46.2)	2064 (46)	
	III, n (%)	162 (8.7)	205 (7.8)	367 (8.2)	
	IV, n (%)	21 (1.1)	35 (1.3)	56 (1.3)	
NYHA	N/A, n (%)	21 (1.1)	25 (1)	46 (1)	0.03
	I, n (%)	311 (16.6)	497 (18.9)	808 (18)	
	II, n (%)	856 (45.8)	1255 (47.8)	2111 (47)	
	III, n (%)	606 (32.4)	719 (27.4)	1325 (29.5)	
	IV, n (%)	76 (4.1)	128 (4.9)	204 (4.5)	
Prior MI, n (%)		101 (5.4)	294 (11.2)	395 (8.8)	<0.001
Prior PCI, n (%)		56 (6.9)	122 (11.6)	178 (9.5)	0.001
Diabetes mellitus, n (%)		438 (23.4)	478 (18.2)	916 (20.4)	<0.001
IDDM, n (%)		183 (9.8)	200 (7.6)	383 (8.5)	0.01
COPD	None, n (%)	1548 (82.8)	2095 (79.9)	3643 (81.1)	0.04
	Treated, n (%)	320 (17.1)	526 (20.1)	846 (18.8)	
	Non-treated/untreated, n (%)	1 (0.1)	2 (0.1)	3 (0.1)	
Hypertension, n (%)		1585 (84.8)	2118 (80.7)	3703 (82.4)	0.001
Dyslipidemia, n (%)		676 (36.2)	966 (36.8)	1642 (36.6)	0.66
EuroSCORE II, median (IQR)		1.2 (0.9–1.6)	0.8 (0.7–1.2)	1 (0.7–1.4)	<0.001

Abbreviations: AV, aortic valve; AR, aortic regurgitation; COPD chronic obstructive pulmonary disease; IDDM, insulin-dependent diabetes mellitus; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention

Table 5. Procedural and clinical outcomes before propensity score matching (PSM)

		Women, n = 1 874	Men, n = 2 636	Total, n = 4 510	*P*-value
Duration of hospitalization, days, median (IQR)		10 (8–14)	10 (8–14)	10 (8–14)	0.14
Valve type	Bioprosthesis	1155 (61.6)	1349 (51.2)	2504 (55.5)	<0.001
	Mechanical	719 (38.4)	1287 (48.8)	2006 (44.5)	
Valve diameter, mm, median (IQR)		21 (21–23)	23 (23–25)	23 (21–25)	<0.001
Cardioplegia	Crystalloid, n (%)	717 (38.5)	930 (35.5)	1647 (36.8)	0.04
	Blood, n (%)	1145 (61.5)	1689 (64.5)	2834 (63.2)	
Complications, n (%)		200 (10.8)	291 (11.1)	491 (11)	0.67
Re-operation	Re-sternotomy, n (%)	98 (8.5)	161 (9.9)	259 (9.3)	0.21
	Secondary sternal repair, n (%)	19 (1.7)	38 (2.3)	57 (2)	
In-hospital mortality, n (%)		70 (3.7)	78 (3)	148 (3.3)	0.15
Death in operating room, n (%)		6 (0.3)	7 (0.3)	13 (0.3)	0.74

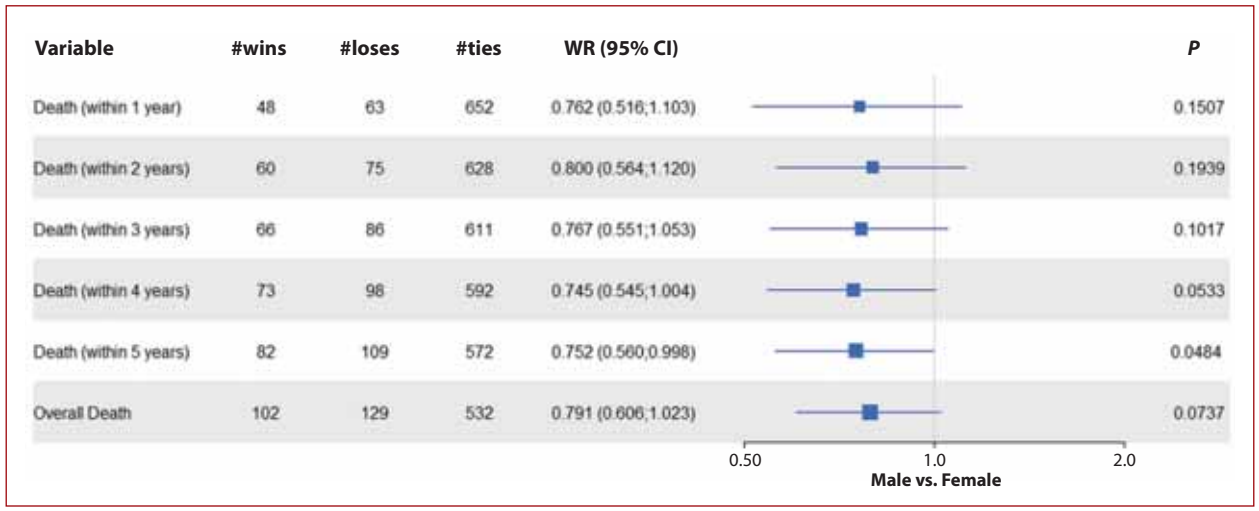

Figure 2. Differences in long-term mortality after surgical aortic valve replacement by sex shown on the forest plot of the win ratio method after propensity score matching

It was postulated that the later presentation of women for SAVR might be related to delayed development of AS in women. Older studies based on echocardiographic data showed that men are twice as likely to be diagnosed with AS [16]. Nonetheless, data from a large national registry from Sweden showed that the frequency of AS is nearly equivalent in elderly women and men [17]. As argued earlier [16], sex discrepancies among patients undergoing SAVR are probably caused by referral bias.

Sex-dependent pathophysiological development of AS was described previously [18]. Women face a greater risk of developing left ventricular concentric geometry in response to AS, decrease in ejection fraction, and fibrosis. As far as calcifications are concerned, women have a lower aortic valve calcium burden than men. Nonetheless, in women, calcifications have a more profound impact on AS severity. Therefore, sex is not associated with AS progression [19, 20].

The histogram representing the average 365-day survival for each year of the study period shows the mortality peak in 2015 with a subsequent tendency to decrease (Figure 3). This finding might be attributed to 240 patients who were qualified for TAVI mostly after 2015 (Supplementary material, *Figure S1*). Their risk profile based on EuroSCORE II was 2.55, higher than that of patients undergoing isolated SAVR. Therefore, we might assume that the transfer of the sickest patients to TAVI procedures has impacted SAVR outcomes. There are many studies supporting TAVI utilization in high- and medium-risk patients, given its favorable outcomes, especially in women. Nonetheless, the majority of TAVI studies were based on octogenarians, which raises doubts as longer life expectancy in women might influence these outcomes [21–26]. Moreover, the studies assessing sex differences in SAVR patients who were at least 80 years old also revealed better outcomes in the women's group [10, 17]. For all patients at that age, the newer generation bioprostheses might offer excellent outcomes [27–30]. In a post-hoc analysis of the SURTAVI study, van Mieghem et al. did not show significant sex differences between SAVR and TAVI groups in 2-year follow-up [9]. Similarly, in a recent analysis, Marzec et al. did not find a statistically significant difference in the 24-month mortality rate between the two methods [31]. Available meta-analyses comparing TAVI and SAVR show distinct benefits of each technique. TAVI seems to reduce the incidence of bleeding, new-onset atrial fibrillation, and acute kidney injury but has a higher rate of vascular complications, prosthesis-patient mismatch, and reinterventions. In terms of all-cause mortality, no significant differences between both methods were found [32, 33]. Noteworthy is the emergence of new surgical techniques that reduce the rate of cerebrovascular events and make SAVR more accessible for patients with COPD, which is a common contraindication for SAVR [34]. Comparable results of TAVI and SAVR in the mentioned studies suggest that both methods should be considered in patients suffering from aortic valve disease. Our study has demonstrated that SAVR is a reasonable option for women with outcomes comparable to men in short- and long-term follow-ups. There was a trend towards better results in women shown in PSM, but this needs to be confirmed in further studies. Also, in the presence of a growing body of evidence suggesting comparable outcomes in men and women after SAVR, female sex as a risk factor for SAVR should be reconsidered [35].

Limitations

This was a single-center retrospective study. Not all determinants of the outcomes could be recorded. The lack of comprehensive echocardiographic data prevented assessment of patient-prosthesis mismatch (PPM). In the case of

late mortality, it was not possible to distinguish between cardiac and non-cardiac causes of death.

CONCLUSIONS

In the present study, crude analysis demonstrated that female sex was not associated with higher in-hospital and late mortality rates after SAVR compared to men. Further studies are needed to confirm long-term benefits in women undergoing SAVR.

Supplementary material

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

Article information

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Uncontrolled blood pressure according to ambulatory blood pressure monitoring values in pregnant women is poorly predictable

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INTRODUCTION

The prevalence of hypertension-related disorders in pregnancy remains a significant clinical problem that contributes to an increase in maternal morbidity and mortality and influences the risk of future cardiovascular complications [1]. It is recommended to monitor blood pressure (BP) during pregnancy using office BP measurements (OBPM) with the support of outpatient measurements, which include home BP (HBPM) and ambulatory BP measurements (ABPM) [2]. ABPM is recognized as the best method for BP monitoring during pregnancy. Its role in management of hypertension in high-risk pregnant women is particularly emphasized [2, 3]. Experts do not indicate one specific algorithm for choosing the method for BP monitoring and the sequence and purposefulness of performing a specific type of BP measurement. Therefore, to define the role and importance of ABPM in relation to OBPM and HBPM, we decided to compare the results of these BP measurement methods in a group of women with high-risk pregnancies.

METHODS

Study group description

The study is a post-hoc analysis of data collected over 4 years (2015–2019) from 79 pregnant women referred to the clinic with a history of primary hypertension with eclampsia (89.9%) or pre-eclampsia (10.1%) in their previous pregnancy/pregnancies. All included women completed the study. The study was approved by the local ethics committee (no. AKBE/71/2018). The characteristics of pregnant women are presented in the Supplementary material.

Description of analyzed variables

Every fifth week of the study, subjects underwent ABPM and OBPM with the last visit scheduled in the 37th week of pregnancy. Before each visit, HBPM measurements were performed. All measurements were performed in accordance with recommendations [2]. For each of the BP measurement methods, arterial hypertension was diagnosed at the commonly accepted BP thresholds (details in the Supplementary material).

Statistical analysis

Continuous variables were presented as mean and standard deviation. Categorical variables were presented as numbers followed by percentages. The reliability of OBPM or HBPM for assessment of ABPM measurement was assessed using Cohen's Kappa. In order to predict an abnormal ABPM result in BP measurement sets with well-controlled OBPM and HBPM values, mixed-effect logistic regression of all possible models including systolic and/or diastolic BP values from OBPM and/or HBPM as predictors was created. The model was evaluated in a randomly selected subset containing 80% of the measurement sets. The final model was selected on the basis of the lowest Akaike information criterion. Furthermore, accuracy of the model was evaluated in the remaining 20% of the data.

RESULTS AND DISCUSSION

During the trial, 706 office visits with BP measurements were performed, and finally,

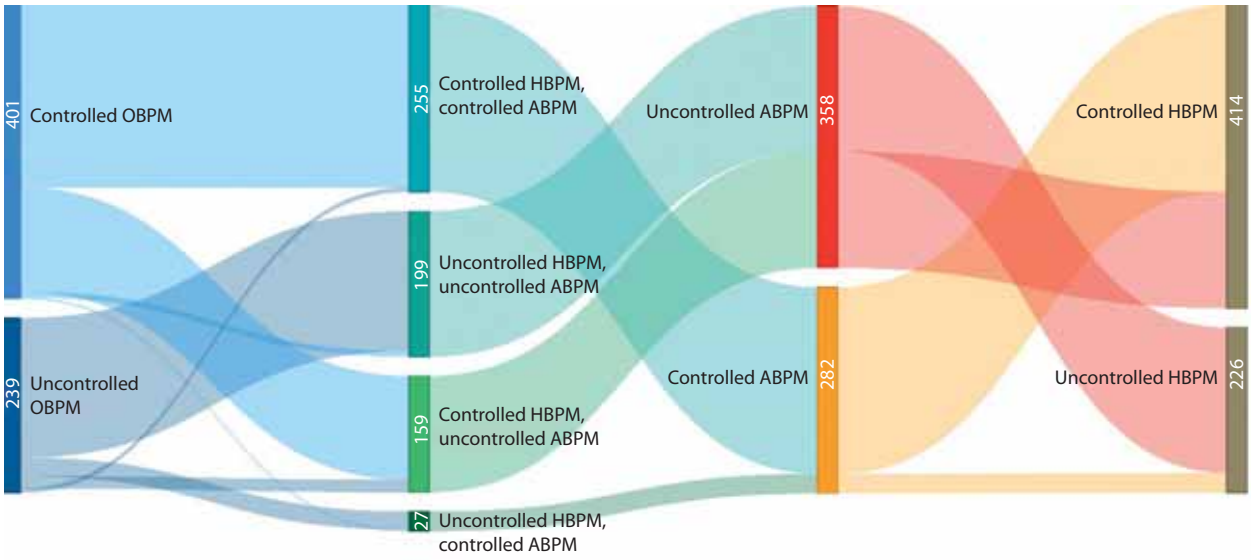

Figure 1. Dependency between controlled/uncontrolled values of OBPM, HBPM, and ABPM in the analyzed group of 640 sets of blood pressure measurements

Abbreviations: ABPM, ambulatory blood pressure measurements; HBPM, home blood pressure measurements; OBPM, office blood pressure measurements

640 (90.7%) complete sets of BP measurements were analyzed. Mean OBPM SBP/DBP was 134.0 (15.9)/83.7 (11.4) mm Hg, and HBPM SBP/DBP was 128.1 (16.6)/79.9 (11.3) mm Hg. Mean ABPM SBP/DBP values during 24-hour monitoring were 122.9 (13.1)/77 (9.9) mm Hg, during the activity period they were 126.9 (13.6)/80.9 (10.4) mm Hg, and at night 113.7 (13.8)/67.9 (9.9) mm Hg.

OBPM values ≥140 and/or 90 mm Hg were present in 239 (37.3%) sets of measurements. HBPM values ≥135 and/or 85 mm Hg occurred in 226 (35.3%) measurements. ABPM values ≥130 and/or 80 mm Hg during 24-hour or ≥135 and/or 85 mm Hg during the activity period or ≥120 and/or 70 mm Hg during night rest were present in 358 (55.9%) sets of measurements.

OBPM

In 401 cases, OBPM was rated as well-controlled; 10 (2.5%) HBPM and 150 (37.4%) ABPM results were recognized as uncontrolled. In sets with well-controlled OBPM, 8 (2%) indicated a lack of BP control in both HBPM and ABPM. In 239 sets of measurements fulfilling the criteria for uncontrolled OBPM, 216 (90.4%) HBPM and 208 (87.0%) ABPM were classified as uncontrolled BP (Figure 1). Reliability of OBPM for assessment of controlled/uncontrolled ABPM results was weak (kappa 0.45).

HBPM

In 414 sets with well-controlled HBPM, there were 23 (5.6%) uncontrolled OBPM and 159 (38.4%) uncontrolled ABPM. In 17 (4.1%) sets, both OBPM and ABPM were uncontrolled. In 226 measurement sets fulfilling the criteria for uncontrolled HBPM, 216 (95.6%) OBPM and 199 (88.1%) ABPM were assessed as uncontrolled. Reliability of HBPM for assessment of controlled/uncontrolled ABPM was weak (kappa 0.44).

ABPM

In 282 well-controlled ABPM, 31 (11%) were uncontrolled in OBPM and 27 (9.6%) uncontrolled in HBPM. Both uncontrolled OBPM and HBPM were in 25 (8.9%) sets and uncontrolled OBPM or HBPM were in 8 sets (2.8%). In 358 sets of uncontrolled ABPM measurements, there were 208 (58.1%) uncontrolled OBPM and 199 (55.6%) uncontrolled HBPM. Both uncontrolled OBPM and HBPM were in 191 (53.3%) sets while 142 measurements were accompanied by well-controlled OBPM and HBPM.

ABPM in relation to OBPM and HBPM

Well-controlled hypertension according to both OBPM and HBPM was in 391 (61.1%) sets of measurements. Among them, there were 142 (22.2%) measurements indicating uncontrolled values according to ABPM. Both uncontrolled OBPM and HBPM were in 216 (33.8%) sets of measurements, and 33 (5.2%) fulfilled the criteria for uncontrolled hypertension in OBPM or HBPM. In subjects with uncontrolled hypertension both in OBPM and HBPM, 191 (88.4%) had uncontrolled hypertension in ABPM. In 33 sets of measurements with uncontrolled OBPM or HBPM, 25 (75.8%) fulfilled the criteria for uncontrolled ABPM.

Prediction of uncontrolled ABPM in subjects with well-controlled values of both OBPM and HBPM

In the training subset of the data with well-controlled values of both OBPM and HBPM, a model was selected for prediction of uncontrolled ABPM. The final logistic regres-

sion model included OBPM SBP, OBPM DBP, and HBPM DBP; the odds ratios for the prediction of uncontrolled ABPM were 1.09 (95% CI, 1.01–1.17), 1.52 (95% CI, 1.25–1.85), and 0.86 (95% CI, 0.72–1.02), respectively, for a 1 mm Hg increase. Using the remaining 20% of BP measurements we computed selected model accuracy equal to 0.592. These results suggest that high SBP and DBP in OBPM and low DPB in HBPM increase the likelihood of poor BP control in ABPM.

Using data from BP measurements in patients with high-risk pregnancy, we showed that the discrepancy between OBPM and HBPM may be considered as a relevant clinical problem. According to our results, physicians assessing BP control only using OBPM may overlook 37.4% of subjects with uncontrolled hypertension according to the ABPM control criterion. Surprisingly, using only HBPM values may result in under-recognition of 38.4% of subjects with ABPM values higher than expected. In our study, achieving ABPM target values of elevated BP treatment was associated with a low rate of uncontrolled OBPM (11%) and HBPM (9.6%) values. The evaluated model showed that physicians can predict uncontrolled ABPM values using data from OBPM and HBPM in fewer than two-thirds of sets of measurements.

Our results remain of special significance when compared to the current guidelines, indicating ABPM superiority in predicting pregnancy outcomes over routine BP measurement [4]. Many clinicians, using the results of studies evaluating the agreement between OBPM, HBPM, and ABPM using the Bland-Altman methodology, may be convinced that HBPM is closest to daily ABPM results. Actually, using the same data as in our study, we also confirmed that finding [5]. However, the assumption that HBPM can be used interchangeably with ABPM is incorrect as shown by Hodgkinson et al. [6] in the systematic review of 20 studies. In their analysis, pooled sensitivity and specificity of OBPM for ABPM were 74.6% (95% CI, 60.7%–84.8%) and 74.6% (95% CI, 47.9%–90.4%), respectively. Pooled sensitivity of HBPM for OBPM and ABPM was 85.7% (95% CI, 78%–91%) and 62.4% (95% CI, 48%–75%).

We did not find similar analyses concerning differences in OBPM, HBPM, and ABPM values, thus our results should be considered new.

However, our study has several limitations. Due to the relatively small sample size and study design, we were not able to evaluate how the discrepancy between OBPM, HBPM, and ABPM impacts the outcome of pregnancy. Also, the day and night period schedule set in ABPM reports may not reflect the day-and-night cycle of our study participants.

In conclusion, our results indicate that good BP control in OBPM or HBPM does not mean achieving controlled BP in ABPM. In addition, based on the results of both OBPM and HBPM, we are unable to predict the result of ABPM. Therefore, especially considering the advantages in terms of predicting pregnancy outcomes, ABPM should be the standard for BP monitoring in pregnant women.

Supplementary material

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

Article information

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Anthracycline-Induced Microcirculation disorders: AIM PILOT Study

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INTRODUCTION

Anthracyclines are the basic therapy for a wide range of solid tumors and hematologic cancers. Anthracyclines remain an important therapeutic option in breast cancer. However, their use is limited by the risk of therapy-related cardiovascular toxicity (CTR-CVT) [1–3]. One of the symptoms of cardiovascular complications from anthracycline use is left ventricular systolic dysfunction. A less known side effect of anti-cancer medications is coronary microcirculation damage [4]. Single reports from experimental studies indicate simultaneous irreversible coronary microcirculation dysfunction (CMD) following exposure to anthracyclines [1]. Many processes leading to the apoptosis of cardiomyocytes undoubtedly involve also vascular endothelial cells, causing their damage and CMD at the same time. Invasive assessment of microcirculation using the index of microcirculatory resistance (IMR) measurement is currently the gold standard in the diagnosis of CMD [4]. It has already been tested on many groups of patients, including stable angina pectoris, acute STEMI, and post-heart transplantation [5]. The advantage of IMR over coronary flow reserve (CFR) is that the IMR measurement is simple, microvascular-specific, quantitative, reproducible, and independent of hemodynamic changes. CMD-associated ischemia increases the risk of major adverse cardiovascular events (MACE) [6, 7]. In selected groups of patients, e.g. after heart transplantation, with hypertrophic cardiomyopathy or ST-segment elevation myocardial infarction, the severity of CMD is a significant independent risk factor for clinical deterioration and death [5, 8, 9].

This study aimed to assess the coronary microcirculation dysfunction in patients with ischemia with non-obstructed coronary artery disease (INOCA) treated with anthracyclines for malignancy.

METHOD

The study presents a retrospective analysis of five consecutive patients previously treated oncologically with typical angina pectoris symptoms, in whom coronary arteriography revealed no significant coronary artery stenosis (stenosis <40% of vessel diameter or 40%–60% of vessel diameter assessed as insignificant in functional testing such as fractional flow reserve [FFR> 0.80], Table 1). All patients were evaluated for CMD using the Coroventis CoroFlow Cardiovascular System (Abbott Vascular, Santa Clara, CA, US). CFR and IMR were assessed as part of the diagnosis of INOCA. CMD was diagnosed when IMR ≥25 and/or CFR <2.0.

Moreover, 12-lead ECG, transthoracic echocardiography, and laboratory tests, including myocardial dysfunction marker assays, were performed in all patients. Table 1 shows the clinical characteristics of patients along with detailed data on the chemotherapy used. Patients were assessed based on the following exclusion criteria: previous radiotherapy, the presence of an acute inflammatory condition (hs-CRP>10 mg/l), systemic connective tissue diseases, treatment with interferon, bleeding diathesis due to platelet or plasma disorders, acute renal failure or chronic kidney disease with GFR <30 ml/min/1.73 m^2, allergy to iodinated contrast media, regadenoson, adenosine, uncontrolled asthma,

Table 1. Clinical characteristics of patients and the results of the microcirculation assessment

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, years	57	59	61	59	54
Sex	Female	Female	Female	Female	Female
BMI, kg/m^2	26	26	27	28	35.9
NYHA class	II	II	II	III	II
CCS class	III	III	III	III	III
HA	Yes	no	Yes	No	Yes
DM	Yes	no	Yes	No	No
Nicotinism	No	yes	No	No	No
Echocardiography					
EF, %	55	25	35	43	60
GLS, %	–14	–10	–11	–8	–18
EDD, mm	48	69	54	56	47
LAVI, ml/m^2	34	66	39	62	24
Location of the cancer	Breast	Ovarian	Lymphoma	Breast	Breast
Time since the end of chemotherapy, months	13	11	13	6	15
Type of chemotherapy					
Doxorubicin	Yes	No	Yes	Yes	Yes
Dosage, mg/m^2	240	0	420	240	240
Cyclophosphamide	Yes	No	Yes	Yes	Yes
Cisplatin	No	Yes	No	No	No
Docetaxel	Yes	No	No	Yes	Yes
Trastuzumab	No	No	No	Yes	Yes
Chest radiotherapy	No	No	No	No	No
Laboratory tests					
NT-proBNP, pg/ml	450	11595	5300	1639	2060
Troponin, ng/ml	0	0.03	0.03	0.7	0.012
LDL-C, mmol/l	1.8	2.6	1.6	5.7	3.2
eGFR, ml/min/1.73 m^3	78	26	61	56	90
Hb, mmol/dl	7.2	6.6	6.4	7.1	7.5
Drugs used					
Beta-blocker	Yes	Yes	Yes	Yes	No
ACEI/ ARB	Yes	No	Yes	Yes	Yes
Ca-blocker	No	No	No	No	Yes
ARNI	No	Yes	No	No	No
SGLT-2	No	Yes	Yes	No	Yes
Statin	No	Yes	Yes	Yes	No
Antidiabetic drugs	No	No	Yes	No	No
Insulin	No	No	Yes	No	No
Assessment of the coronary microcirculation:					
CFR	1.9	3.2	2.4	1.9	1.6
IMR	32	10	39	37	62
FFR	0.91	0.9	0.86	0.94	0.93

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; ARNI, angiotensin receptor-nephrilysin inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; NT-proBNP, N-terminal pro hormone B-type natriuretic peptide; CCS, Canadian Cardiovascular Society; CFR, coronary flow reserve; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; EDD, end-diastolic diameter; EF, ejection fraction; ESD, end-systolic diameter; FFR, fractional flow reserve; GLS, global longitudinal stress; HA, hypertension; Hb, hemoglobin; IMR, index of microvascular resistance; LAVI, left atrial volume index; LDL-C, low-density lipoprotein cholesterol; NYHA, New York Heart Association

2nd and 3rd-degree atrioventricular block, or lack of informed consent.

RESULTS AND DISCUSSION

All five described patients had cancer. Three of them were diagnosed with breast cancer, one with lymphoma, and one with ovarian cancer. Four patients received chemotherapy with anthracyclines, while the ovarian cancer patient was administered cisplatin-based chemotherapy. On admission, all patients had symptoms of typical class III angina pectoris as defined by the Canadian Cardiovascular Society. None of the patients under analysis had been previously diagnosed with cardiovascular diseases. Left ventricular ejection fraction (LVEF) varied between 25% and 60%. The highest dose of anthracyclines was administered to the patient treated for lymphoma.

All patients underwent invasive coronary angiography, and then, due to no significant lesions in coronary arteries, a simultaneous assessment of coronary microcirculation was performed. CMD with a significantly increased IMR was revealed in all patients who were administered anthracyclines in the past. The patient who received non-anthracyclines chemotherapy presented normal coronary microcirculation function despite significantly impaired ejection fraction.

The presence of anthracyclines-related cardiotoxicity was proportional to the dose administered — the higher the dose, the higher the probability. With a dose of 400 mg/m^2, the risk of symptomatic heart failure (HF) was 3%, with 550 mg/m^2 — 7% and with doses of 700 mg/m^2 — as many as 18% [2]. The risk of cardiotoxicity increased up to 35% if defined as an abnormal increase in cardiac biomarkers, such as troponin or NT-proBNP. It should be noted that no cardiac-safe dose of anthracyclines was determined. Persons with higher risk of cardiotoxicity include patients over 65 years, women, persons with low body weight, persons with a history of heart disease as well as patients who underwent chest radiotherapy [10].

The damage to coronary microcirculation due to anthracyclines administration is a new issue. In animal models, upon anthracyclines administration, permanent microcirculation damage was detected already at the subclinical stage [11]. Both a decrease in the density of the capillary network and dysfunction of other microcirculation vessels were demonstrated. Several mechanisms of anthracycline cardiotoxicity were proposed. Oxidative stress, initiated by doxorubicin, causes mitochondrial damage, which then leads to the apoptosis of both cardiomyocytes and endothelial cells. Moreover, through inhibition of topoisomerase IIb, therapeutic doses of doxorubicin can lead to direct DNA damage to endothelial cells and their further apoptosis in the non-oxidative mechanism [12]. Sodium-calcium and sodium-potassium pumps (Na+/K+-*ATP*ase) also become damaged, which leads to the cells being overloaded with calcium ions and the death of the myocyte.

Our study has shown that CMD occurs both in patients with evident left ventricular systolic function damage and in patients with normal or slightly reduced ejection fraction. In line with the experimental studies, this may indicate that CMD clinically precedes evident cardiomyocyte dysfunction. Taking into account the irreversible cardiotoxicity mechanism of anthracyclines, by detecting this process at the stage of microcirculation and initiating cardio-protection, we can prevent patients from developing evident heart failure. The above hypothesis undoubtedly needs to be confirmed in subsequent prospective studies.

Article information

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Large unstained cell count is a useful predictor of coronary artery disease co-existence in patients with severe aortic stenosis

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INTRODUCTION

The burden of aortic valve stenosis (SA) is growing due to demographic changes connected with population aging [1]. The appropriate diagnosis especially in patients with angina pectoris symptoms is of utmost importance due to its association with limited life expectancy. Coronary artery disease (CAD) and aortic valve degeneration share similar pathogenetic factors including lipid accumulation and calcium deposition [2]. There is a limited utility of angina pectoris symptoms in CAD diagnosis in patients with SA since chest pain is typical of both diseases. Previous reports demonstrated a 50% prevalence of angiographically significant coronary artery disease in patients presenting angina pectoris symptoms with already diagnosed SA [3].

Noninvasive stress tests are characterized by low specificity, and exercise tests usually performed in the assessment of coronary artery disease are contradicted in symptomatic SA patients. Several attempts to include non-invasive laboratory markers in diagnostics were undertaken [4, 5]. Some simple laboratory investigations might help in evaluation of cardiovascular patients. This study aimed to find a non-invasive easily accessible marker for detecting coronary artery disease in patients with aortic stenosis.

METHODS

We analyzed 200 consecutive patients with symptomatic SA with or without coronary artery disease admitted to the cardiac surgery department between November 2017 and September 2022. Subjects with active endocarditis or CAD with moderate SA and patients with a history of malignancy or rheumatic disorders were excluded from the study. The final study group comprised 190 patients with severe SA assigned to group 1 (n = 85, 44.7%) with absence or group 2 (n = 105, 55.3%) with the presence of CAD defined as coronary artery atherosclerotic changes covering at least 50% of the artery lumen. Demographic and clinical data were analyzed. Blood samples were collected on admission, and the results were related to echocardiographic findings.

All patients referred for a surgical procedure had preserved left ventricular ejection fraction. Echocardiographic intra- and inter-observer variability may be related to pre- and postoperative differences in the visualization; however, it remains low in the experienced centers. The echocardiographic methodology was presented in Supplementary material no. 2.

The study was approved by the local Institutional Ethics Committee (no. 198/2021).

Statistical analysis

Analysis was performed using MedCalc® Statistical Software version 20.027 (MedCalc/Software Ltd, Ostend, Belgium). Detailed information was presented in Supplementary material no. 3.

Table 1. Uni- and multivariable analysis for CAD prediction in SA patients

Parameters	Univariable analysis			Multivariable analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age (per 1 year)	1.062	1.021–1.104	0.003	1.056	1.012–1.101	0.012
Sex, male	1.139	0.623–2.084	0.67	—	—	—
DM	2.792	1.460–5.338	0.002	2.765	1.413–5.410	0.003
HA	1.142	0.560–2.329	0.72	—	—	—
COPD	0.634	0.165–2.437	0.507	—	—	—
PAD	1.209	0.529–2.766	0.65	—	—	—
AF	2.222	0.879–1.205	0.05	—	—	—
LUC	1.890	1.122–3.182	0.02	1.737	1.040–2.901	0.035

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CI, confidence interval; COPD, chronic pulmonary obstructive disease; DM, diabetes mellitus; HA, arterial hypertension; LUC, large unstained cells; OR, odds ratio; PAD, peripheral artery disease; SA, aortic stenosis

RESULTS AND DISCUSSION

Preoperative echocardiographic characteristics revealed a difference between groups in a median (interquartile range [IQR]) transvalvular aortic gradient: 58 (50–67) mm Hg vs. 54 (46–61) mm Hg ($P = 0.005$) and presented in detail in Supplementary material no. 1, *Table S1*. Patients in group 2 were older, and diabetes and atrial fibrillation occurred more often in this group. Detailed demographic and clinical data are presented in Supplementary material no. 1 and *Table S2*, and preoperative laboratory investigations in Supplementary material no. 1 and *Table S3*.

Large unstained cell (LUC) count was the only laboratory parameter from whole blood count excluding serum C-reactive protein, which varied in both subgroups ($P = 0.007$).

In the multivariable logistic regression model with a backward stepwise elimination method (Table 1), age ($P = 0.010$), diabetes mellitus ($P = 0.003$), and LUC count ($P = 0.035$) were revealed as predictors of the co-existence of CAD and severe SA even despite statin therapy. For LUCs, the estimated odds ratio [OR] was found to be 1.737 (95% confidence interval [CI], 1.040–2.901).

The multivariable analysis and ROC analysis established that the following indicators have the highest significance for CAD co-existence: LUC count above 0.19 K/μl (OR, 1.737; 95% CI, 1.040–2.901; $P = 0.035$; AUC = 0.602 with sensitivity of 68% and specificity of 51%), age (OR, 1.056; 95% CI, 1.012–2.101; $P = 0.010$; AUC = 0.612 with sensitivity of 82% and specificity of 36%), and diabetes mellitus (OR, 2.765; 95% CI, 1.413–5.410; $P = 0.003$; AUC = 0.608, giving sensitivity of 43% and specificity of 79%). Detailed information regarding uni- and multivariable analysis was presented in Table 1.

Our analysis presents a new approach to assessment of CAD co-existing with SA based on whole blood cell count analysis. To our best knowledge, this is the first study indicating that LUC count obtained from whole peripheral blood analysis is a simple and reliable predictor of CAD disease in SA patients.

There is over 50% co-existence of CAD in patients with severe SA [3]. The identification of accompanying diseases is crucial for therapy planning. Established CAD in SA was related to significantly higher risk of cardiac mortality [7]. The normal results of exercise tests were found in one-fifth of patients with asymptomatic SA and silent CAD [8]. Such observations indicate the necessity for conducting alternative non-invasive tests in this group of patients.

Both degenerative SA and CAD share similar risk factors including male sex, arterial hypertension, diabetes mellitus, smoking, and hypercholesterolemia. In our multivariable analysis, age and diabetes mellitus were found significant for CAD prediction.

Chest pain is the most typical presentation of obstructive CAD. In SA, anginal symptoms are related to an imbalance between hypertrophic myocardium oxygen demands acting in increased wall stress, secondary to left ventricular compensatory afterload and its blood flow supply [9]. Exercise tests may be inconclusive, especially in asymptomatic patients. Coronary flow reserve (CFR) in patients with SA is impaired due to reduced diastolic filling time and elevated left ventricular pressure combined with perivascular and myocardial fibrosis [10].

In our analysis, we focused on inflammatory characteristics in both diseases. The significance of inflammatory activation as an arterial hypertension trigger was postulated [11]. The results of our study point out the role of possible predictors for CAD co-existence in SA patients based on whole blood count analysis.

The link between altered monocytic phenotype and hypertension has been already shown [12]. The novelty of our finding is in presenting for the first time the importance of LUC in cardiovascular disorders. Knowledge about LUCs is scarce, and their role and significance are often overlooked. LUCs include activated lymphocytes and peroxidase-negative cells. Though LUCs are claimed to lack specificity, they represent a group of cells including blasts, atypical lymphocytes, plasma cells, and peroxidase-negative neutrophils [13]. Our previous report showed a prognostic value of LUC in assessing inflammatory activation and carotid artery stenosis characteristics [14].

Our results confirm previous reports of atherosclerosis development in patients with SA characterized by chronic inflammatory activation and show that this phenomenon may rely on a more advanced innate immune response

characterized by LUCs. The impossibility of evaluating the potential influence of the anti-inflammatory effect of statins and antidiabetic treatment may be a limitation of our study. In conclusion, a LUC count above 0.19 K/μl in whole blood analysis can be regarded as an indicator for possible co-exitance of coronary artery disease in patients with aortic stenosis.

Article information

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Are the European Society of Cardiology guidelines on lipid-lowering treatment implemented in morbidly obese patients qualified for bariatric surgery?

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INTRODUCTION

The primary aims of atherosclerotic cardiovascular disease (ASCVD) prevention are to reduce morbidity and mortality as well as increase life expectancy [1]. An important aspect of this prevention is control of apo-B-containing lipoproteins, which contribute to the induction and progression of ASCVD [1]. Prompt diagnosis and implementation of lipid-lowering treatment at every stage of dyslipidemia result in a better prognosis and lowers the risk of cardiovascular events [1, 2].

Adiposity is another major risk factor of ASCVD. This condition increases the risk of developing cardiovascular disease (CVD) by promoting dyslipidemia, diabetes mellitus (DM), and other disorders [1]. According to recent reports, 12.5% of the world's population is obese [3]. This number is twice as great in Poland [4].

We aimed to assess physicians' adherence to the latest guidelines on primary CVD prevention. To address this problem, we focused on the pharmacological treatment of dyslipidemia in morbidly obese patients before bariatric surgery. Our objective was to assess CVD risk, indications for hypolipidemic agents' introduction, and their efficacy in this group of patients.

METHODS

We enrolled consecutive patients 35 years of age or older, with morbid obesity, who had been admitted to the surgery ward to undergo bariatric surgery and agreed to participate in the study. The recruitment took place between December 2021 and April 2022. The exclusion criteria were secondary CVD prevention, chronic kidney disease, and familial hypercholesterolemia.

Medical records were used to characterize patients.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional ethics committee. Informed consent was obtained from each study participant.

IBM SPSS Statistics for Windows, Version 28.0. (Armonk, NY: IBM Corp) software was used for statistical analysis. Continuous data values were presented as mean (standard deviation [SD]) or median (interquartile range [IQR]), and qualitative data as numbers and percentages. The χ^2 test and Fisher's test were used to compare qualitative data, while Student's t-test (for data with normal distribution) and the Mann-Whitney U-test (for variables with other than normal distribution) were used for quantitative data. Continuous variables were first checked for normal distribution with the Shapiro-Wilk test. For all tests, a *P*-value less than 0.05 was considered significant. A detailed description of the study methods is presented in Supplementary material.

RESULTS AND DISCUSSION

We enrolled 57 patients with morbid obesity (n = 41; 71.9% women) at a median (IQR) age of 46 (38–51) years. More than one-fourth (n = 15; 26.3%) had DM. Detailed basic characteristics are presented in Supplementary material, *Table S1*. The mean (SD) non-high-density lipoprotein cholesterol (non-HDL-C) level

Table 1. Comparison between hypolipidemic treatment groups in terms of basic characteristics and selected parameters

	Did not require lipid-lowering treatment (n = 30)	Required lipid-lowering treatment (n = 27)	*P*-value
Age, years, median (IQR)	45.50 (39.00–51.00)	48.00 (37.00–52.00)	0.88
Female sex, n (%)	25 (83.3)	16 (59.3)	0.04
BMI, kg/m^2, median (IQR)	40.41 (37.13–46.65)	42.52 (38.57–47.40)	0.24
Maximal noted body weight, kg, median (IQR)	126.50 (108.00–141.00)	130.00 (120.00–164.00)	0.23
Waist circumference, cm, median (IQR)	111.00 (108.00–128.00)	125.50 (114.00–132.00)	0.01
Hip circumference, cm, median (IQR)	132.00 (121.00–145.00)	133.50 (122.00–139.00)	0.64
Waist/hip ratio, mean (SD)	0.89 (0.02)	0.93 (0.02)	0.09
Active smoker, n (%)	0 (0)	10 (37.0%)	<0.001[a]
SBP, mm Hg, mean (SD)	132.81 (2.18)	137.26 (2.73)	0.20
DBP, mm Hg, mean (SD)	82.98 (1.61)	84.19 (1.37)	0.57
CVD risk, %, median (IQR)	2 (1–2)[b]	4 (3–5.25)[c]	<0.001
ALT, U/l, median (IQR)	41.00 (28.00–59.00)	56.00 (46.00–77.00)	0.02
Total cholesterol mmol/l, mean (SD)	4.18 (0.16)	4.55 (0.14)	0.09
HDL-C mmol/l, median (IQR)	1.15 (1.07–1.37)	1.11 (1.01–1.21)	0.24
Non-HDL-C, mmol/l, mean (SD)	2.94 (0.15)	3.41 (0.14)	0.02
LDL-C, mmol/l, mean (SD)	2.49 (0.14)	2.85 (0.11)	0.05
TG, mmol/l, median (IQR)	1.27 (0.96–1.59)	1.31 (0.92–1.56)	0.94
Glucose, mmol/l, median (IQR)	5.53 (5.01–6.29)	5.76 (5.18–6.64)	0.37
HBA1c, %, median (IQR)	5.60 (5.40–5.90)	5.90 (5.60–6.40)	0.02
CK, U/l, median (IQR)	211.50 (152.00–301.00)	203.00 (151.00–260.00)	0.81
Creatinine, µmol/l, mean (SD)	71.82 (1.99)	72.14 (3.13)	0.93
eGFR, ml/min/1.73 m^2, mean (SD)	88.24 (3.25)	90.85 (3.50)	0.59

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; CK, creatine kinase; CVD, cardiovascular disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides

[a]More than 20% of expected counts were <5. [b]CVD risk calculated for 27 individuals. [c]CVD risk calculated for 17 individuals

was 3.16 (0.11) mmol/l, low-density lipoprotein cholesterol (LDL-C) 2.66 (0.09) mmol/l, median (IQR) serum concentration of triglycerides (TG) was 1.28 (0.94–1.56) mmol/l, total cholesterol 4.3 (3.8–4.9) mmol/l. Ten patients (17.5%) were smokers or have quitted during the last stage of preparation for surgery (≤3 months before surgery). Half of the patients had a high CV risk (n = 29; 50.9%), followed by low-moderate (n = 26; 45.6%), and very high (n = 2; 3.5%). More than one-fifth (n = 12; 21.1%) of study participants had hypercholesterolemia diagnosed before enrollment. Of these, ten subjects (17.5%) had some sort of pharmacological treatment. Most of them were statins-only users (n = 6; 60% of patients on hypolipidemic treatment), two (20%) were on fibrates, one (10%) had statin and fibrate, and one (10%) took statin and ezetimibe. However, only one of those patients had the LDL-C level within normal limits, while all others could have their treatment intensified. Two patients (3.5%, with dyslipidemia diagnosed earlier) had no treatment introduced at the time it was required.

Dyslipidemia was newly diagnosed in other 15 patients. Altogether, almost half of the study population (n = 27; 47.4%) had hypercholesterolemia but was on no or insufficient treatment. This number included 5 (8.8%) participants with hypertriglyceridemia. None of the previously mentioned patients met the exclusion/discontinuation criterion for statin treatment, which is creatine kinase >4 times the upper limit of normal, and only 4 (14.8% of those in need of lipid-lowering therapy) could take these drugs because of their alanine aminotransferase levels, which were >3 times the upper limit of normal [2].

As shown in Table 1, the patients who required dyslipidemia treatment had higher levels of alanine aminotransferase, non-HDL-C, and LDL-C. Moreover, the group that needed hypolipidemic treatment consisted mostly of men.

Although there is a large number of previously published articles on lipid profile and pharmacological lipid-lowering treatment in morbidly obese patients before bariatric surgery, they do not provide data on undiagnosed lipid metabolism disorders or untreated patients [7–9]. Our study is the first to provide this information.

In our work, the percentage of morbidly obese patients with hypercholesterolemia before bariatric surgery was comparable to other research, although the percentage of our participants with hypertriglyceridemia was significantly lower compared to 24% and 53% reported in the literature [5, 8, 9]. This discrepancy might partially result from the diagnostic criterion we used when setting the threshold value of TG: 2.3 mmol/l [1].

The average levels of LDL-C and TG presented in our article (2.66 and 1.28 mmol/l, respectively) are lower than the values reported in a similar study from Austria (3.12 and 1.78 mmol/l) [6], Singapore (3.05 and 1.66) [7], and the US (2.88 and 1.74 mmol/l) [10]. Conversely, serum levels of non-HDL-C in the Austrian study (3.9), and total cholesterol shown in the Singaporean investigation (4.9 mmol/l) were lower than those quoted in our article (3.16 and 4.3 mmol/l,

respectively). Furthermore, the perioperative statin user ratio observed in our study was much lower in comparison to the results reported in American publications (10.5% vs. 24.5%, and 34%) [10, 12].

Our investigations, showing insufficiencies in the pharmacological treatment of dyslipidemia in morbidly obese patients before bariatric surgery, have some limitations. One factor that might have influenced the outcomes was the COVID-19 pandemic, which reduced healthcare accessibility. Another reason may be the lack of patient adherence to prescribed medications. In any case, our results should encourage all physicians involved in treating morbidly obese patients to actively screen them for dyslipidemia and regularly evaluate effectiveness of lipid-lowering treatment. There are three main reasons why the above-mentioned checks should be performed particularly in individuals qualified for bariatric surgery. First, the process of preparing for surgery should last 6–12 months, so there is plenty of time to introduce effective treatment before, hypothetically, more effective intervention [13]. Second, quite a considerable number, reaching 40% of post-bariatric patients, do not demonstrate dyslipidemia remission. What is more, its relapse rate may come up to 24% [14]. Lastly, patients on preoperative statins may have a higher DM rate and hypertriglyceridemia remission [11,14].

The main limitation of our research is the fact that the study was conducted in one bariatric center, and the enrolled group was relatively small. Moreover, we did not have data on target organ damage in DM patients, which might have impaired their CV risk assessment. Nevertheless, if we had possessed this information, we could only have assigned such patients to the higher CV risk group, which would support the outcomes.

In conclusion, our study is the first to show that morbidly obese patients before bariatric surgery may be underdiagnosed and undertreated for dyslipidemia. These findings, if confirmed by further research involving a larger number of clinical centers, would indicate a need for revisiting clinical practices applied to patients qualified for bariatric surgery.

Supplementary material

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

Article information

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Initial experience with transvenous lead extraction of His bundle pacing leads

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INTRODUCTION

The use of conduction system pacing (CSP) is expanding globally in the treatment of patients with bradycardia, atrioventricular conduction disorders, and those requiring cardiac resynchronization therapy (CRT), through such techniques as His bundle-branch pacing (HBP) and left bundle-branch area pacing (LBBAP). The increase in the use of implantable devices with HBP and LBBAP has led to the first-ever recommendations for permanent pacing using HBP pacing [1, 2]. This growing interest in CSP, along with the rapidly expanding evidence base for CSP, is expected to result in a significant increase in the number of CSP patients in the coming years.

However, the long-term performance of CSP can be impacted by the learning curve of operators and anatomical challenges. In this population, HPB patients are more likely to suffer from high pacing thresholds leading to a higher likelihood of transvenous lead extraction (TLE). Furthermore, complications such as lead-dependent infective endocarditis (LDIE), local infections of the device pocket (LI), lead dysfunctions, and the presence of redundant/inactive leads can also contribute to an increased number of TLE procedures.

Currently, there is a lack of large data on TLE procedures of CSP lead extraction, particularly HBP leads in the adult population. Our study aimed to present the initial experience of performing TLE procedures in patients with HBP leads utilizing a non-stylet-driven Medtronic 3830 lead (MDT 3830, Medtronic Inc, Minneapolis, MN, US) from a tertiary center's perspective.

METHODS

A prospective analysis of the records included all patients with HBP leads who underwent TLE from October 2011 to February 2023. The patient inclusion criteria were the presence of an HBP lead and the need for TLE regardless of indication. The Research and Ethics Committee of Jagiellonian University approved the study protocol (KBET/259/B/2011), and written informed consent was obtained from all patients for using their anonymized data in the present study. The study protocol conformed with the Declaration of Helsinki and complied with the Good Clinical Practice guidelines.

In this study, patients whose HBP leads had been implanted for less than one year before the procedure were also included in the analysis. Data were collected from a prospectively maintained database comprising records on device implantation, follow-up on the device, medical information obtained from general cardiac centers during the index admissions for TLE, and data on 30-day complications after the procedure. We analyzed the data on the presence of non-functional/abandoned leads, age of extracted leads, fluoroscopy time, extraction techniques used during TLE, effectiveness of TLE, complete/incomplete removal for each lead targeted, and complications occurring during the intra-operative and 30-day post-operative period.

Table 1

Patient	Sex	Age, year	Pacing system	LVEF, %	Indication for TLE	Dwell time HIS pacing lead, months	Tools	Results of the TLE procedure	Fluoroscopy time, minutes
No 1	M	76.3	CRT-D HIS	24	Lead dysfunction	17.3	T	Full success	0.18
No 2	F	66.1	CRT-D HIS	35	Lead dysfunction	22.0	T	Full success	0.083
No 3	M	65.8	CRT-D HIS	50	Upgrade	10.9	CSF	Full success	6.42
No 4	M	79.7	CRT-P HIS	17	LDIE	6.9	T	Full success	0.1
No 5	M	73.1	CRT-D HIS	26	LDIE	7.8	T	Full success	0.05
No 6	M	66.5	CRT-D HIS	38	Local infection	15.1	T	Full success	0.1
No 7	M	61.2	CRT-D HIS	25	Local infection	17.0	T	Full success	0.05
No 8	M	68.3	CRT-D HIS	20	Upgrade	19.8	T	Full success	0.1
No 9	M	75.1	CRT-D HIS	35	Upgrade	43.3	C	Full success	2.88

Abbreviations: C, lead removal with polypropylene sheets; CRT-D HIS, cardiac resynchronization therapy with His bundle pacing; CSF, lead removal with polypropylene sheets combined with stabilizing the lead via femoral access; T, simple traction; LDIE, lead-dependent infective endocarditis; LVEF, left ventricular ejection fraction; TLE, transvenous lead extraction

The effectiveness of TLE procedures was defined according to the current Heart Rhythm Society (HRS) and European Heart Rhythm Association (EHRA) consensus [3, 4]. The description of the TLE procedure was presented in our earlier article [5].

Statistical analysis

Continuous variables were presented as median and interquartile range (IQR) or minimum and maximum values. Categorical variables were presented as counts and percentages.

RESULTS AND DISCUSSION

The study involved nine patients who met the inclusion criteria, one of whom was female, with a median (IQR) age of 68.3 (65.9–75.7) years and a range of 61–79 years. All patients had cardiac implantable electronic devices (CIED) with HBP using a non-*stylet*-driven Medtronic 3830 lead (MDT 3830, Medtronic Inc, Minneapolis, MN, US). Seven patients had CRT with HBP (HOT-CRT), and two patients had an ICD with HBP. All CIEDs were implanted for primary prevention on the left side of the chest. TLE was performed due to LDIE (2 patients), LI (2 patients), and non-infectious indications (5 patients). In patients with non-infectious indications, three patients required TLE due to an increase in their HBP threshold, and two patients with HOT-CRT and complete ipsilateral venous occlusion required additional placement of an atrial lead. In addition, 33.3% of patients had significant ipsilateral venous occlusion. The median (IQR) lead dwell time was 17.0 (9.3–20.9) months, and the majority of extracted CSP leads were over a year old.

The patients in our study had a high prevalence of comorbidities, including dyslipidemia (100%), atrial fibrillation (88.9%), ischemic heart disease (77.8%), hypertension (77.8%), diabetes (55.5%), history of myocardial infarction (55.5%), previous cardiac surgery (44.4%), and chronic kidney disease (44.4%).

TLE with the Medtronic 3830 lead was technically challenging due to its lumenless design, narrow caliber, cable-fixed exposed helix, and inability to use stylets. Furthermore, the high tensile strength of the Medtronic 3830 lead due to the presence of an inner cable and a non-retractable helix may pose a risk of myocardial avulsion [6, 7]. Nonetheless, the extraction efficacy of all targeted HBP leads was high and achieved 100%. Five leads were removed using simple traction, while four leads required more mechanical extraction tools, including Byrd dilators (Cook Medical). In two patients, an HBP lead was used to retrieve venous access due to complete ipsilateral venous occlusion, with stabilization of the HBP leads via a femoral approach with a Needle Eye Snare. The median (IQR) fluoroscopy time was 0.1 (0.07–1.53) minutes. The longest fluoroscopy times were recorded when HBP electrodes were used to regain venous access. There were no major or minor intra-procedural complications (Table 1).

While TLE procedures of CSP lead extraction are well documented in the pediatric population, there are limited data in the adult population [8]. The study by Vijayaraman et al. is the only report of retrospective analysis of 30 adult patients who underwent TLE of HBP leads, with a mean dwell time of 25 (18) months, which, in most cases, were successfully extracted with manual traction alone [9]. Additional data were derived from case descriptions such as our previous case study, where we reported a successful complex mechanical extraction of an HBP lead to retrieve venous access in an upgrade procedure [10].

TLE procedures, although safe, carry the risk of both major and minor complications, as demonstrated by Tajstra et al., who presented a TLE complication rate of approximately 5.6% in more than 800 patients. When determining the factors associated with TLE procedure complications, the authors showed that the presence of comorbidities such as prior dialysis, chronic kidney disease, and ventricular tachycardia were independent factors of higher risk of TLE-related in-hospital complications. Furthermore, heart failure and older age can independently affect 12-month mortality [11]. In the analyzed small population of HBP patients, the high percentage of effectiveness and safety of TLE procedures was achieved despite the high prevalence of comorbidities which, in our opinion, can be explained

by the short lead dwell time and the experience of the operators. However, it is reasonable to assume that with an increased lead dwell time, the profile of safety and complications of TLE procedures will be similar to large-scale studies.

An additional area of interest is the issue of performing TLE procedures involving HBP leads in patients with complex clinical situations. On this basis, as we described earlier, the implementation of HBP appeared to be an effective and safe pacing method in a heart transplant recipient [12]. Although we did not observe additional complications while performing TLE procedures in heart transplant recipients, managing malfunctioning or infected HBP leads is impaired by the lack of large-scale data on TLE procedures in this group of patients.

In conclusion, based on the analyzed study population, the TLE procedure appears to be safe and effective. However, to obtain more reliable assessment of its long-term effectiveness and safety in an expanding population of CSP patients, it is necessary to conduct a large multicenter prospective study.

Article information

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Routine use of procedural sedation and analgesia for transcatheter edge-to-edge mitral valve repair

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INTRODUCTION

Transcatheter edge-to-edge repair (TEER) of the mitral valve has become a well-established treatment for moderate-to-severe secondary mitral valve regurgitation in patients not eligible for classical surgery [1]. It is the most widely used technique of transcatheter mitral valve repair in Poland [2]. It effectively reduces the rate of heart failure (HF)-related hospital admissions and improves symptoms and quality of life [3]. The TEER procedure is associated with similar safety in patients with multiple comorbidities compared to less frail patients qualified for surgical procedures [4]. Therefore, it appears reasonable to assume that minimally invasive mitral valve repair should involve minimally invasive anesthetic management.

TEER is typically performed under general anesthesia (GA). There are, however, reports of this procedure performed under procedural sedation and analgesia (PSA) [6].

In the current study, we evaluated the safety and feasibility of the PSA protocol in twenty-six patients undergoing mitral TEER.

METHODS

Preoperative care

The choice of anesthesia management for TEER depends on several factors and should be chosen by the Heart Team individually for each patient. The key to therapeutic success is excellent communication between a cardiologist, cardiac surgeon, and anesthesiologist.

The patient's medical history, anatomy, and procedural course can affect the choice of anesthesia method. Following the "less-is-more" principle, all patients in our center are qualified for PSA unless indications for GA are present. Among the most frequent GA indications are neurological disorders, possible difficulties in maintaining an open airway, and trouble maintaining a still supine position. Also, the expected length of the procedure and any foreseeable technical difficulties related to mitral valve anatomy should be considered.

A contraindication to PSA is the patient's lack of consent, which may result from fear and poor understanding of the procedure. Usually, a conversation and a detailed explanation of the upcoming procedure result in consent for PSA. In addition, proper education reduces anxiety, and premedication is typically not needed.

Intraoperative care

The surgical procedure is performed in a hybrid operating theater. The surgical team includes cardiologists, cardiac surgeons, anesthesiologists, radiology technicians, and nurses. Also, a cardiac surgery team remains on-call if a sternotomy is required. An interventional echocardiographer is responsible for intraoperative transesophageal echocardiography (TOE).

The hybrid room setup for TEER under PSA is shown in Figure 1. Anesthetic management includes monitoring of ECG, SpO_2, invasive blood pressure (IBP), diuresis, and temperature. A heating mattress placed under the patient is used to prevent intraoperative hypothermia without affecting the quality of X-ray imaging. High flow nasal oxygen therapy (HFNOT) provides respiratory support with fresh gas flow of 40–60 l/min and an inspira-

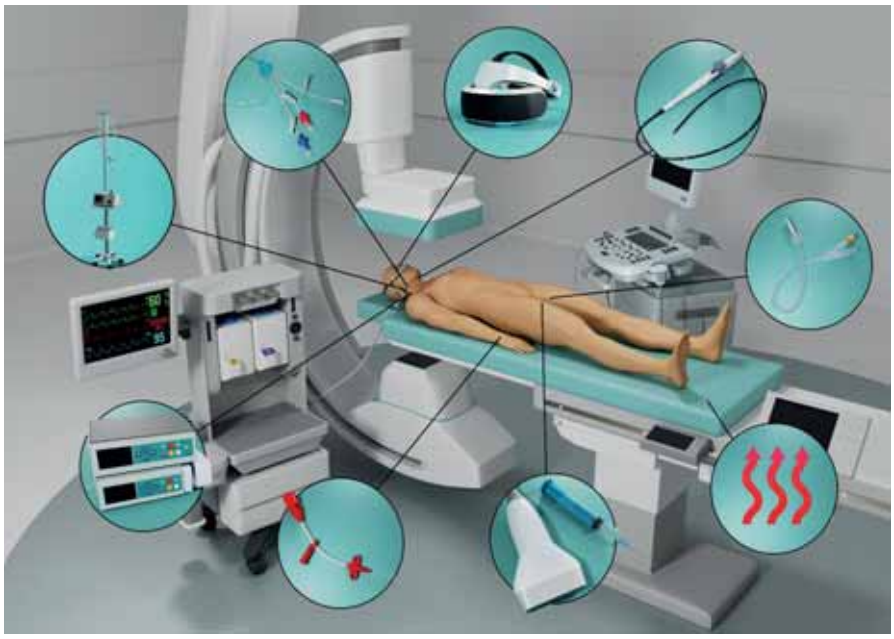

Figure 1. Hybrid room setup for transcatheter edge-to-edge repair

tory fraction of oxygen (FiO_2) 40%–50% adjusted according to SpO_2. In addition to precisely titrating FiO_2, HFNOT allows high flow rates. Such excess provides an adequate volume of fresh gas mix and produces continuous positive airway pressure, potentially reducing the size of pulmonary atelectasis. Next, a peripheral venous 18G cannula is placed, and an intravenous infusion of dexmedetomidine 0.2–0.7 µg/kg/h is started and maintained during the procedure with a target of 0/–1 pt. in Richmond Agitation Sedation Scale (RASS). Because of the need for invasive blood pressure monitoring, radial artery cannulation is performed in every patient. Central venous cannulation through the right internal jugular vein under ultrasound guidance is done routinely for the same reason. A Foley catheter is inserted during sedation.

For local access site anesthesia, 0.5% ropivacaine is administered under ultrasound guidance. If not contraindicated, preemptive 1.0 g paracetamol and 1.0 g metamizole are administered intravenously as part of multimodal analgesia.

The placement of the TOE probe is done after superficial anesthesia of the pharyngeal wall with 10% lidocaine. Suctioning excess saliva from the oral cavity is done with a dental suction device.

To enhance the patient's experience and comfort even further, in several cases, we have successfully used virtual reality (VR) goggles to play a video previously selected by the patient. Such an approach was well received by the patients.

Postoperative care

After the procedure, the patient is transferred to the Cardiac Intensive Care Unit for 24 hours and subsequently transferred to the cardiac ward according to clinical status.

The following aspects were considered in the analysis of the rationale for performing TEER procedures under PSA: (1) early complications, including hemodynamic and respiratory stability during the procedure; (2) postoperative complications; (3) surgical complications; (4) hospitalization time; and (5) in-hospital mortality.

Statistical analysis

Descriptive Statistics was performed with StatsDirect 3.1 software (StatsDirect LDT, Birkenhead, UK). Quantitative variables are presented as median and interquartile range (IQR). Qualitative variables are presented as absolute values and percentages.

RESULTS AND DISCUSSION

Between March 2021 and July 2022, twenty-seven TEER procedures were performed in our hospital. Of the operated patients, only one (3.7%) had elective general anesthesia, and the remaining (26/27, 96.3%) underwent TEER under PSA. Procedural success was achieved in all patients.

The median age of the patients was 74 (67–81) years old, and the median EuroSCORE was 7.1 (4.8–11.4). The median procedure time was 105 (80–120) minutes.

We did not observe any serious adverse events during the anesthesia procedure.

To ensure hemodynamic stability, intraoperative catecholamine infusion was administered in only one case (3.8%). Most patients, including those with respiratory diseases, underwent the procedure without respiratory complications (25/26, 96.2%). Only in one case (3.8%), a transient face mask ventilation was necessary due to hypoventilation without subsequent complications. No case required conversion to GA.

In the postoperative period, the total time of HFNOT support was <24 hours. Respiratory complications requiring passive oxygen therapy with nasal cannula >48 hours occurred in four cases (15.4%). The most prolonged oxygen

support lasted eight days in a patient with respiratory failure caused by pneumonia.

The most incidental surgical complication was minor bleeding and access site hematoma, which occurred in seven cases (26.9%). Major bleeding requiring transfusion of red blood cells and/or blood products in the postoperative period was reported in two patients (7.7%). One patient (3.8%) required surgical management of access site bleeding.

The median length of hospital stay was 7 (5–8) days, and the time from procedure to discharge was 5 (4–6) days. There were no in-hospital deaths.

The main advantage of general anesthesia during TEER is full control of intraoperative conditions. However, general anesthesia has known disadvantages. The use of general anesthesia in patients can lead to prolonged mechanical ventilation, increased risk of ventilation-associated pneumonia (VAP), and potentially increased costs of the procedure. As shown for transcatheter aortic valve implantation (TAVI), performing the procedure without GA can significantly reduce the length of hospital stay and costs [5].

TEER in most centers is done under GA because of the prolonged procedural time, implantation of multiple clips, use of stop-breath maneuver during grasping, and widespread perception that only GA provides adequate patient comfort during the procedure. However, progress in technology and growth in operators' experience have led to a significant shortening of procedural times. Therefore, PSA has become a valid alternative. Moreover, a trend was shown toward overall clinically shorter procedure time for patients undergoing TEER with sedation compared with GA [6].

A meta-analysis [6] did not show statistically significant differences between sedation and GA in terms of the effectiveness of the procedure, mortality, and most common periprocedural complications. One study showed a decreased need for vasopressors in patients undergoing TEER under sedation compared to GA [7]. The patients undergoing TEER under PSA had a comparable total length of hospital stay, with shorter ICU stay.

Previous studies comparing the use of GA vs. PSA for TEER procedures have shown comparable safety and effectiveness of the procedure in patients undergoing such anesthesia [6].

This preliminary analysis provides a rationale for using PSA as an alternative to GA during TEER procedures. Specific PSA protocols for TEER procedures are lacking. This publication presents validated procedural management and sedation protocol that can be adopted in other centers performing TEER. Prospective comparisons to other PSA GA protocols are needed.

Article information

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Peripheral intravascular lithotripsy paving the way for Impella-assisted multivessel high-risk percutaneous coronary revascularization

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In cases of challenging percutaneous coronary intervention (PCI) in patients with poor left ventricular ejection fraction (LVEF), when the risk of cardiosurgical treatment is unacceptably high, left ventricular assist devices (LVADs) increase safety by minimizing periprocedural ischemia, preventing hemodynamic instability, and allowing time for lesion preparation and optimization techniques [1]. Impella CP (Abiomed, Danvers, MA, US), which is the predominantly used LVAD in high-risk PCI cases, requires a minimum 19 French (F) access site, preferably with little tortuosity en route to the ascending aorta. Advanced peripheral atherosclerosis within the iliofemoral axis may pose a serious challenge during the introduction of an LVAD [2].

A 77-year-old male multimorbid patient with ischemic cardiomyopathy (LVEF, 35%) and a symptomatic chronic coronary syndrome (class III in the Canadian Cardiology Society functional scale) was qualified by the Heart Team for multivessel percutaneous coronary angioplasty, supported with an LVAD. The initial coronary angiogram revealed multivessel coronary disease with a significant left main lesion involving the proximal segments of the left anterior descending (LAD) and circumflex (LCx) arteries, a long lesion in the proximal and medial segments of the LAD (Figure 1A), and a subtotal ostial lesion in the right coronary artery (RCA) (Figure 1B). A computed tomography scan revealed severe tortuosity in the left iliofemoral axis and a significantly heavily calcified tandem lesion in the right common and external iliac arteries, with a minimum diameter of 3.4 mm (Figure 1C). The left subclavian artery was also stenosed, which excluded it as an alternative access site. Under angiographic control (using right radial access and a pigtail catheter), we obtained right femoral access with a 6 F sheath, subsequently deployed two automated mechanical sutures, and exchanged them for an 8 F sheath. We then performed intravascular lithotripsy (IVL) in the right common and external iliac arteries using a Shockwave C2 7.0/60 mm IVL catheter deployed with 4–6 atmospheres (Shockwave Medical, Santa Clara, CA, US), with eight applications (20 seconds each) and obtained optimal lesion resolution (Figure 1D). After changing to a 19 F sheath, we introduced the Impella CP System (Abiomed, Danvers, MA, US), with permanent support of 3.6 l/min. Initially, we performed RCA PCI with implantation of a 3.5/18 mm drug-eluting stent (DES) (Figure 1F). Consequently, using an extra backup 3.5, 7 F guiding catheter, we performed LM/LAD/LCx PCI using the double-kissing-crush technique with three DES (Figure 1E). All procedures were guided by intravascular ultrasound, which confirmed the optimal effect. The right femoral access site was closed using two Perclose ProStyle devices (Abbott Vascular, Santa Clara, CA,

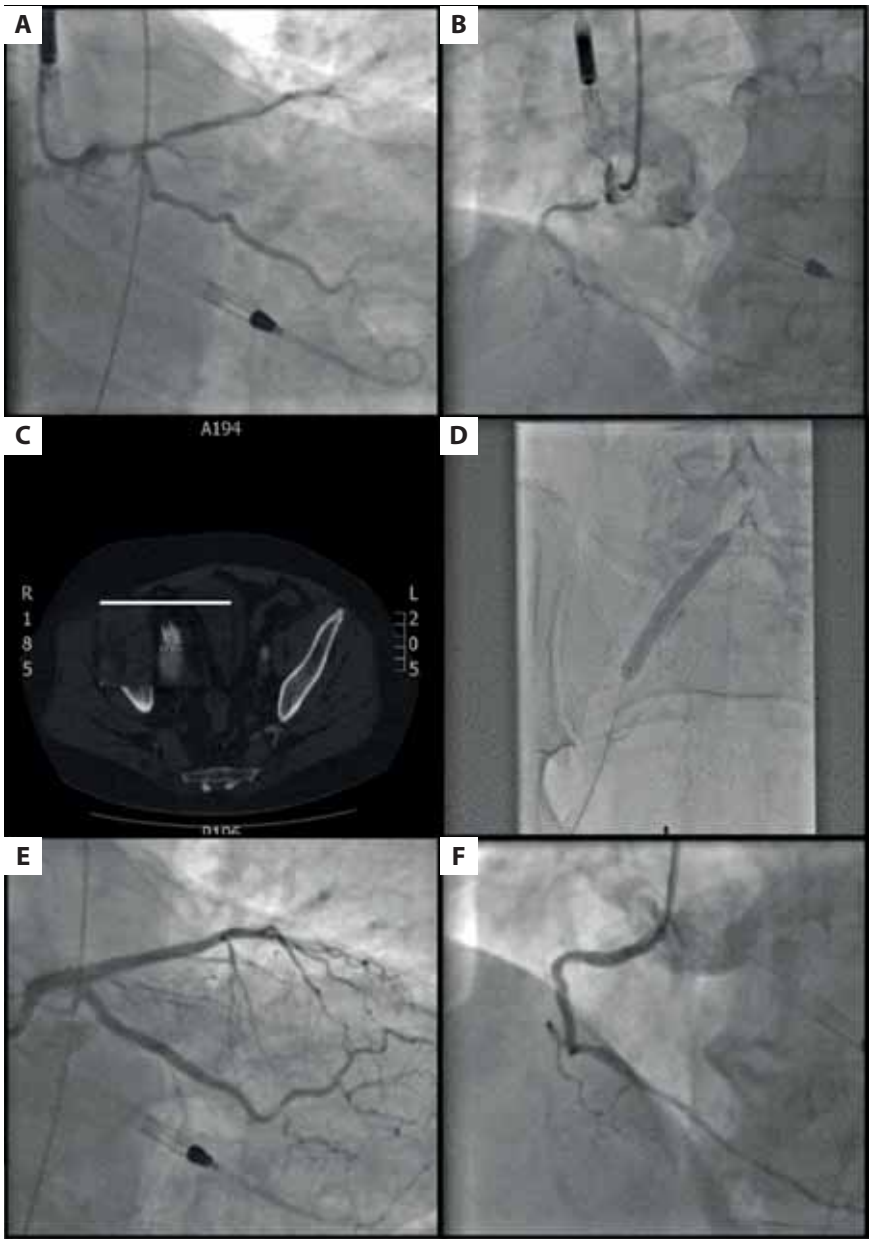

Figure 1. A. Coronary angiography of the left coronary artery showing severe diffuse disease. **B.** Coronary angiography of the right coronary artery showing a severe ostial lesion. **C.** Computed tomography angiography showing almost 360° calcification within the common and external iliac arteries. **D.** Peripheral intravascular lithotripsy with the optimal angiographic result. **E.** Final angiographic result in the left coronary artery. **F.** Final angiographic result in the right coronary artery

US) and one AngioSeal 8 F System (AS; St. Jude Medical, St. Paul, MN, US), with the optimal angiographic result [3] (Figure 1F). The dose length product was 1289 mGy, and the contrast dose was 180 ml.

Peripheral artery disease co-exists with coronary artery disease in more than 40% of cases [4]. Calcified lesions within the iliofemoral axis pose a serious challenge to using LVADs but may be overcome by applying contemporary techniques, such as IVL. Complications related to peripheral IVL are rare and include mainly device malfunction (56.5% in a recent report) [5]. In accordance with the manufacturer's guidelines, the device is contraindicated when the lesion is uncrossable with a 0.014 guidewire as well as in cases of in-stent restenosis.

Article information

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Yet another explanation for Pheidippides' death?

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According to a legend, about 2500 years ago, Pheidippides, a legendary Greek hemerodrome, or courier, died shortly after running from Marathon to Athens to bring the news about the Greek victory over the Persians. The very cause of his death remains undetermined [1].

We want to propose yet another explanation for Pheidippides' death based on the case of a 35-year-old man — an amateur ultramarathon runner who was admitted to the emergency department with severe fatigue and skeletal muscle pain lasting over two days after a 210 km 24-hour run. His history was negative for anabolic steroids or other medication.

His Glasgow coma scale score on admission was 13 points. His electrocardiography (ECG) on admission (Figure 1) showed bradycardia with junctional rhythm 25/min. After administration of atropine 0.5 mg *i.v.*, the rhythm accelerated to 45 BPM with no visible P waves. Elevations of J-point in the anterior leads and broad peaked T waves were observed. Echocardiography showed hypokinesis of the apical segments of the left

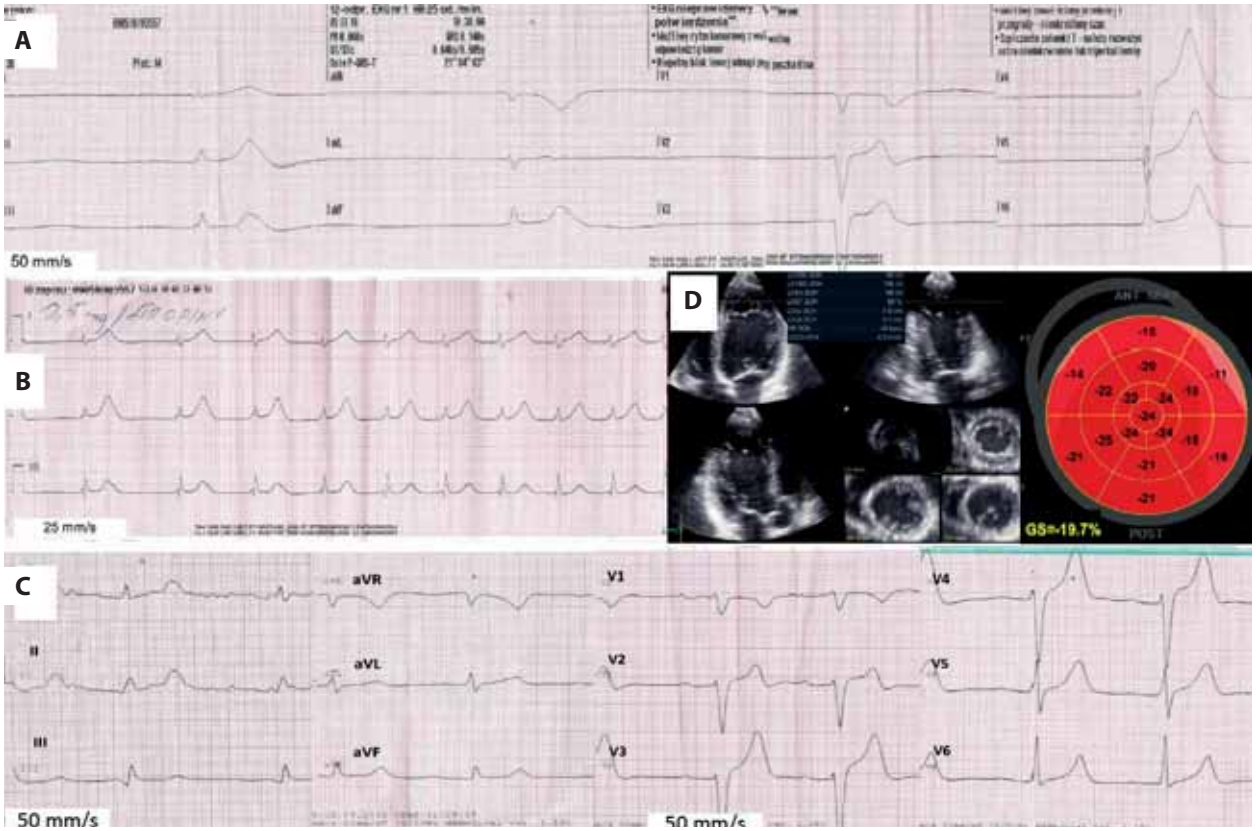

Figure 1. A. Electrocardiography (ECG) on admission shows bradycardia with junctional rhythm 25/min. **B.** After administration of atropine 0.5 mg i.v., the rhythm accelerated to 45 BPM with no visible P waves. Elevations of J-point in the anterior leads and broad peaked T waves were observed. **C, D.** ECG and transthoracic echocardiography on discharge showing restoration of normal ECG and normal left ventricular function (ejection fraction, 58%; global longitudinal strain, 19.7%)

ventricle with ejection fraction of 40%, with no significant valvular disease. After bladder catheterization, dark-colored brown urine was obtained.

Blood tests showed severe hyperkalemia (8.4 mmol/l) with a high creatinine level (6.18 mg/dl) and low estimated glomerular filtrated rate (eGFR, 11.05 ml/min/1.73 m^2), along with extreme serum myoglobin concentration (>30 000 ng/ml), CK-MB mass (>300 ng/ml), and elevated troponin T (0.109 ng/ml), white blood cell count, and C-reactive protein. The patient was diagnosed with exercise-related rhabdomyolysis, which led to acute kidney injury with consecutive hyperkalemia, and hemodialysis in the intensive care unit was introduced. He recovered after 4 weeks, with normal electrocardiography and normal left ventricular function (ejection fraction [EF], 58%, global longitudinal strain [GLS], 19.7%) restored.

Rhabdomyolysis with renal failure may represent a possible explanation for Pheidipiddes' death [2] — especially while taking into account that the distances he covered were similar to those made by our patient. The Athenian runner had run from Athens to Sparta (212 km) in 4 days, and on the next day — again ran from Athens to the battlefield near Marathon (40 km) and back to Athens to bring the news of victory. Both he and our patient were properly trained with previous experience in running similar distances.

Article information

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A patient with non-ST-segment elevation myocardial infarction complicated by distal perforation of the left anterior descending artery

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An 80-year-old male patient with non-ST-segment elevation myocardial infarction, disqualified from coronary artery bypass surgery due to high surgical risk, was admitted for further invasive treatment. His medical history included inferior wall myocardial infarction in 2005, New York Heart Association (NYHA) class II heart failure with reduced ejection fraction of 35%, hypertension, type 2 diabetes mellitus, hyperlipidemia, and nicotine dependence.

Coronary angiography revealed subtotal stenosis of the distal left main artery (LM), involving bifurcation of the left anterior descending artery (LAD) and the circumflex artery (LCx) (Figure 1A). The right coronary artery presented diffuse atherosclerosis without significant stenosis. Therefore, the patient was qualified for high-risk percutaneous coronary intervention (PCI) of the LM/LAD/LCx. He was preloaded with ticagrelor and aspirin before PCI.

During the procedure, unfractionated heparin was administrated, and the activated clotting time was maintained above 250 s. We applied an EBU 3.5 7 F guide catheter via right femoral access. Due to severe calcification, we effectively performed rotablation of the LM with the proximal segments of the LAD and LCX using a 1.5 mm burr (Supplementary material, *Videos S1, S2*). We obtained expansion of a full non-compliant (NC) 2.5 mm balloon and sequentially implanted a stent into the LCx (Supraflex Cruz 2.5 × 20 mm) and the LM/LAD (Ultimaster 3.5 × 24 mm) using the DK-crush technique. The first and second "kissing balloon" inflation was accomplished with 2.5 mm (LCx) and 3.5 mm (LAD) NC balloons, respectively. We performed a proximal optimization technique (POT) of the LM with a 5.0 mm balloon (Figure 1B). Intravascular ultrasound (IVUS) confirmed the optimal stent apposition (Figure 1C).

However, after removing the guidewire from the coronary artery (Sion Blue, Asahi Intecc, Japan), we noticed a distal LAD perforation (Supplementary material, *Video S3*). The guidewire was reintroduced into the vessel, and a 2.0 mm balloon was expanded, occluding the distal segment (Figure 1D). Despite several attempts at prolonged inflation, bleeding into the pericardium persisted. Autologous fat embolization was also unsuccessful. Due to hemodynamic instability in the course of increasing cardiac tamponade, effective decompression of the pericardial sac was performed, stabilizing the patient's condition. Because of the complexity of PCI, we decided not to administer protamine. Subsequently, we decided to close the distal LAD with a vascular coil. We delivered three vascular coils (Optima Coil System, BALT USA LLC), resulting in the complete cessation of bleeding (Figure 1E). The patient was transferred to the Intensive Care Unit in stable condition without any visible pericardial fluid on echocardiographic examination. After 4 hours, the patient's clinical condition deteriorated due to the re-accumulation of pericardial fluid and increasing cardiac tamponade, leading to cardiac arrest in the form of pulseless electrical activity (PEA). After ineffective pericardial puncture attempts, emergency thoracotomy was performed, resulting in pericardial sac decompression and return of hemodynami-

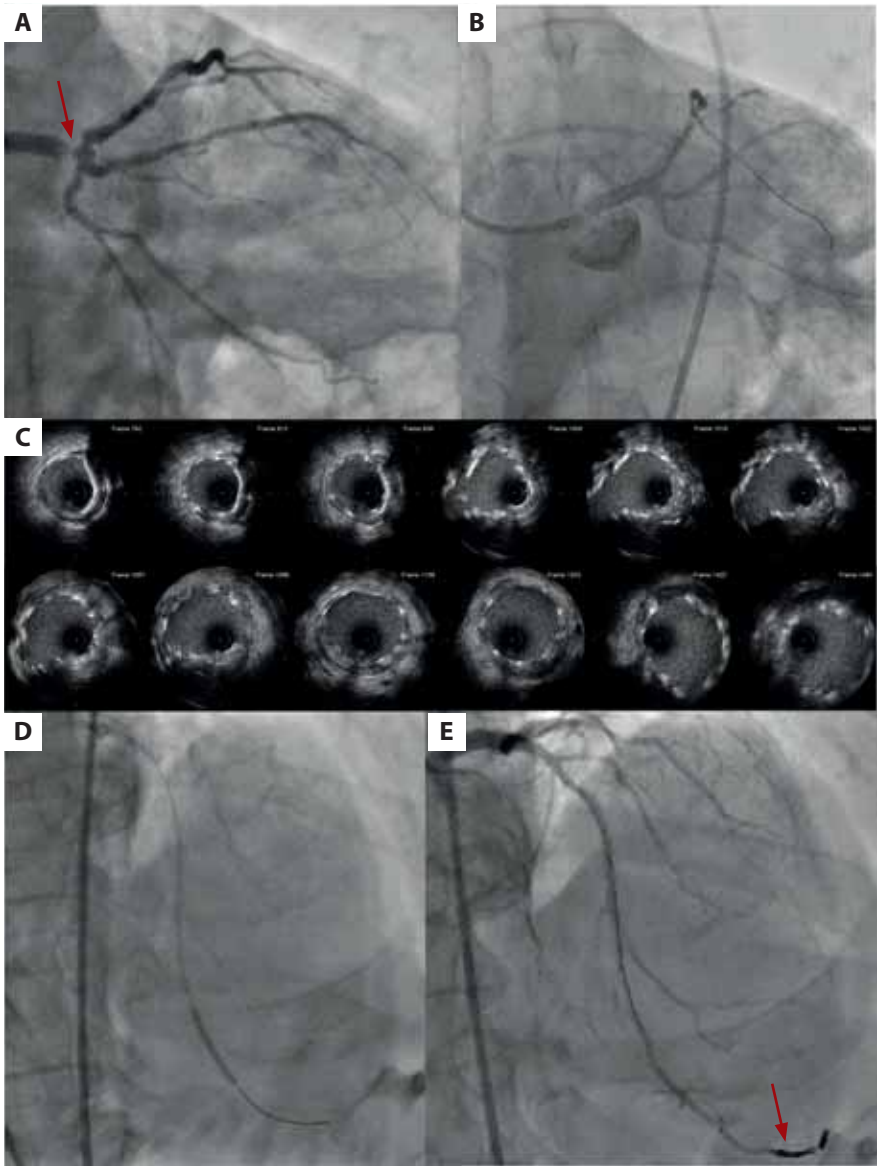

Figure 1. A. Baseline angiography of the left coronary artery with critical stenosis of the left main (LM), proximal anterior descending (LAD), and circumflex artery (LCX) (red arrow). **B.** The final angiographic result. **C.** Final IVUS cross-sections of the LM and the LAD, with a well-expanded stent. **D.** The balloon expanded in the distal segment of the LAD occluding the artery. **E.** The vascular coils placed in the distal segment of the LAD, closing the flow in the artery (red arrow)

cally efficient circulation. Unfortunately, the patient died the following day because of severe metabolic acidosis and multiple organ failure.

Distal coronary perforation is often caused by guidewire-related vessel injury and is more common for hydrophilic wires [1], as in our case. A looped wire tip is considered safer than a straight tip, reducing inadvertent migration into a distal segment or small branches [2]. It seems that with extensive damage to the small vessels, bleeding may continue despite occluding the main supplying artery.

Supplementary material

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

Article information

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Isolated persistent left superior vena cava associated with anomalous left hepatic vein drainage into the right atrium accidentally discovered after sternotomy

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A 57-year-old woman with a medical history of arterial hypertension and atrial fibrillation was admitted for mitral valve surgery because of moderate mitral regurgitation registered on transthoracic echocardiography. Due to a borderline indication for surgical treatment, a transesophageal echocardiographic examination was performed preoperatively. Although its focus was on mitral regurgitation, which was confirmed as moderate (regurgitation grade 2/3, the mitral valve annulus 3.8 cm), the bicaval view could not be seen despite multiple attempts. No other abnormalities were registered.

After induction of anesthesia, which proceeded without difficulties, median sternotomy was performed. After pericardiotomy, normocardia, situs solitus and the presence of venous anomalies were noticed by the surgeon. At that time, the presence of the persistent left superior vena cava (PLSVC), agenesis of the right superior vena cava (RSVC) and double inferior vena cava were suspected. The operation was abandoned for additional diagnostics. Contrast-enhanced computed tomography (CECT) of the heart showed the presence of a PLSVC draining into the right atrium (RA) via the dilated coronary sinus (CS), along with the agenesis of the RSVC (Figure 1A, B). CECT of the abdomen showed anomalous left hepatic vein (LHV) drainage into the RA (Figure 1C, D). To the best of our knowledge, a combination of these anomalies has not been described so far. Another curiosity is that it was discovered in such a clinical scenario. Considering the discovered congenital anomalies on the one hand and a moderate grade of mitral regurgitation on the other, the Heart Team and the patient made a joint decision to continue with conservative medical treatment.

The PLSVC is an embryologic remnant of the left superior cardinal vein seen in 0.1% to 0.3% of healthy adults [1]. Most cases of PLSVCs are associated with RSVC, a condition known as duplication of the superior vena cava [1, 2]. The PLSVC with the agenesis of an RSVC is extremely rare, and it is known as an isolated PLSVC [3]. The diagnosis can be easily missed unless specific preoperative testing is carried out, such as a cardiac computed tomography scan. It is often discovered incidentally during an examination of heart disease, central venous line insertion, or pacemaker implantation. The PLSVC usually drains into a dilated CS, and its catheterization can cause hypotension, angina, and perforation of the heart, causing tamponade and cardiac arrest [1]. Therefore, when congenital systemic venous anomalies are suspected, accurate anatomical assessment of the venous system to detect possible coexistent cardiac anomalies is useful before insertion of central venous catheters, pulmonary artery catheters, pacemakers, or defibrillator leads.

Abnormal drainage of the LHV into the RA is very rare. Its occurrence may be explained

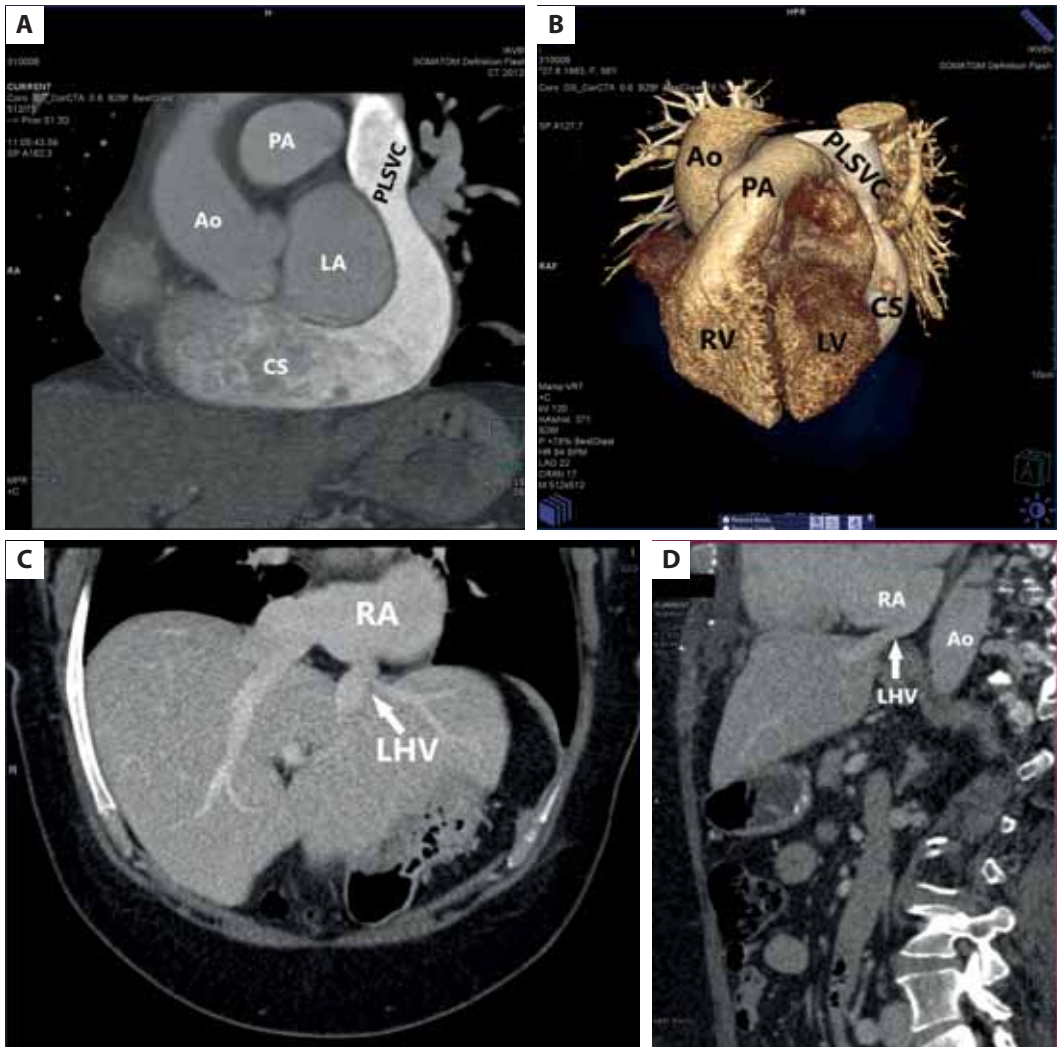

Figure 1. A, B. Contrast-enhanced CT of the heart: the presence of a PLSVC draining into the right atrium via the dilated CS, along with agenesis of the right superior vena cava **C, D.** Contrast-enhanced CT of the abdomen: anomalous LHV drainage into the RA

Abbreviations: Ao, ascending aorta; CS, coronary sinus; CT, computed tomography' LA, left atrium; LHV, left hepatic vein; LV, left ventricle; PA, pulmonary artery; PLSVC, persistent left superior vena cava; RA, right atrium; RV, right ventricle

by the persistence of the left vitelline connection with the left sinus horn and the ductus venosus during the fetal period [4]. Such abnormal hepatic vein drainage usually has no clinical significance, but this anomaly may present potentially fatal challenges to the donor operation if not determined preoperatively, especially when the left lobe is the choice for explantation [4].

By retrospectively analyzing our patient's echocardiographic examination results and knowing her anatomical abnormalities, we could conclude that the inability to see the bicaval view on transesophageal echocardiography should have raised suspicion of potential venous anomalies.

Article information

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Alternative three-point lead configuration for successful external DC cardioversion in a seven-foot-tall former basketball player

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Direct current cardioversion (DCCV) is commonly used to restore sinus rhythm in patients with atrial fibrillation (AF). Unfortunately, it is still ineffective in up to 30% of patients. The outcome of the procedure can be affected by multiple factors, including AF duration, position and size of electrodes, left atrial (LA) diameter, patients' body features, and transthoracic impedance [1–3]. Although several modifications of standard DCCV were implemented to improve its effectiveness, including the transesophageal approach, vector-change, and dual DC shocks [4–5], it still can be challenging in obese or extremely large individuals.

We present a case of a 41-year-old male, a former professional basketball player, referred to our department for cardioversion of persistent symptomatic (European Heart Rhythm Association [EHRA] score IIa) AF after three unsuccessful DCCV attempts in the preceding three weeks. The patient was first diagnosed with paroxysmal AF in 2016 and since then was successfully cardioverted 6 times. After he retired from his professional basketball career, he gained weight, and on admission, he weighed 136 kg and was 213 cm tall (body mass index [BMI], 30 kg/m^2). Written informed consent was obtained from the patient before the procedure. Transthoracic echocardiography revealed an enlarged LA (4.7 cm) and normal left ventricular ejection fraction (66%). The patient was anticoagulated with rivaroxaban 20 mg q.d., and subsequent transesophageal echocardiography revealed no intracardiac thrombi.

Considering the previous unsuccessful DCCV attempts — despite using both classical anterolateral and changed-vector anteroposterior lead configuration, combined with manual pads compression and 360 J maximum energy — we decided to switch to an ad-hoc modified three-point lead arrangement, which is, in fact, a combination of the two mentioned configurations. A Zoll M-series biphasic external defibrillator (Zoll, Chelmsford, MA, US) with dedicated adhesive external patches was used. The anterior electrode was placed in the right parasternal line just below the clavicle; the posterior electrode was positioned on the back in the left paraspinal line on the Th4-Th6 level between the vertebrae and the scapula; the lateral electrode was placed in the apical region (Figure 1A and 1B). The connectors were cut off, and insulation was removed from the distal parts of the wires. Then the wires of the posterior and the apex electrodes were electrically connected by twisting together and clamping with pean forceps. The anterior electrode's wire was likewise connected to another surgical instrument. Both instruments, now considered the electrodes/poles, were placed on the electrically insulated table at the bedside (Figure 1C). In deep sedation (140 mg propofol *i.v.*), the defibrillator's paddles were placed over the forceps, and 360 J DC shock was applied, restoring sinus rhythm.

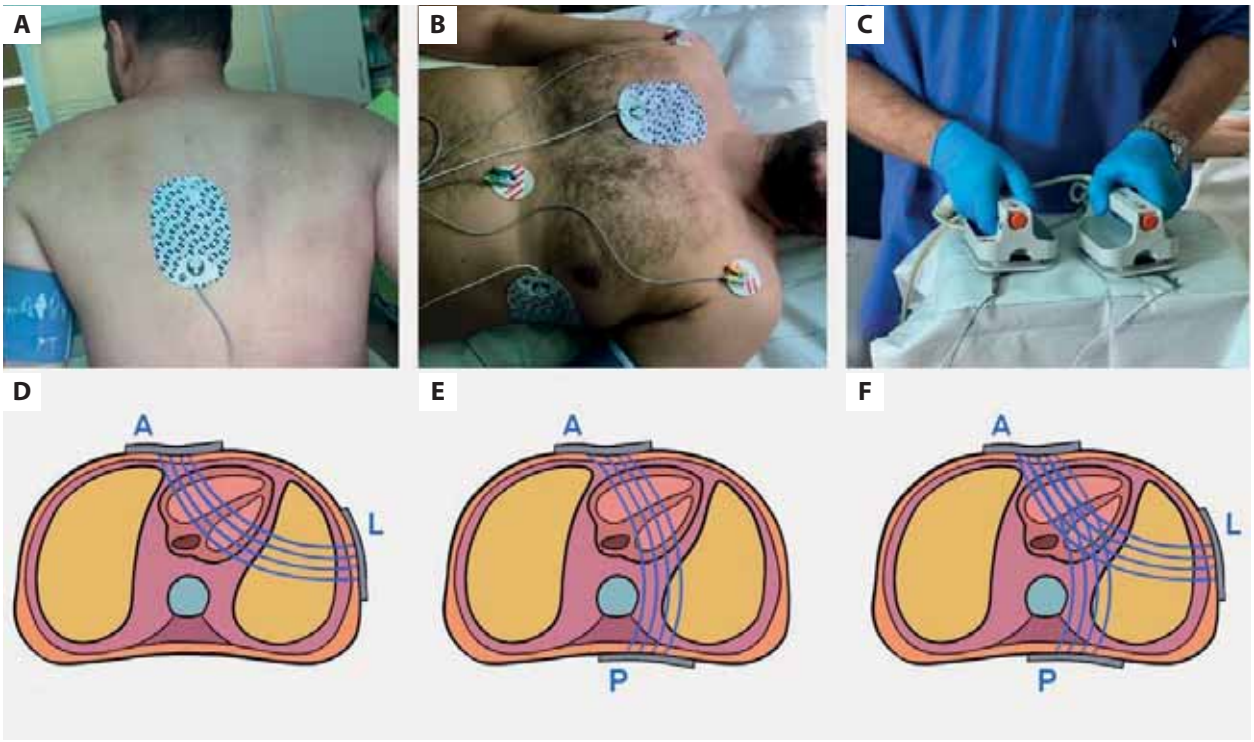

Figure 1. Ad-hoc modified three-lead configuration for external direct current cardioversion (DCCV) (panels **A–C**) and different current vectors and density during altered lead configuration for external DCCV: anterolateral (panel **D**), anteroposterior (panel **E**), and split antero-postero-lateral (panel **F**)

With standard DCCV, the current density in the heart tissue is similar in both recommended configurations: anterolateral and anteroposterior (Figure 1 D and 1E). With the anterior pad left in position and the other split equally to lateral and posterior locations (Figure 1F), both vector modification and possibly an increase of current density in the atria can be achieved. The proposed three-point DCCV procedure can be effective in restoring sinus rhythm when the standard approach fails.

Article information

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Left atrial appendage closure in a patient with hemophilia C. An option or the only antithrombotic treatment for patients with a rare bleeding disorder?

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Atrial fibrillation (AF) prevalence in the adult population is estimated between 2% and 4%. AF increases the risk of stroke approximately 5-fold. To prevent stroke, we use anticoagulant therapy, which is recommended in patients with a CHA_2DS_2-VASc score of ≥2 in men or ≥3 in women and should be considered in patients with a CHA_2DS_2-VASc score of 1 in men or 2 in women. In patients with contraindications to chronic anticoagulant therapy, an alternative is percutaneous left atrial appendage closure (LAAC) [1, 2].

We present a description of the left atrial appendage closure procedure in a patient with contraindications for long-term anticoagulant treatment due to congenital hemophilia C.

A 72-year-old man with hemophilia C (a hereditary bleeding disorder characterized by factor XI deficiency) and permanent atrial fibrillation (AF), without any kind of antithrombotic therapy, was referred to our center by his cardiologist. His medical history included hypertension, ventricular arrhythmia, prostate cancer treated by prostatectomy 6 years earlier, and post-traumatic subdural hematoma 16 years earlier.

The CHA_2DS_2-VASc score was estimated at 2, and his HAS-BLED score was 3. After evaluation, his case was presented at the Heart Team consultation, and the patient was qualified for LAAC.

Transesophageal echocardiography (TEE) revealed a thrombus of 0.8 cm diameter (Figure 1A) in the left atrial appendage (LAA). Laboratory tests showed an increase in activated partial thromboplastin time (APTT) at 82.9 sec with a normal international normalized ratio (INR) — 1.4. The LAAC procedure was postponed. The patient was consulted by a hematologist, who disqualified him from any kind of antithrombotic treatment. The patient was discharged from the hospital, and the next evaluation was scheduled after 2 months to check the presence of the thrombus.

After 2 months, TEE was performed, which showed a presence of spontaneous contrast in the left atrial appendage, which on the bottom had gelatinous consistency and was on the verge of clotting (Figure 1B). The APTT was also increased this time, and the INR level was normal. Factor XI level was evaluated at 1.4%. It was decided to perform the procedure shortly without contrast injection for device positioning in the left appendage (navigating with TEE only).

After 7 days, we admitted the patient again. This time during TEE, no thrombus was found in LAA (Figure 1C). Only a presence of spontaneous contrast was noticed, which was not a contraindication to the LAAC procedure. It was decided to perform the procedure. Due to heritage factor XI deficiency, the patient had a consultation with a hematologist who recommended 6 units of fresh frozen plasma (FFP) within 12 hours before the planned procedure. After transfusion, factor XI level was 23.6% and APTT was 37.1 seconds, and 2 more units of FFP were transfused in the operating room just before the procedure. After that preparation, the patient underwent successful percutaneous left atrial appendage closure using a 35mm Watchman FLX device (Figure 1D–F). The procedure went without

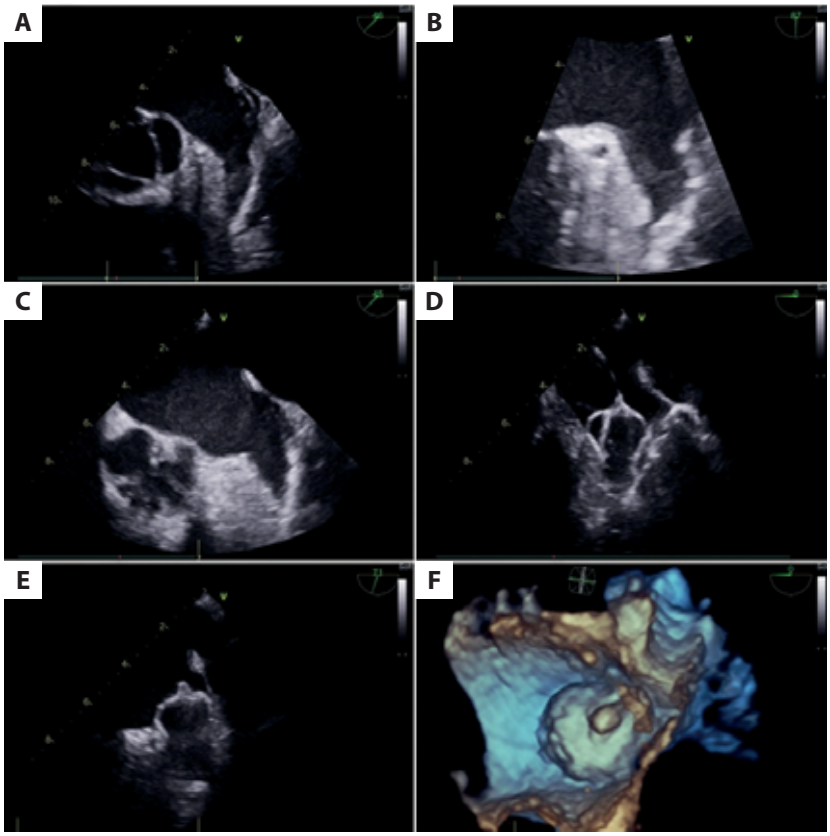

Figure 1. A. Thrombus of diameter 0.8 cm in the LAA. **B.** Spontaneous contrast in the LAA, which has gelatinous consistency on the bottom and is on the verge of clotting. **C.** Spontaneous contrast in the LAA. **D.** A 35 mm Watchman FLX device in the LAA, before release, intraprocedural 2D TEE. **E.** A 35 mm Watchman FLX device in the LAA after release, intraprocedural 2D TEE. **F.** A 35 mm Watchman FLX device in the LAA after release, intraprocedural 3D TEE

Abbreviations: 3D, 3-dimensional; 2D, two-dimensional; LAA, left atrial appendage; TEE, transesophageal echocardiography

complications. In the postoperative period, further 2 units of FFP were transfused. On the first day after LAAC, the level of factor XI was 28.9%, and APTT was 26.3 seconds. No hemorrhagic complications during further hospitalization occurred. On the 4th day after LAAC, TEE confirmed the correct position of the closure device. The same day, the patient was discharged from the hospital in stable condition.

To our knowledge, it is the first reported case of percutaneous left atrial appendage closure in a patient with hemophilia C. We found only 17 described cases of LAAC in patients with hemophilia (15 hemophilia A, 2 hemophilia B), none in Poland [3–5]. In our opinion, after appropriate preparation, LAAC is a safe strategy in patients with hemophilia C and AF.

Article information

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Ross-Konno procedure as a rescue operation in a newborn with critical aortic stenosis

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The treatment of critical aortic stenosis in early infancy continues to be challenging. The severity of aortic stenosis and concomitant pathologies determine treatment after birth. Mostly, interventional balloon valvuloplasty is the first choice of treatment; alternatively, surgical valvuloplasty and Ross or Ross-Konno procedures can be performed. Some patients with poor left ventricular function, fibroelastosis, mitral valve stenosis, and insufficiency may be considered for Norwood operation. The Ross-Konno procedure provides relief for left ventricular tract (LVOT) obstruction. During the operation, LVOT is widened with a patch, a pulmonary autograft is implanted into the transected aortic root, and the pulmonary valve is replaced with a prosthesis. The high risk of the procedure is associated with low body weight, initial dysfunction of the left ventricle (LV), myocardial fibroelastosis, and other cardiac defects [1–5]. The operation is performed mostly in older children and adults. However, we present a successful Ross-Konno procedure performed in a 14-day-old newborn with critical aortic stenosis treated ineffectively with interventional and surgical valvuloplasty.

According to the medical history, the female newborn was delivered at term, weighing 3200 g and scoring 9 Apgar points. Vital signs were unstable with a fast regular heart rate of 170/min, mean arterial pressure of 36–40 mm Hg, and SaO_2 of 84% in lower extremities. Prostaglandin E1 (PGE1) infusion provided general condition stabilization. Transthoracic echocardiography (TTE) revealed a critically stenotic aortic valve with a hypoplastic annulus of 5 mm (Z-score –3.2) with poor contractility of the LV, myocardial fibroelastosis, hypoplastic aortic arch, and isthmus coarctation.

Interventional balloon aortic valvuloplasty with a Tyshak 5 mm balloon catheter was moderately effective, with ejection fraction improvement of up to 50%. However, due to a high-pressure gradient of 60 mm Hg, a decision about surgical treatment was made (Figure 1A, B, Supplementary material, *Video S1, S2*).

A surgical examination revealed a highly dysplastic, unicuspid aortic valve. We performed aortic valvuloplasty: commisurotomy and leaflet shaving, and subsequently aortic arch and isthmus dilation with end-to-side anastomosis. The residual aortic stenosis with symptoms of cardiopulmonary failure required reoperation with the Ross-Konno technique.

A cardiopulmonary bypass was established via median sternotomy with bicaval cannulation. The aortic root was transected, and the aortic valve tissue was resected. After the pulmonary autograft was harvested, a Konno incision was made. A PhotoFix patch was used to enlarge the aortic annulus. Finally, the pulmonary autograft was implanted into the aortic root, and the coronary ostia were implanted. The pulmonary valve was replaced with a prosthesis Contegra 12 mm (Figure 1C–E, Supplementary material, *Video S3, S4*). Postoperative pulmonary branch stenosis required balloon plasty and right pulmonary artery stent implantation (Palmaz Blue 6 mm × 12 mm) (Supplementary material, *Video S5*).

The postoperative period was uneventful, and the child was discharged home. In 3-month follow-up, the infant was in good condition. TTE showed normal left ventricular

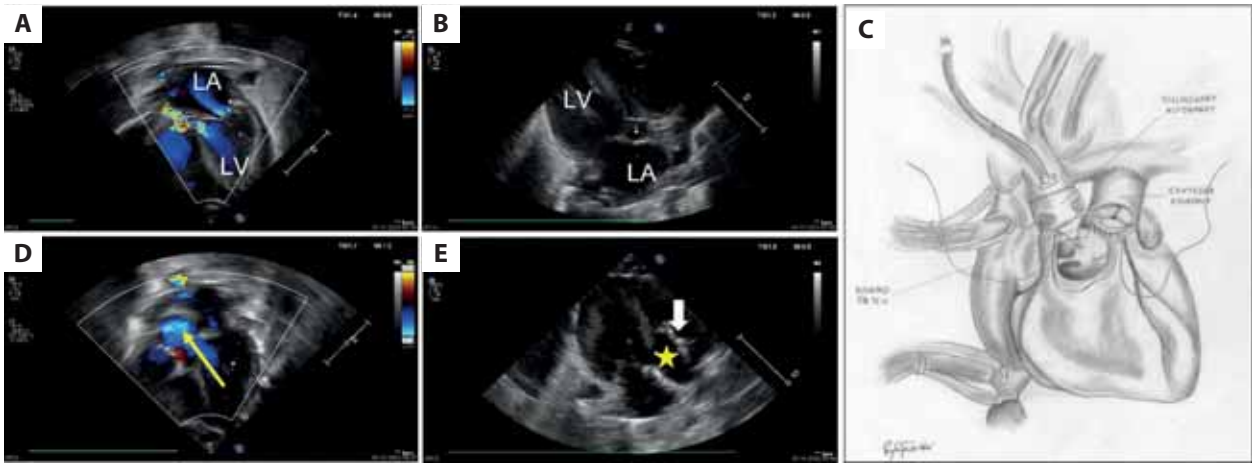

Figure 1. A. TTE. Apical 5-chamber view with color Doppler flow following balloon valvuloplasty — residual severe aortic stenosis and moderate mitral regurgitation with left atrium enlargement. **B.** TTE. 2DE. Longitudinal axis of the LV with a hypoplastic aortic annulus, left ventricular hypertrophy, and left atrial dilation. **C.** A scheme of the Ross -Konno procedure: LVOT widening with a patch (Konno patch). Pulmonary autograft implanted into the transected aortic root. The pulmonary valve replaced with a prosthesis (Contegra conduit). **D.** TTE. 5-chamber view with color Doppler flow: wide LV outflow tract following the Ross-Konno operation (yellow arrow) with normal LV dimension. **E.** TTE. 2DE. Longitudinal axis of the LV. A PhotoFix patch (white arrow) widening the outflow tract and aortic annulus. Pulmonary autograft in the aortic position (yellow asterisk)

Abbreviations: LA, left atrium; LV, left ventricle; LVOT, left ventricular tract obstruction; TTE, transthoracic echocardiography, 2DE two-dimensional

ejection fraction (72%) and moderate pulmonary branch stenosis.

The Ross-Konno procedure in early infancy is an alternative for patients with critical aortic stenosis with severe dysplasia of the aortic valve to provide biventricular repair.

In patients with acceptable left ventricle function, the Ross-Konno procedure with reconstruction of the aortic arch is a preferable option to the Norwood procedure.

Supplementary material

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

Article information

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Percutaneous deactivation of a left ventricular assist device due to pump thrombosis

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A left ventricular assist device (LVAD) is indicated in patients with advanced heart failure and is most commonly used as destination therapy or bridge to heart transplantation [1, 2]. Recently, with the development of the third generation of these devices, a significant decrease in the number of LVAD-related thromboembolic complications has been observed [3]. However, patients with an LVAD may still experience serious adverse events. We present a patient with a continuous-flow LVAD in whom the device was successfully deactivated with percutaneous Amplatzer implantation due to pump thrombosis.

A 62-year-old male with a history of advanced heart failure with reduced left ventricular ejection fraction (LVEF, 20%) due to dilated cardiomyopathy and pulmonary hypertension after LVAD implantation in 2018 (Heartware HVAD, Heartware International, Framingham, Massachusetts) as a bridge to transplantation was admitted to a tertiary cardiovascular center following a critical LVAD alarm. On admission, the patient reported weakness and reduced exercise capacity for the previous several hours. Laboratory assessment revealed elevated lactate dehydrogenase (LDH): 372 U/L (n = 125–220) and NT-proBNP: 4017 pg/ml (n <125), while International Normalised Ratio (INR) was 1.96. Transthoracic echocardiography confirmed LVAD thrombosis with no flow in the LVAD outflow cannula. Computed tomography angiography of the aorta depicted a patent conduit between the aorta and the LVAD.

Subsequently, catheter-based percutaneous LVAD deactivation with implantation of an Amplatzer occluder to the LVAD outflow graft was performed (Figure 1A, B, Supplementary material, *Video S1,* and *S2*). The patient was not LVAD-dependent and remained hemodynamically stable; he was treated with

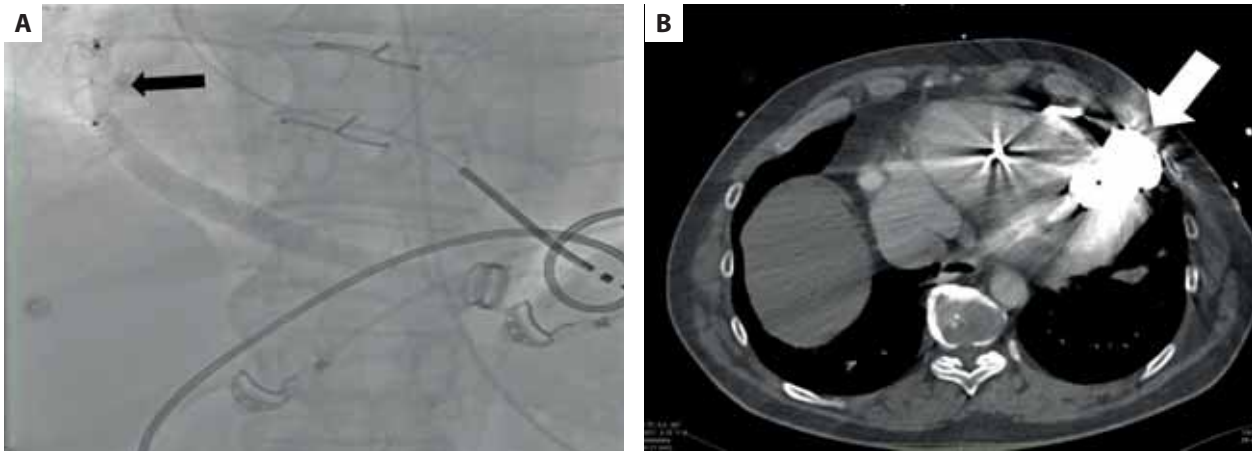

Figure 1. A. Angiography after implantation of the Amplatzer occluder to the left ventricular assist device outflow graft, an arrow shows the Amplatzer occluder. **B.** Computed tomography angiography of the aorta. An arrow shows an inflow cannula

levosimendan and required no catecholamines. LVEF remained stable during hospitalization. Anticoagulation was continued. Two weeks after LVAD deactivation, right heart catheterization was performed, and no pulmonary hypertension was found. After discussion, the Heart Team qualified the patient for an urgent heart transplantation. The hospitalization was uneventful and after two weeks the patient requested to be discharged from the hospital against medical advice. The patient remained hemodynamically stable at 1-month follow-up. Although the heart donor was found after 14 days, the operation was not performed because the patient had died at home due to sudden cardiac arrest shortly before the planned procedure. The patient's family refused to give consent for an autopsy of the deceased.

Pump thrombosis is a potentially lethal complication of LVAD therapy that may occur as a result of different mechanisms [4]. Percutaneous LVAD deactivation is a relatively safe and effective method that can be used in properly selected patients as an alternative to surgical treatment in pump thrombosis [5]. Based on our experience, we believe that a patient with pump thrombosis should be regarded as an urgent heart transplant candidate provided there are no contraindications for heart transplantation.

Supplementary material

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

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Left atrial membranous structure discovered on echocardiography

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Left atrial (LA) anatomy and physiology provide a synergistic value in proper cardiac function. Transthoracic echocardiography is the first-choice modality for its assessment. Additional LA structures that may be visualized are thrombi, vegetations, heart tumors, external compression or a diaphragm dividing the LA in cor triatriatum [1, 2], though, sometimes these structures prove to be normal anatomic variants [3]. In some cases, multimodality imaging, including cardiac magnetic resonance, computed tomography, transesophageal, and contrast echocardiography, is necessary for final diagnosis of LA pathology. The last one may be particularly useful when other methods remain inconclusive since it provides additional functional information, such as the presence of communication between the chambers [4].

A 48-year-old woman, without a history of cardiovascular disease, was referred to our cardiac outpatient center for further assessment of an additional membranous structure in the LA visualized on transthoracic echocardiography. She was suffering from dry cough for many years, arthralgia (mainly involving the small joints of the upper limb – the metacarpophalangeal and interphalangeal joints), and muscle stiffness. Moreover, she had two miscarriages. Raynaud's phenomenon was not present. Transthoracic echocardiography showed a linear structure in the upper part of the LA, visible in all echocardiographic views, without signs of flow obstruction (Figure 1A–D). There was no pericardial effusion at other sites. Color Doppler investigation revealed no communication between the sides of the abnormal structure. The probability of pulmonary hypertension was low. Multiple options were initially taken into account, such as cor triatriatum, LA dissection, or external compression. There were no signs of other cardiac lesions that can accompany cor triatriatum, such as atrial septal defect, anomalous venous return, bicuspid aortic valve, or dilated sinus venosus. Transthoracic echocardiography was performed again several weeks later. Although the view of the LA had not changed, evident pericardial effusion was present in all echocardiographic views. This image suggested that the membranous structure was the LA wall compressed by pericardial fluid, which was confirmed by cardiac magnetic resonance (Figure 1 E, F). The distinctiveness of this case derived from the anatomy of the heart resulting in the fluid accumulating first by the LA, in the oblique sinus of the pericardium, which was atypical and led to further investigation. The presence of pericardial effusion required extended diagnostics, which revealed highly elevated anti-nuclear antibodies HEp-2 (nucleolar pattern). Due to the presence of clinical and serological symptoms indicating an autoimmune systemic disease, the patient was hospitalized at the rheumatology department with the diagnosis of an undifferentiated connective tissue disease as she failed to meet the criteria for a specific autoimmune disorder. The amount of pericardial effusion and the view of the LA were stable during further follow-up.

Our diagnostic process has led us from suspecting a cor triatriatum sinister, through pericardial effusion, to the diagnosis of undifferentiated connective tissue disease. Although echocardiography remains the imaging modality of choice for visualization of pericardial effusion, there is a need for multimodality imaging in cases with unusual presentation. Since it has various underlying etiologies and multiple clinical pictures, in-depth diagnostics is required.

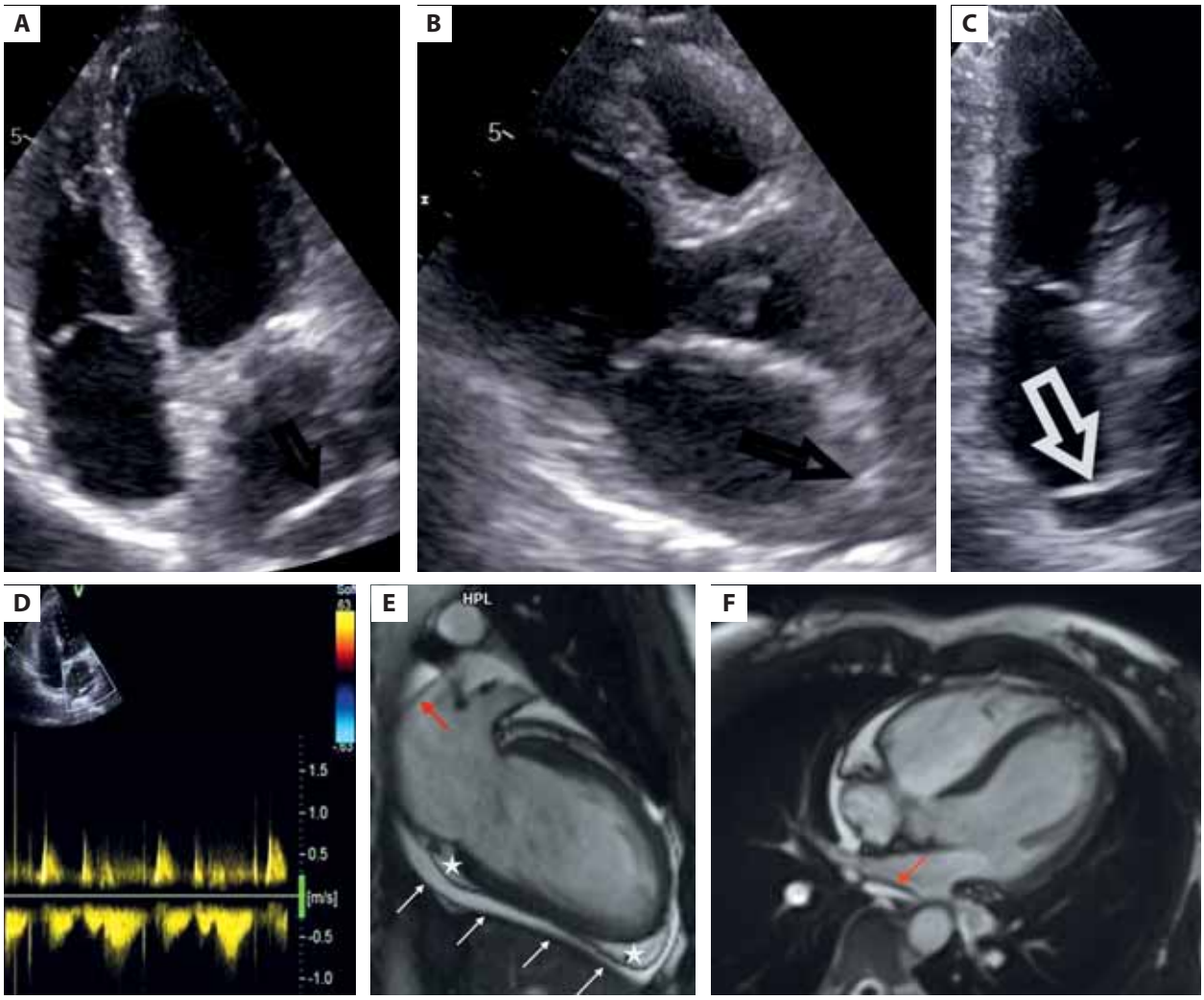

Figure 1. A–D. Transthoracic echocardiography. **A–C.** Additional membranous structure in the left atrium (arrows); four-chamber view (**A**), parasternal long axis view (**B**), two-chamber view (**C**). **D.** No significant gradient across the membrane on continuous wave Doppler; four-chamber view. **E, F.** Cardiac magnetic resonance imaging performed a few months later showing pericardial effusion mainly in the oblique sinus of the pericardium (red arrows); fluid along the inferior wall (white arrows); epicardial fat (asterisks)

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A wearable cardioverter-defibrillator vest as a diagnostic and therapeutic tool after COVID-19

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A 29-year-old female patient, previously in excellent health, presented with recurrent fainting caused by ventricular tachyarrhythmia three months after contracting COVID-19. An ambulatory Holter ECG showed a brief episode of non-sustained ventricular tachycardia (nsVT) at a rate of 270 bpm, which coincided with the presyncope (Figure 1A). The patient's resting ECG was normal, and an electrophysiology study did not reveal inducible arrhythmia. Additionally, a cardiac magnetic resonance (CMR) scan did not demonstrate features of myocarditis (Figure 1B, Supplementary material, *Video S1*).

However, during hospitalization, the patient experienced recurrent nsVT, indicating increased vulnerability to sustained ventricular arrhythmia (Figure 1D). It was assumed that this arrhythmia was related to recent COVID-19 infection and would likely resolve spontaneously. To monitor and treat the arrhythmia, the patient was offered a wearable cardioverter-defibrillator (WCD) instead of an implantable cardioverter-defibrillator (ICD). The patient was started on bisoprolol and electrolyte replacement, received education and training on using the WCD, and was subsequently discharged home (Figure 1C). The next day, the patient was readmitted with an electrical storm recorded by the WCD. The patient experienced 11 episodes of ventricular tachycardia with a cycle length ranging from 220 to 240 milliseconds and a duration varying from 40 to 220 seconds, including five episodes occurring at intervals of at least 5 minutes (Figure 1E–F). The patient did not lose consciousness during the electrical storm episodes and was able to abort the high-voltage therapy by simultaneously pressing two buttons on the WCD unit (Supplementary material, *Text S2*). The arrhythmia was successfully treated with amiodarone infusion.

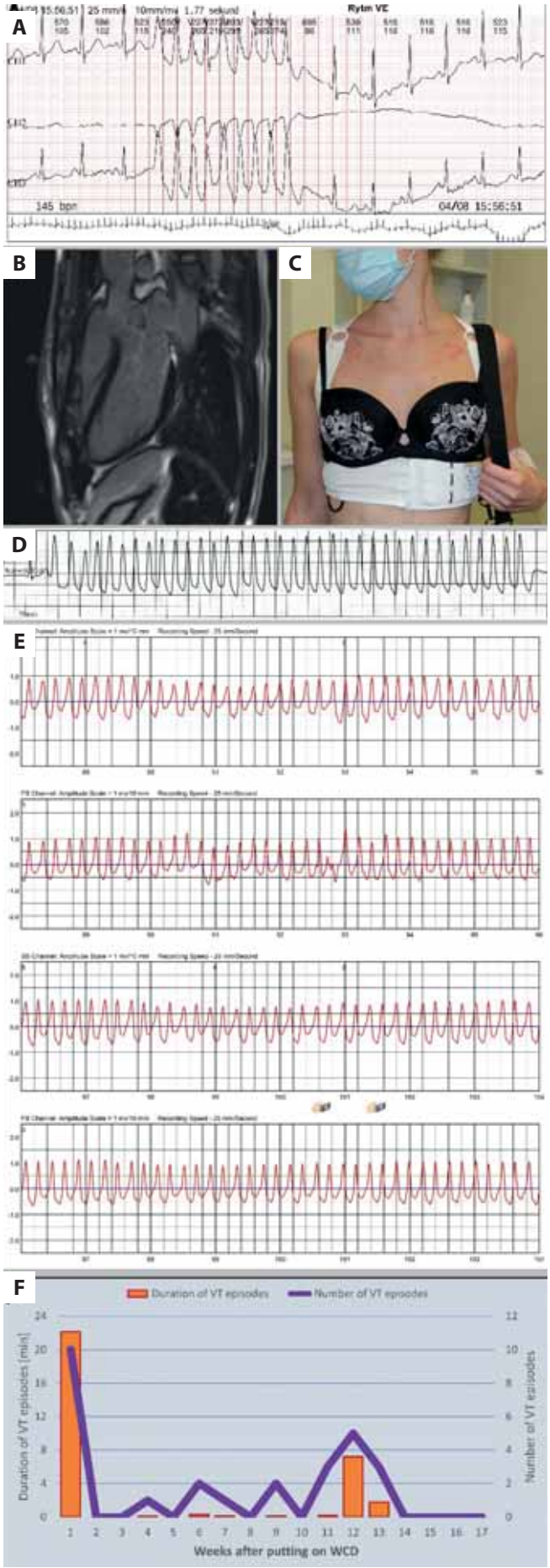
Additionally, an ablation procedure was performed (Supplementary material, *Text S3*).

Six weeks later, the patient experienced another episode of an electrical storm which was recorded by the WCD. The patient was treated at the Emergency Department with oral propafenone and electrolyte replacement. The patient was admitted electively four months later to reassess the need for a WCD or ICD.

Holter ECG showed 286 single ventricular ectopics and one pair. The arrhythmia frequency in the WCD memory was down-trending (Figure 1F). Given the reduction of the arrhythmia, the WCD treatment was discontinued. However, due to uncertainty surrounding the post-COVID-19 arrhythmia, an ICD implantation was offered but not accepted by the patient. In the 14-month follow-up, the patient remained well with no reported syncope or palpitations.

In young women, myocarditis has been reported as one of cardiac complications of COVID-19, and it has been associated with increased risk of sudden cardiac death (SCD) [1, 2] (Supplementary material, *Text S4*).

We observed a decrease in the arrhythmia burden during follow-up, indicating a self-limiting course of the disease. Using a WCD as a bridge therapy can be an effective temporary solution in cases where the patient is at risk of SCD but is not yet a candidate for a permanent ICD implantation [3]. In this case, the WCD was a valuable diagnostic and therapeu-



tic tool to prevent SCD [4]. Eventually, the arrhythmia resolved, and the patient decided not to have an ICD implanted, which, in hindsight, turned out to be the right decision, and the patient was not burdened with unnecessary therapy. This case highlights the importance of a shared decision-making process between the healthcare provider and the patient, where the patient's values, preferences, and concerns are taken into account when making treatment decisions. In summary, we believe the WCD is a valuable option for patients with ventricular arrhythmia in the setting of recent SARS-CoV-2 infection and myocarditis.

Supplementary material

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Figure 1. A. Ambulatory Holter electrocardiography (ECG) monitoring: episodic non-sustained ventricular tachycardia (nsVT) at a rate of 270 bpm. **B.** Cardiac magnetic resonance: three chamber long-axis apical view of the left ventricle. Late gadolinium enhancement imaging indicates no post-inflammatory lesions with normal global left and right ventricular systolic function. **C.** The patient wearing a wearable cardioverter defibrillator. **D.** ECG monitoring during hospitalization (record from the bedside monitor): an approximately 8-second episode of nsVT. **E.** Trace of one of the ventricular tachycardia episodes (the pictograms show the moments when two buttons on the device are pressed simultaneously to interrupt the high-voltage therapy). **F.** Trend of arrhythmia burden over the follow-up period (number of episodes and their duration)

Incessant septal ventricular tachycardia in a patient with hypertrophic cardiomyopathy after failed unipolar and bipolar ablation. Is ethanol septal ablation a solution?

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The treatment of ventricular tachycardia (VT) in patients with hypertrophic cardiomyopathy (HCM) is challenging due to the complex substrate and thickness of the muscle [1, 2]. The majority of patients have a scar at the basal or middle interventricular septum on enhanced gadolinium magnetic resonance imaging (MRI) [3]. Spatial fibrosis distribution in the grossly hypertrophied septum can promote deep re-entrant circuits, which can be challenging during ablation [4].

We present a 56-year-old male patient with a long history of HCM and VT with implanted implantable cardioverter defibrillator (ICD), who was successfully treated with amiodarone for 15 years. In 2011, he developed hyperthyreosis, and amiodarone was stopped. Several months later, he experienced numerous ICD interventions for VT. From 2012 to 2015, he underwent five ablations, during which he presented several forms of VT originating from the interventricular septum and left ventricular summit. Ablation of septal VT was successful for several months but resulted in an atrioventricular block which required an upgrade to cardiac resynchronization therapy with defibrillator (CRT-D). In 2016, the patient underwent unipolar radiofrequency re-ablation for LV summit VT and bipolar ablation of mid-septal VT guided by the CARTO 3 system. Right and left ventricular endocardial mapping revealed low-voltage substrates (bipolar <0.5 mV) representing the scar and fractionated potentials on both sides of the thick septum (27 mm). As pace-mapping in the high septum replicated clinical VT, bipolar ablation was performed accordingly to the previously described technique [5]. After the procedure, aortic regurgitation developed presumably as a consequence of LV summit ablation, and the patient underwent aortic valve replacement (ablation was performed from both sides of the left aortic cusp). After that, the patient was free from VT for 2 years when he presented the incessant form of slow VT and progressive heart failure (Figure 1A).

The standard approach with the CARTO 3 system was unsuccessful due to fibrosis and the lack of septal excitability (Figure 1B). As the earliest potentials were recorded under the aortic valve (–30 ms), we decided to perform transcoronary mapping. Coronary angiography showed a small septal branch supplying the upper part of the intraventricular septum under the aortic valve annulus (Figure 1C). An angioplasty pilot (BMW) with an over-the-wire (OTW) balloon (1.25 × 12 mm) was inserted into the several branches of the septal artery finally finding the earliest fractionated potentials, preceding QRS by –64 ms with 12/12 matching between paced rhythm and VT morphology (Figure 1D, E). After the balloon was inflated for contrast injection, VT slowed down and stopped. At this stage, two injections of 2 ml 96% ethanol were performed with 120 seconds of artery occlusion. After 15 minutes, VT could not be induced with pacing with up to 4 extra stimuli. The next day, the patient reported chest pain, and laboratory tests showed high-sensitivity cardiac troponin T (hs-TnT) 3561 pg/ml, which normalized after 2 days. The patient was followed up with home monitoring (Biotronik) for the next 36 months and presented no VT recurrence.

Transcoronary ethanol ablation can be an effective alternative for ventricular tachycardia

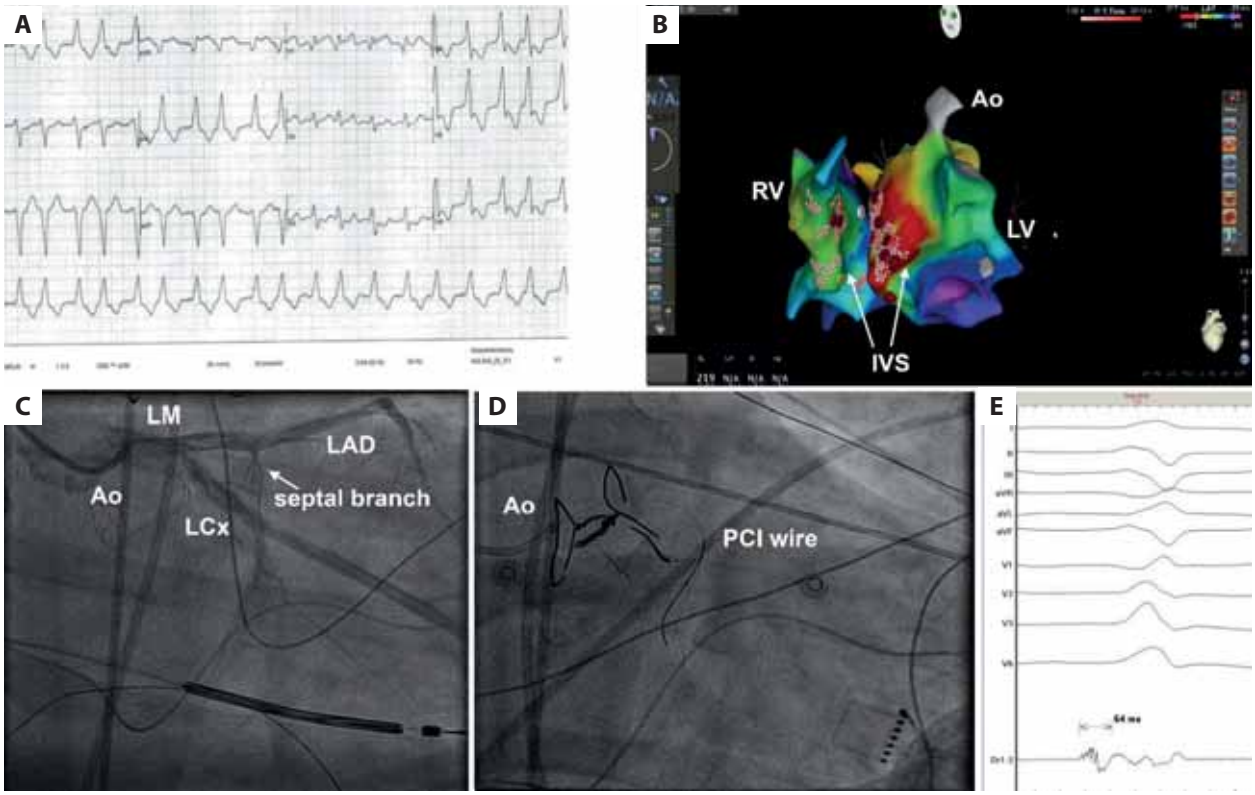

Figure 1. A. Twelve-lead ECG of clinical VT treated with ethanol ablation. **B.** CARTO bipolar map of RV and LV. Extensive scarring present at the left-sided septum where previous ablations were performed. **C.** Coronary angiography (RAO 30). **D.** PCI wire mapping in the septal branch at the site of best potentials. **E** Local potential recorded by the PCI wire at the site of ethanol ablation

Abbreviations: Ao, aortic valve; ECG, electrocardiography; IVS, interventricular septum; LAD, left anterior descending artery; LCx, left circumflex artery; LM, left main artery; LV, left ventricle; PCI, percutaneous coronary intervention; RV, right ventricle; VT, ventricular tachycardia

after failed RF catheter ablation. As the procedure is technically challenging, it is unlikely to be used as the first choice of treatment, but it should be considered as an alternative method after RF ablation failes.

Supplementary material

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

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Which strategy for calcified coronary plaque modification in patients with low ejection fraction?

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In the era when more and more complex patients require percutaneous coronary treatment, a combination of different interventional methods is necessary. In patients with heavily calcified coronary lesions and, additionally, poor left ventricular ejection fraction, the simultaneous use of the plaque modification technique along with mechanical circulatory support can contribute to final success.

A 44-year-old man with symptomatic chronic coronary syndrome and diagnosed advanced heart failure was admitted to our center to complete his diagnostics and be qualified for further treatment. The patient was obese with a body mass index of 33, a smoker, and with a positive cardiovascular family history and pancreatitis in anamnesis. On echocardiography, his left ventricle was dilated with ejection fraction of 23% and inferior wall dyskinesis. Coronary angiography revealed multivessel disease including 80%–90% stenosis of the left main (LM) and left anterior descending arteries and with the proximally occluded right coronary artery (Figure 1A). After discussion, the Heart Team disqualified the patient from open heart surgery (mainly because of very low ejection fraction) and qualified him for complex percutaneous coronary intervention.

In initially performed high-definition intravascular ultrasound examination, significant calcifications including the LM (300°–360°) were seen (Figure 1B). This finding substantially increased the risk of the procedure because some kind of plaque modification technique would be necessary as well as, possibly, left ventricular support. First, from currently available calcification modification devices, we chose intravascular lithotripsy (IVL, Shockwave Medical, Fremont, CA, US), instead of rotational and orbital atherectomy. Second, we decided to use Impella CP support (Abiomed, Danvers, CO, US), but only if necessary. Our strategy was to place a pigtail catheter in the left ventricle to monitor end-diastolic pressure during balloon inflation. However, even during 5 seconds of IVL use, blood pressure was decreasing, and left ventricular end-diastolic pressure was increasing, which prevented us from achieving full balloon deployment (Figure 1C). Impella support was, therefore, necessary to finish the procedure.

With functioning Impella, full 8 cycles of IVL were applied with visible temporary ventricular-aortic uncoupling on the Impella monitor. We managed to deploy the balloon fully after that (Figure 1D). Finally, 3 stents in the LM and left anterior descending arteries were implanted without complications and with patent side branches (Figure 1E). Final confirmation of the widening of the calcified lesions and proper stents apposition was obtained by intravascular ultrasound (Figure 1F).

When percutaneous intervention with calcified plaque modification is necessary, different methods can be considered, including cutting/scoring balloons, very high-pressure balloons, rotational atherectomy, orbital atherectomy, and IVL. The risk is higher in cases of complex lesions and accompanying heart failure [1, 2]. Every strategy has its advantages and disadvantages. For instance, rotational and orbital atherectomy carry an increased risk of no/slow-flow phenomenon. On the other hand, an IVL balloon requires 10 seconds of vessel occlusion, which in the case of LM disease is of great importance. Bal-

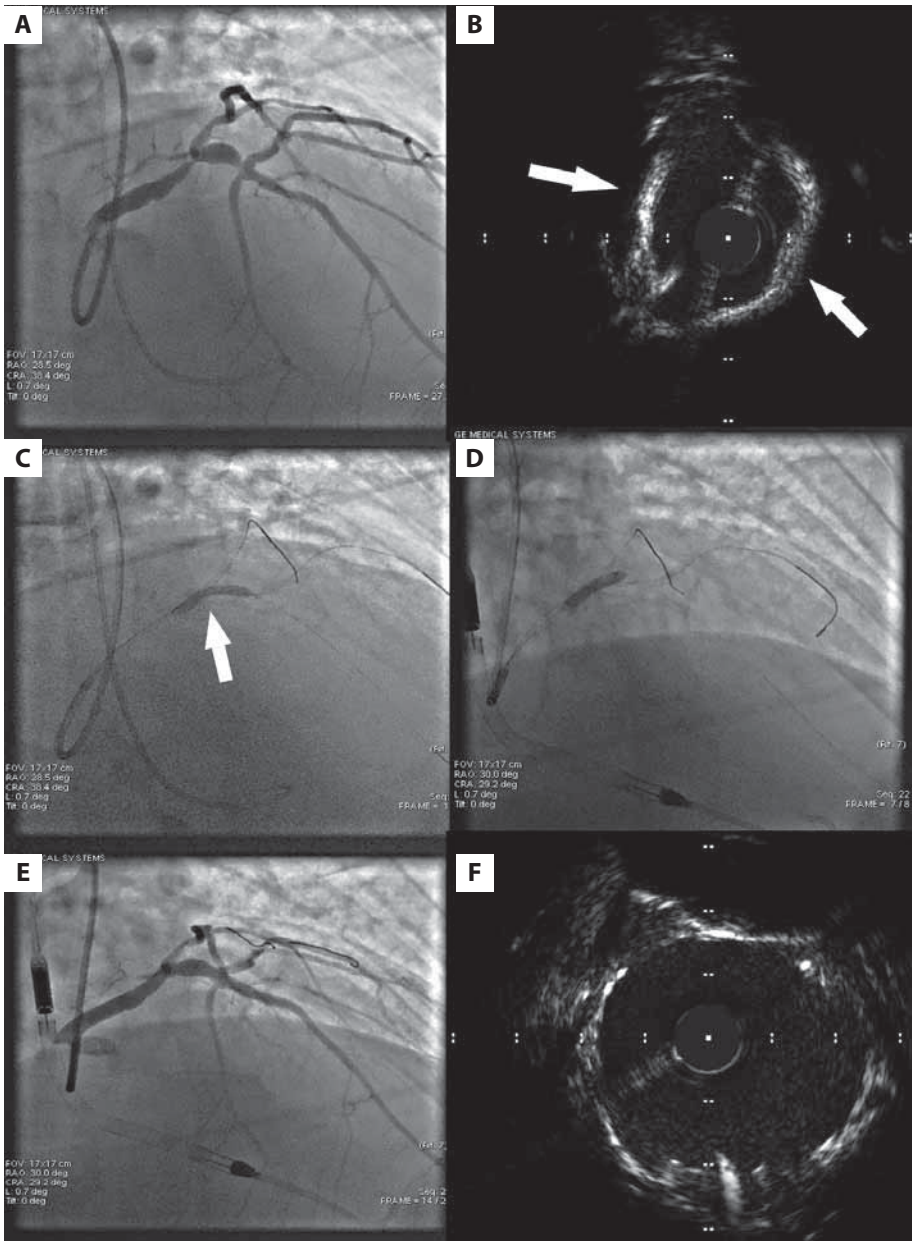

Figure 1. A. Coronary angiography revealing tight stenoses in the left main and left anterior descending arteries. **B.** Intravascular ultrasound with visible excessive calcifications in the left main (white arrows). **C.** Not fully deployed balloon (white arrow) during predilatation and with a pigtail catheter in the left ventricle. **D.** Full balloon opening after using intravascular lithotripsy with a functioning Impella device. **E.** Final coronary angiography after implantation of 3 stents. **F.** Intravascular ultrasound showing proper stent apposition in the calcified plaques.

loon techniques can modify deep calcium, while atherectomy devices are more effective in tight stenoses [3]. After deep analysis of coronary angiography and, importantly, intravascular imaging, we are better prepared to choose a proper device for each patient. Notably, sometimes each of the 3 calcium debulking methods can be acceptable, and sometimes we have to use 2 of them together [4].

Article information

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Combined orbital atherectomy and intracoronary lithotripsy assisted by mechanical circulatory support in a patient with NSTEMI and the last remaining vessel

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Severely calcified coronary stenoses remain a significant challenge during percutaneous coronary intervention (PCI), often requiring advanced devices for lesion preparation [1–3]. Such high-risk intervention (hr PCI) is even more demanding if performed within a last remaining vessel in patients presenting with acute coronary syndromes, sometimes requiring additional mechanical cardiac support (MCS) [4].

A 67-year-old male smoker presented with non-ST-segment elevation myocardial infarction. He had the following comorbidities: hypertension, hypercholesterolemia, orally controlled diabetes, chronic pulmonary obstructive disease, and peripheral artery disease. Echocardiography showed decreased left ventricular ejection fraction of 30% with a scar of the inferior and lateral walls and hypokinesia of the septum and anterior wall. Coronary angiography revealed chronic total occlusion of the right and circumflex coronary artery, with very weak collateral flow and severely and diffusely narrowed left main (LM) and left descending arteries (LAD) with calcifications (Figure 1A). His SYNTAX Score I was 49.5. The patient was discussed with the Heart Team and scheduled for hr PCI with MCS due to diffuse disease of the LAD. Owing to low bleeding risk, prasugrel was administered. The right radial artery in which a 7in6 French sheath was inserted for PCI was also used for appropriate angiographically guided puncture of the right femoral common artery. After obtaining right femoral access, two suture-mediated closure systems were inserted followed by insertion of a dedicated 19 F MCS sheath with subsequent Impella CP (Abiomed, Danvers, MA, US) placement within the left ventricle. Next, a 7-French extra backup guide catheter was introduced in the LM ostium. A Viperwire Advance (CSI, St. Paul, MN, US) facilitated orbital atherectomy (OA) with the Diamondback 360 coronary system (CSI, St. Paul, MN, US). Thanks to a glide assist feature, the 1.25 mm crown was able to go across all tight and calcified lesions to the relatively healthy mid portion of the LAD, and OA was launched going backward with 80k rpm and forward with the same speed. After treatment of the medial part of the LAD, OA with 120k rpm was performed within the proximal part of the LAD, including several passes with low and high speed. No pressure drop was noticed during OA (Figure 1B). Afterward, intracoronary imaging with the use of high-definition intravascular ultrasound (HD-IVUS; Boston Scientific, Natick, MA, US) revealed 360° calcium arches within the LM and LAD (Supplementary material, *Figure S1*). Despite aggressive pre-dilatation with 2.0, 2.5, and 3.0 non-compliant balloons, the balloons could not fully open, so intracoronary lithotripsy (IVL; Shockwave Medical, Fremont, CA, US) was used with 3.5 and 4.0 balloons which fully expanded at 4–6 atmospheres after application of 80 pulses of ultrasound energy (160 pulses in total). During IVL, a flat pressure curve was observed (Figure 1C). Finally, three drug-eluting stents were successfully implanted, followed by post-dilation with non-compliant balloons. Optimal angio-

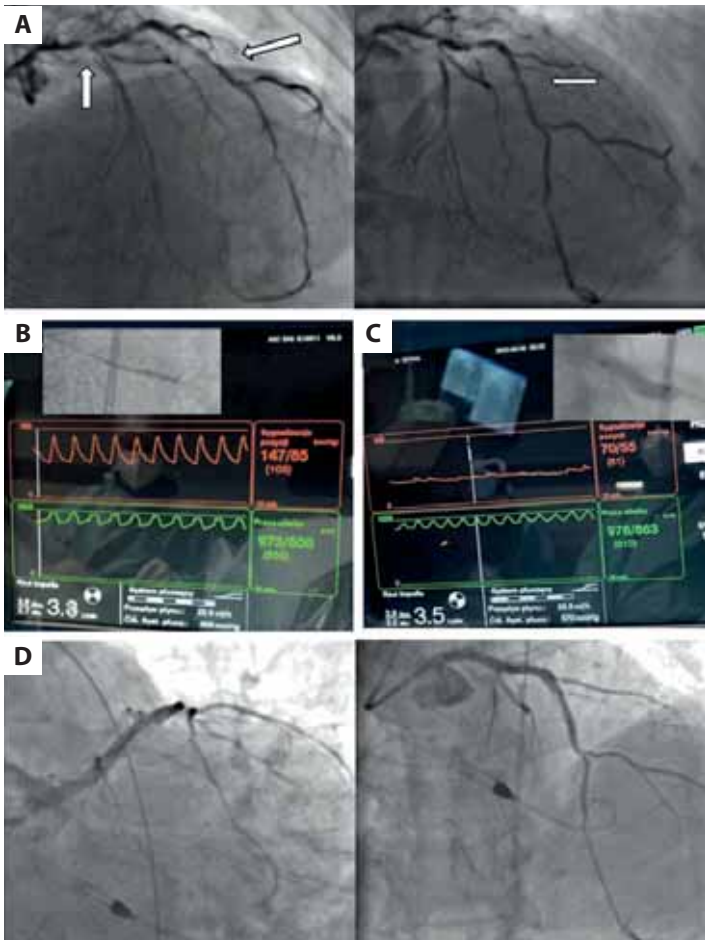

Figure 1. A. Coronary angiography with severe narrowing and excessive calcifications (white arrows) within the left main and left anterior descending arteries. **B.** Aortic pressure curve during orbital atherectomy showing normal waveform. **C.** Aortic pressure curve flattening during intravascular lithotripsy application. **D.** Final angiographic result in the left main and left anterior descending arteries

graphic result of PCI was confirmed with HD-IVUS (Figure 1D and Supplementary material, *Figure S2*). The MCS system was withdrawn, and the large bore access was closed. No bleeding complications occurred. On discharge, the patient presented with left ventricular ejection fraction of 45% and no symptoms of angina.

Article information

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Rapid morphological transition during the course of Takotsubo syndrome: A mysterious phenomenon with subtle implications

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Factors and associated mechanisms that particularly predispose to the evolution of atypical morphological patterns [1–4] in the setting of takotsubo syndrome (TTS) have been poorly understood. As a general rule, it may be suggested that the higher the severity of initial adrenergic discharge, the more likely the evolution of atypical TTS variants (basal, global, etc.) [2, 3]. Therefore, these variants have been mostly associated with relatively extreme conditions such as pheochromocytoma with adrenergic crisis [2, 3]. On the other hand, the emergence of diverse morphological patterns (in a consecutive manner) [1–4] during a single TTS course seems to be even more atypical and enigmatic in the clinical setting. The recent article by Pan et al. [1] has described a case of TTS with a midventricular pattern (complicated by severe mitral regurgitation [MR]) that subsequently transformed into a classical apical ballooning pattern. Therefore, we would like to comment on further implications of this interesting case.

Notably, rapid morphological transition in the setting of TTS (during a single disease course) has been very rarely reported [1–4]. This may suggest it is underdiagnosed possibly due to certain factors such as lack of further serial echocardiographic imaging during the TTS course and late TTS presentation (after the established transition). Previously, TTS with a morphological transition pattern was also called "fast wandering TTS" [2, 4]. In particular, this phenomenon was observed in patients with pheochromocytoma-induced TTS [2, 3]. In general, pheochromocytoma-induced TTS has a higher likelihood of presenting with atypical morphological patterns mostly in the absence of an overt physical or emotional TTS trigger. It has worse in-hospital outcomes largely due to a variety of factors, including extreme adrenergic discharge, delayed diagnosis, and persistent myocardial abnormalities [2, 3]. Importantly, rapid transition from a regional to a global TTS pattern was also suggested to have prognostic implications in patients with pheochromocytoma-induced TTS [3].

Based on that, we suggest that the reported patient [1] needs to be further examined for potential pheochromocytoma (as the trigger of TTS) *via* imaging modalities and biochemical tests due to the suspicious findings (including the absence of a significant TTS trigger, relatively young age, initial presentation with an atypical TTS pattern followed by its rapid transition to another myocardial territory) [1]. Did the patient have signs of (or a history suggestive of) extreme adrenergic discharge such as coronary slow flow pattern on angiogram, paroxysmal severe hypertension, bouts of headache, and malignant arrhythmogenesis [2, 3]? If pheochromocytoma is identified as the trigger of the TTS episode, the presence of residual myocardial abnormalities may also be quite likely, and they need to be further investigated with advanced echocardiographic modalities (including strain, etc.), along with the management of pheochromocytoma [2].

Alternatively, the "fast wandering TTS" pattern may also arise in the absence of any organic source of extreme adrenergic discharge (including pheochromocytoma).

In certain TTS episodes, this dynamic pattern may simply emerge as a protective or counterbalancing mechanism against life-threatening mechanical complications such as acute MR, severe outflow tract gradient, and severe ballooning in the initially affected myocardial territory. In that patient [1], rapid transition of wall motion abnormalities from the mid-ventricle to the apical territory apparently terminated severe MR which, if persistent, might have led to acute pulmonary edema and/or hemodynamic compromise. In other terms, this "rapid transition pattern" [1] might have emerged as a critical physiological response aiming to abort acute MR, rather than being a coincidental phenomenon. Similarly, rapid transition of TTS-related wall motion abnormalities from the apex to other myocardial regions might possibly arise as a neutralizing mechanism against an impending or existing severe outflow tract gradient (a mechanical complication generally encountered in the setting of apical ballooning pattern [2]). On the other hand, rapid morphological transition may emerge in a small portion of patients with TTS [1–4] (even if they have mechanical complications or extreme adrenergic discharge) suggesting the pivotal role of patient-related factors in the evolution of this phenomenon. Notably, a significant individual variation may also exist in the clinical features of this phenomenon such as its temporal characteristics (early vs. late transitions, etc.), site of transition (to the neighboring or distant myocardial segment), and number of morphological transitions during a single TTS course (single vs. multiple). However, the above-mentioned ideas are largely speculative and need to be further investigated.

In conclusion, rapid morphological transition might have important pathogenetic and clinical implications in TTS patients [1–4] which still need to be established in detail.

Article information

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Rapid morphological transition during the course of Takotsubo syndrome: A mysterious phenomenon with subtle implications. Author's reply

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We are most grateful to Dr. Yalta and colleagues for their interest in our case report [1], in which we showed two rare phenomena of midventricular takotsubo syndrome (TTS), mitral regurgitation (MR) independent of left ventricular outflow tract obstruction (LVOTO) and transition to the apical type in a single course.

Dr. Yalta rightly observed that the patient needs to be further investigated for a potential pheochromocytoma. Since the patient had a sudden sharp pain under the xiphoid, with sweating, nausea, and vomiting immediately after drinking boiled root soup 6 hours earlier, we performed an emergency chest abdominal CT scan 1 hour after admission and did not find any evidence of pheochromocytoma. Unfortunately, this patient did not receive a serum catecholamine test. The subsequent emergency angiography 3 hours after admission showed coronary slow flow, and the patient did not experience paroxysmal severe hypertension, bouts of headache, or malignant arrhythmogenesis during the course of the disease. Therefore pheochromocytoma was excluded as the cause of TTS. What is more, independent of a systemic increase in catecholamine concentrations through the hypothalamic-pituitary-adrenal axis, a local neurally mediated increase in catecholamine release at the myocardial level may also occur [2]. Apart from the locus coeruleus, neural impulses descend (from the rostral pons) into the posterior hypothalamus triggering norepinephrine release from sympathetic nerve terminals supplying the myocardium and coronary circulation. That is why plasma catecholamine concentrations are not always elevated.

As type transition during a single TTS course is rare, the factors and associated mechanisms are poorly understood. We partly agree with Dr. Yalta's hypothetical suggestion that "dynamic pattern may simply emerge as a protective or counterbalancing mechanism against life-threatening mechanical complications" [3]. Dr. Yalta speculated that "rapid transition of wall motion abnormalities from the midventricular to the apical territory apparently terminated severe MR, which, if persistent, might have led to acute pulmonary edema and/or hemodynamic compromise" [3]. Generally, MR is more likely to occur in apical TTS but is rare in midventricular TTS. Two independent mechanisms may cause acute MR, systolic anterior motion (SAM) of the mitral valve in association with dynamic LVOTO and apical tethering of the subvalvular mitral valve apparatus [4, 5]. These two mechanisms are common in apical TTS. Therefore, it seems that the transition from apical to midventricular type is more helpful in prognosis than the transition from midventricular to apical type. It was strange in our case that severe MR rapidly disappeared with the improvement of cardiac function and did not recur in the following apical TTS. We would like to propose another hypothesis that type transition may be seen as a self-resting/regulating mechanism of the myocardium during TTS. Based on the adrenergic hypothesis, the resting/regulating mechanism could be explained as a different spatiotemporal response to plasma catecholamine of different cardiac segments or spa-

tiotemporal difference in cardiac sympathetic excitability at different segments. This spatiotemporal difference may ensure a certain degree of cardiac function rather than complete myocardial akinesis when a large amount of serum catecholamine is released or the cardiac sympathetic nerve is excessively excited.

We agree that a significant individual variation may also exist in the clinical features of this phenomenon including its temporal characteristics (early vs. late transitions, etc.), site of transition (to the neighboring or distant myocardial segment), and number of morphological transitions during a single TTS course (single vs. multiple), etc. However, the above-mentioned hypothesis needs further investigation. Multicenter large sample studies about dynamic cardiac ultrasound imaging during the acute phase of TTS, even at hourly intervals, are important for understanding type transition during a single disease course and may reveal the nature of TTS evolution.

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The course and treatment of COVID-19 in heart transplant recipients

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We read with interest an article by Nowak et al. [1] presenting the results of a case series study of heart transplant recipients infected with SARS-CoV-2. Since the study group consisted of only 5 patients, and, therefore, conclusions should be drawn with caution, there is an undeniable trend toward a decrease in COVID-19 complications in the era of the predominance of Delta and Omicron variants, vaccination, and antiviral treatment [1] compared to the first phase of the pandemic in Poland [2]. All the presented patients [1] were hospitalized, but none required mechanical ventilation or ICU admission, and the only death was related to septic shock, not COVID-19 *per se*. In contrast, a recent study by Hazan et al. [3] demonstrated that of 57 hospitalized cases (of which 51 were confirmed to be infected with either Delta or Omicron variants), 53% required ICU admission, 38% required mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO), and 38% died, with a higher rate of complications in Omicron-infected patients, even though 75% of them were fully vaccinated. However, Hazan [3] reported that only 4% of patients received antiviral treatment. In this context, we agree with Nowak et al. that there is still a need for rapid diagnosis of COVID-19 and early initiation of antiviral treatment in immunocompromised patients.

What caught our attention in the article by Nowak et al. [1] was that 2 of 5 patients had pulmonary aspergillosis. The authors did not explain whether aspergillosis was diagnosed in the course of COVID-19 or whether it was a pre-existing condition. Van Grootveld et al. [4] recently showed that the incidence of COVID-19-associated pulmonary aspergillosis reached up to 15% of patients admitted to the ICU, but data on the coexistence of COVID-19 and pulmonary aspergillosis in stable hospitalized patients are scarce. Therefore, we are curious about the prevalence of pulmonary aspergillosis in heart transplant recipients hospitalized at the authors' center during the study period. Furthermore, given our own experience with difficulties in diagnosing fungal infections, we would like to ask how the diagnosis of aspergillosis was confirmed. Antifungal treatment with triazole derivatives causes fluctuations in immunosuppression due to interactions with calcineurin inhibitors. This leads to another question: what were the tacrolimus concentrations at the time of COVID-19 diagnosis (in the aspergillosis group versus other patients)?

Since COVID-19 was mostly diagnosed in the first year after transplantation or shortly after acute rejection, it is likely to be associated with extensive immunosuppression. Balancing the risk of acute organ rejection with the risk of infectious complications needs a careful adjustment of immunosuppression regimens. Kolonko et al. [2] reported that in one-third of heart transplant recipients, the dose of immunosuppressants was reduced after COVID-19 diagnosis, except for the dose of calcineurin inhibitors which remained unchanged. Did Nowak and colleagues follow any rules, or was the immunosuppressive treatment adjusted only on a case-by-case basis? Furthermore, an interesting fact has been observed previously [2]: in kidney transplant recipients, a significant increase in median tacrolimus levels was noted during the first weeks of COVID-19 when compared to the mean values before infection. Do the authors have similar observations?

At the end of the discussion of immunosuppressive therapy during COVID-19 treatment, we would like to mention ritonavir-

-boosted nirmatrelvir, another drug approved and now available for the early treatment of mild to moderate COVID-19. Due to the ritonavir component of the combination, a strong cytochrome P450 (CYP) 3A4 inhibitor and a P- glycoprotein inhibitor, many significant drug-drug interactions could be expected. In general, it is recommended to temporarily withhold certain immunosuppressants (e.g., tacrolimus, everolimus, sirolimus) and reduce the dose of others (e.g. cyclosporine) during ritonavir-boosted nirmatrelvir administration [5]. Any change in immunosuppressive regimen should be individualised and discussed with a transplant physician.

Article information

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The course and treatment of COVID-19 in heart transplant recipients. Author's reply

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Dear Editor,

Thank you very much for the opportunity to contribute to the current discussion on post-transplant patients with COVID-19, by referring to the letter of Anna Drohomirecka and Tomasz Zieliński [1] published in *Kardiologia Polska* (*Kardiol Pol*, *Polish Heart Journal*) as a commentary on our article entitled: "The course and treatment of COVID-19 in heart transplant recipients: A case series from the late phase of the pandemic". Given the high risk of infectivity and mortality due to COVID-19 in heart transplant recipients and the need to improve the care of our patients, the exchange of institutional experience between transplant centers is of great importance. We believe that *Kardiol Pol* is an excellent platform for the cardiac and transplant community to share knowledge and experience in this field.

Pulmonary aspergillosis in heart transplant recipients with COVID-19

COVID-19-associated fungal infections, including COVID-19-associated pulmonary aspergillosis (CAPA), have been well described [2] and defined as secondary (fungal-after-viral) infections; however, the data on the prevalence of invasive pulmonary aspergillosis preceding COVID-19 are limited. We described 2 cases of heart transplant recipients with COVID-19 initially infected with aspergillosis. The diagnosis in both cases was established in the early post-transplant period according to the guidelines of the International Society for Heart and Lung Transplantation [3] including clinical and laboratory criteria (positive bronchoalveolar lavage testing for Aspergillus galactomannan) and the results of computed tomography of the chest. Both patients were treated with voriconazole and had a tacrolimus concentration of 17.3 ng/ml and 10.2 ng/ml at the time of COVID-19 diagnosis (compared to the other 2 patients with a tacrolimus concentration of 10.3 ng/ml and 13.3 ng/ml). Referring to the observation of kidney transplant recipients with COVID-19, we also noted a trend towards higher tacrolimus concentrations during COVID-19 compared to earlier periods in our patients.

The management of immunosuppressive regimens during anti-COVID treatment

Treatment of post-transplant patients, especially immunosuppressive management, always requires an individual approach. Moreover, in the absence of established rules, decisions are often made based on individual and institutional clinical experience. During the pandemic, it was common practice to discontinue or reduce the treatment with antimetabolites; however, reports on the effect of mycophenolate on the course of infectious diseases are contradictory. While some studies suggest an impaired immune response to SARS-CoV-2 vaccination in individuals treated with mycophenolate [4], others show a beneficial effect of the drug on the course of COVID-19 and indicate the antiviral properties of mycophenolate itself [5].

Referring to immunosuppressive management during anti-COVID treatment, we considered the actual intensity of immunosuppression, time from transplant or rejection event, and type of anti-COVID treatment (antivirals or biologics). Our overall strategy for early post-transplant patients on antiviral therapy was to maintain background therapy with tacrolimus and mycophenolate mofetil and closely monitor drug levels with dose

adjustments. In cases of neutropenia, we temporarily discontinued anti-metabolite treatment.

Article information

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Co-existing cardiomyopathy in the setting of congenital coronary artery anomalies: Further insights into pathogenetic and clinical aspects

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In clinical practice, coronary artery anomalies (CAAs) have been rarely encountered, and usually, they encompass a variety of congenital abnormalities in the origin, course, and termination of major coronary arteries [1–3]. Fortunately, most of these anomalies are clinically benign [2, 3]. However, certain CAAs (such as anomalous left coronary artery arising from the pulmonary artery [ALCAPA] or anomalous coronary arteries with an interarterial or intramural course) might be particularly associated with unfavorable outcomes including sudden cardiac death (SCD) [3]. In particular, emerging myocardial dysfunction significantly contributes to the adverse prognosis in the setting of CAAs [3]. The recent report by Silva et al. [1] describes a middle-aged male with an anomalous left coronary artery arising from the contralateral aortic sinus with diverse courses of its major branches [1]. Notably, the patient also had idiopathic left ventricular systolic dysfunction [1]. Accordingly, we would like to make further comments on potential implications of various cardiomyopathy patterns in the setting of CAAs.

First, certain CAAs (such as ALCAPA or myocardial bridge) might directly account for significant myocardial injury through induction of acute or chronic coronary syndromes (due to severe coronary hypoxemia, enhanced atherogenesis, vasospasm, etc.) [2, 3]. In the long term, a substantial amount of ischemic myocardial injury followed by a compensatory remodeling process might lead to ischemic cardiomyopathy in this context [3]. Even though, the anomalous coronary artery seems patent in such patients [1], it might potentially have subtle abnormalities such as an existing short intramural segment with an intermittent narrowing (that might have gone undetected) or episodes of coronary vasospasm (that might only be detected with a coronary vasoreactivity test). Given the absence of late gadolinium enhancement on cardiac MRI [1], extensive myocardial hibernation or stunning due to episodic ischemia might also serve as a potential trigger of cardiomyopathy in such patients (and, hence, indicate further tests for myocardial viability). We also wonder about other electrocardiographic (ECG) findings (Q waves, etc.), if they are available [1].

Second, myocardial dysfunction (manifesting as non-ischemic cardiomyopathy) and CAAs might independently arise as the major components of certain congenital cardiac anomalies such as tetralogy of Fallot (TOF) [2, 3]. Moreover, various combinations of these abnormalities (congenital cardiac defects, CAAs, and cardiomyopathy) might emerge as part of a systemic syndrome. In this regard, the patient might potentially harbor such a systemic syndrome due to his suspicious findings including mental, auditory, and visual deficits along with an existing horse-shoe kidney [1]. Accordingly, did the authors plan genetic counseling for further phenotypical analysis of the patient? Importantly, isolated non-ischemic cardiomyopathy (due to various triggers) might also arise coincidentally in those with CAAs.

Finally, and more subtly, certain forms of isolated familial cardiomyopathies and major CAAs might also co-exist in certain settings

[4]. Notably, there has been a particular co-existence of hypertrophic cardiomyopathy and anomalous origin of coronary arteries [4]. More specifically, a mitochondrial gene mutation (*MT-TK* gene encoding transfer RNA) was previously identified in a young patient with an anomalous left coronary artery arising from the right aortic sinus together with apical hypertrophic cardiomyopathy [4]. Notably, deafness and cardiomyopathy (hypertrophic or dilated) similar to the features of the patient described in [1] were previously interpreted as the manifestations of this gene mutation [4]. Therefore, the patient [1] might be in the late (burned-out) phase of hypertrophic cardiomyopathy primarily characterized by relative wall thinning and systolic dysfunction. Alternatively, he might have familial dilated cardiomyopathy primarily presenting with systolic dysfunction [1]. Importantly, certain forms of familial cardiomyopathy might have significantly worse outcomes including SCD [4], which potentially indicates the need for implementing preventive strategies including implantable cardioverter-defibrillator (ICD) therapy in the relatively early stages of the disease course. Taken together, genetic analysis (for gene mutations implicated in familial cardiomyopathies) together with subsequent family screening (with imaging modalities) might enable further risk-stratification and management of this patient along with an early diagnosis of CAAs and/or familial cardiomyopathy, if any, in his family members.

In conclusion, co-existing myocardial dysfunction in the setting of major CAAs seems to be a multifaceted phenomenon with important implications [1–4]. Importantly, differentiation between various cardiomyopathy patterns in patients with CAAs (largely through advanced imaging modalities, genetic analysis, etc.) might allow proper risk stratification and management of these patients and their family members.

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Expert opinion of the Polish Cardiac Society on therapeutic targets for LDL cholesterol levels in secondary prevention of myocardial infarction

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ABSTRACT

Cardiovascular diseases account for 43% of deaths in Poland. The COVID-19 pandemic increased the number of cardiovascular deaths by as much as 16.7%. Lipid metabolism disorders are observed in about 20 million Poles. Lipid disorders are usually asymptomatic, they cause a significant increase in the risk of cardiovascular diseases. Up to 20% of patients who experience acute coronary syndrome (ACS) may experience a recurrence of a cardiovascular event within a year, and up to 40% of these patients may be re-hospitalized. Within 5 years after myocardial infarction, 18% of patients suffer second ACS and 13% from a stroke. Lipid-lowering therapy is an extremely important element of comprehensive management, both in primary and secondary prevention, and its main goal is to prevent or delay the onset of heart or vascular disease and reduce the risk of cardiovascular events. A patient with a history of ACS belongs to the group with very high risk of cardiovascular events due to atherosclerosis. In this group of patients, low-density lipoprotein cholesterol levels should be maintained below 55 mg/dl (1.4 mmol/l). Many scientific guidelines define the extreme risk group, which includes not only patients with two cardiovascular events within two years, but also patients with a history of ACS and additional clinical factors: peripheral vascular disease, multivessel disease (multilevel atherosclerosis), or multivessel coronary disease, or familial hypercholesterolemia, or diabetes with at least one additional risk factor: elevated Lp(a) >50 mg/dl or hs-CRP >3 mg/l, or chronic kidney disease (eGFR <60 ml/min/1.73 m^2). In this group of patients, the low-density lipoprotein cholesterol level

should be maintained below 40 mg/dl (1.0 mmol/l). Achieving therapeutic goals in patients after ACS should occur as soon as possible. For this purpose, a high-dose potent statin should be added to the therapy at the time of diagnosis, and ezetimibe should be added if the goal is not achieved after 4–6 weeks. Combination therapy may be considered in selected patients from the beginning. After 4–6 weeks of combination therapy, if the goal is still not achieved, adding a proprotein convertase subtilisin/kexin type 9 protein inhibitor or inclisiran should be considered. In order to increase compliance with the recommendations, the Polish Cardiac Society and the Polish Lipid Society propose to attach in the patient's discharge letter a statement clearly specifying what drugs should be used and what LDL-C values should be achieved. It is necessary for the doctor to cooperate with the patient so that the patient follows the recommendations and takes medicines regularly to achieve and maintain therapeutic goals.

Key words: ezetimibe, hypercholesterolemia, inclisiran, myocardial infarction, PCSK9 inhibitors, secondary prevention, statins

Cardiovascular diseases have been the leading cause of death in Poland for many years — accounting for as much as 43% of all deaths in our country [1]. The COVID-19 pandemic has further significantly increased cardiovascular problems due to the lack of well-functioning preventive programs — especially in primary prevention. Problems with accessibility of the centers with specialized care, offices of primary care physicians, outpatient specialized care, and patients' concerns about visits to healthcare facilities have also contributed to worse outcomes. An increase in risk factors for cardiovascular disease among Poles, including the most common lipid disorders that can affect more than 60% of the population can also be an explanation for the observed phenomenon [2].

In 2020 (the first year of the COVID-19 pandemic), there were more than 67 000 more deaths than in 2019, some of which were directly caused by SARS-CoV-2 virus infection, while the rest were deaths from complications of chronic diseases. Among chronic diseases, the largest increase in deaths in 2020, compared to 2019, was recorded in cardiology (up 16.7%), as well as in diabetic patients (up 15.9%) [3]. According to data from the Central Statistical Office, the number of deaths in 2021 was 154 000 higher than the average for the last 50 years and more than 42 000 higher than in 2020 — this difference was due to both an increase in deaths from SARS-CoV-2 infection (24.9%) and chronic diseases, primarily cardiovascular diseases (17.2%) [4].

There is a significantly higher risk of cardiovascular disease in people with untreated hypercholesterolemia, which in most cases is asymptomatic until the first cardiovascular event, such as myocardial infarction, stroke, or peripheral vascular disease, occurs [5]. In Poland, we have about 20 million people with hypercholesterolemia [6]. Most of them are not aware of it. It is estimated that about 140 000 Poles suffer from familial hypercholesterolemia, and it has only been diagnosed in about 5% of patients so far [6, 7].

Patients who have had acute coronary syndrome (ACS) have an increased risk of recurrent cardiovascular events, which in Poland can affect up to 20% of patients within a year after the incident, and the risk of re-hospitalization for cardiovascular causes within a year after a myocardial infarction is more than 40% [6, 8]. The annual mortality rate calculated from the beginning of hospitalization for myocardial infarction in Poland is 17.3%, the three-year mortality rate reaches 28.2% [8, 9], and the 5-year mortality rate reaches 35% [10]. Within 5 years after myocardial infarction, 18% of patients suffer recurrent myocardial infarction and 13% a stroke [10]. At the same time, as indicated by the European Society of Cardiology (ESC) guidelines on cardiovascular disease prevention, Poles belong to a high cardiovascular-risk group, and hypercholesterolemia, affecting nearly 60% of the population, is the most important modifiable and least controlled risk factor for cardiovascular disease [11–13].

Hypolipemic treatment is an extremely important part of comprehensive management in both primary and secondary prevention, with the main goal of preventing or delaying the onset of cardiovascular disease and reducing the risk of cardiovascular events [14–16].

The recommendations of the International Lipid Expert Panel (ILEP) and the 2021 PolA/CFPiP/PCS/PSLD/PSD/PSH (Polish Lipid Association/College of Family Physicians in Poland/Polish Cardiac Society/Polish Society of Laboratory Diagnostic/Polish Society of Diabetology/Polish Society of Hypertension) guidelines, based on available data, further supplement the definition of extremely high cardiovascular risk, compared to the 2019 European Atherosclerosis Society/ESC guidelines [6, 13, 17]. It not only includes patients after 2 vascular events in the last 2 years but also patients after the first presentation of ACS with additional clinical criteria (Table 1) [6]. Similarly, the recommendations of the Section of Cardiovascular Pharmacotherapy of the Polish Cardiac Society, contained in the Third and Fourth Sopot Declaration, distinguish a group of extremely high-risk patients in whom it is recommended to achieve an even lower therapy goal for low-density lipoprotein cholesterol (LDL-C) — below 35 mg/dl (0.9 mmol/l). This includes patients after multiple cardiovascular events and/or revascularizations, with multivessel coronary artery disease, after left coronary artery trunk intervention, with atherosclerosis of multiple vascular beds or progression of coronary artery disease, despite maintaining LDL-C <55 mg/dl (<1.4 mmol/l) [18].

The current ESC guidelines on prevention and dyslipidemia recommend, in patients at very high cardiovascular risk, lowering LDL-C, by at least 50% and below 55 mg/dl (1.4 mmol/l). Moreover, in patients with a subsequent vascular event within 2 years, a reduction of LDL-C to below 40 mg/dl (1.0 mmol/l) can be considered [11]. This also applies to the aforementioned extreme-risk patients defined according to the 2021 PolA/CFPiP/PCS/PSLD/PSD/PSH guidelines. These complement the definition of extreme cardiovascular risk, which not only applies to patients after 2 vascular events but also to patients in primary prevention and after ACS with additional clinical criteria (Table 1) [6].

The 2021 PolA/CFPiP/PCS/PSLD/PSD/PSH guidelines explicitly suggest what therapy should be implemented for patients in each risk group (Table 2) [6].

Thus, in very high-risk patients, which includes post-ACS patients, combination therapy is warranted to achieve therapeutic goals and should be instituted as soon as possible, and in some cases immediately after the diagnosis of lipid disorders (Table 3) [6,11]. In addition, the PolA/CFPiP/PCS/PSLD/PSD/PSH guidelines for the first time recommend considering in such patients the use of a combination drug pill containing a statin and ezetimibe (fixed-dose combination), not only to achieve the therapeutic goal quickly but also to improve treatment adherence [6]. In patients at high and very high risk persisting despite statin treatment with the maximum tolerated dose, it is recommended to add ezetimibe as early as 4–6 weeks after hospital discharge (for this purpose, lipidogram parameters should be routinely assessed 4–6 weeks after hospital discharge), and if even this is not enough to achieve therapeutic goals, it is recommended to add a proprotein convertase subtilisin/kexin type 9 (PCSK9) protein inhibitor (alirocumab, evolocumab)/inclisiran (after further 4–6 weeks).

Indeed, in most very high-risk patients, the only chance to achieve the therapeutic goal is by applying the principles of "the lower, the better" and "the sooner, the better" [6]. It should be noted that in Poland, maximum tolerated doses of statins are rarely used (<5%), and fully reimbursed optimal standard therapy — that is, high-dose statin combined with ezetimibe, which lowers LDL-C by about 65%, is used in only 18% of patients during the first year after myocardial infarction, according to the latest results of the KOS-LIPID study [19].

Table 1. Definition of extreme cardiovascular risk categories in patients after acute coronary syndrome (ACS) [6]

Risk category	2021 PolA/CFPiP/PCS/PSLD/PSD/PSH guidelines
Extreme	Patients in primary prevention with Pol-SCORE >20%. Status after ACS and one of the following: • another vascular event within the past 2 years • peripheral vascular disease or multivessel disease (multilevel atherosclerosis) • multivessel coronary artery disease • familial hypercholesterolemia • diabetes and at least one additional risk factor: elevated Lp(a) >50 mg/dl, hs-CRP >3 mg/l, or chronic kidney disease (eGFR <60 ml/min/1.73 m^2)

Abbreviations: eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein (a)

Table 3. Expected effect of LDL-C lowering depending on the combination of hypolipemic drugs used [11]

Treatment	Average reduction in LDL-C level
Moderate intensity statin treatment	≈30%
High intensity statin treatment	≈50%
High intensity statin + ezetimibe combined treatment	≈65%
PCSK9 inhibitor	≈60%
PCSK9 inhibitor PCSK9 + high intensity statin treatment	≈75%
PCSK9 inhibitor PCSK9 + high intensity statin + ezetimibe combined treatment	≈85%

Abbreviations: PCSK9, proprotein convertase subtilisin/kexin type 9; other — Table 2

Table 2. Proposed hypolipemic therapy in patients at extreme and very high cardiovascular risk [6]

Risk group	LDL-C	Non-HDL-C	Therapy — 2021 PolA/CFPiP/PCS/PSLD/PSD/PSH guidelines
Extreme risk	<40 mg/dl (1,0 mmol/l)	<70 mg/dl (1.8 mmol/l)	**Extremely intensive hypolipemic therapy (LDL-C reduction by 80%–85% vs. baseline)** Atorvastatin 40–80 mg/d + Alirocumab/Evolocumab Rosuvastatin 20–40 mg/d + Alirocumab/Evolocumab Atorvastatin 40–80 mg/d + Ezetimibe 10 mg/d + Alirocumab/Evolocumab Rosuvastatin 20–40 mg/d + Ezetimibe 10 mg/d + Alirocumab/Evolocumab Atorvastatin 40–80 mg/d + Inclisiran 300 mg/every 3/6 months[a] Rosuvastatin 20–40 mg/d + Inclisiran 300 mg/every 3/6 months[a]
Very high risk	<55 mg/dl (1.4 mmol/l) and lowering LDL-C by ≥50% vs. baseline	<85 mg/dl (<2.2 mmol/l)	**Very intensive hypolipemic therapy (LDL-C reduction 60%–80% vs. baseline)** Atorvastatin 40–80 mg/d + Ezetimibe 10 mg/d Rosuvastatin 20–40 mg/d + Ezetimibe 10 mg/d Atorvastatin 40–80 mg/d + Ezetimibe 10 mg/d + Bempedoic acid 180 mg/d Rosuvastatin 20–40 mg/d + Ezetimibe 10 mg/d + Bempedoic acid 180 mg/d Rosuvastatin 10 mg + Ezetimibe 10 mg/d + Bempedoic acid 180 mg/d* Atorvastatin 20 mg + Ezetimibe 10 mg/d + Bempedoic acid 180 mg/d Alirocumab 150 mg biweekly Evolocumab 140 mg biweekly Rosuvastatin 5–10 mg/d (+Ezetimibe 10 mg/d) + Alirocumab/Evolocumab/Inclisiran[a] Atorvastatin 10–20 mg/d (+Ezetimibe 10 mg/d) + Alirocumab/Evolocumab/Inclisiran[a] Simvastatin 20–40 mg/d (+Ezetimibe 10 mg/d) + Alirocumab/Evolocumab/Inclisiran[a]

[a]The recommended dose is 300 mg of inclisiran in a single subcutaneous injection administered for the first time, again after 3 months, and every 6 months thereafter

Abbreviations: LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non high-density lipoprotein cholesterol

The results of the POLASPIRE study indicate that in Poland, in patients with ACS, the rate of prescribing high-dose statins on discharge from cardiac units is only 68% [20]. As a result, only 38% of patients achieved LDL cholesterol levels below 1.8 mmol/l (<70 mg/dl) one year after hospital discharge, and 16% below 1.4 mmol/l (<55 mg/dl) [20].

Successful treatment of lipid disorders is primarily about achieving LDL-C targets. Treatment success is expressed by the number of cardiovascular events avoided. Critical to the success of dyslipidemia therapy is the establishment of the right relationship between the physician and the patient, which allows the patient to understand what the disease is, as well as the goal and expected effects of treatment. Data from the WOBASZ II study indicate that with respect to the general Polish population, only 6% of people with hypercholesterolemia are treated effectively, 15% are treated ineffectively, and the rest are either unaware of the disease or do not receive drug treatment [6, 21]. To increase the effectiveness of treatment and the number of very high-risk patients in the therapeutic target, immediate combination treatment with a statin and ezetimibe, preferably in the form of a combination pill, is now recommended [6]. As early as April 2021, the ILEP proposed that post-ACS patients with baseline high LDL-C levels (>100 mg/dl [2.5 mmol/l] for previously suboptimally treated patients and >120 mg/dl [3 mmol/l] for untreated patients) and patients with familial hypercholesterolemia and extremely high cardiovascular risk should receive immediately combination treatment to accelerate the achievement of the therapeutic goal of LDL-C and reduce the risk of cardiovascular complications [17]. This approach has subsequently been adopted by both the European Atherosclerosis Society Task Force, the 2021 PolA/ /CFPiP/PCS/PSLD/PSD/PSH guidelines, and numerous expert opinions that propose this approach for all very high-risk patients [6, 22–24].

In day-to-day practice, effective LDL-C lowering and achieving targeted therapeutic goals is a huge challenge. An example is the multicenter observational DA VINCI study, conducted in 2017–2018 in 18 countries, including Poland. The study enrolled 5888 patients and assessed the achievement of therapeutic goals in accordance with the 2016 and 2019 ESC guidelines [25]. In Poland, in a very high cardiovascular-risk group, the therapy goal for LDL-C, according to the current 2019 guidelines, was achieved in only 17% of patients [2]. The reason for such unsatisfactory results was undoubtedly the infrequent use of high-dose statins and combination treatment with ezetimibe. The results of this registry indicate that in daily practice, combination therapy with statins and other hypolipemic drugs is necessary to achieve the goal of therapy. Among other potential reasons for such a low success rate of LDL-C lowering therapy are (on the physician's side) diagnostic and therapeutic inertia and (on the patient's side) low adherence, reluctance to use high doses of statins and combination therapy, concern about statin-related side effects, the high cost of drugs such as PCSK9 inhibitors (alirocumab, evolocumab) or inclisiran, and limited reimbursement indications [14, 26].

The results of a meta-analysis involving data from nearly 4.2 million patients worldwide indicate that the prevalence of statin intolerance is 9.1%. However, if intolerance is diagnosed using various definitions, including the ILEP definition, it is between 5.9% and 7% [27, 28]. It is estimated that full statin intolerance affects only 2% of patients [29]. Simplifying, statin intolerance should be defined as the inability to use statin therapy that is adequate to the existing cardiovascular risk, both as to formulation and dose [30]. In summary, the consequence of statin intolerance is not only the lack of statin treatment due to clinical or biochemical symptoms but also the phenomenon of taking too low a statin dose or "too weak" a statin in relation to cardiovascular risk [30, 31].

Lipid disorders are still a diagnostic and therapeutic challenge. The difficulty is proper risk assessment of patients, choosing appropriate treatment, and patient adherence to pharmacological but also non-pharmacological recommendations: proper diet, weight reduction, or regular exercise [32]. Added to this is therapeutic inertia. It consists of an inappropriate choice of therapy; the most common challenge is insufficient intensive treatment with statins and failure to use combination therapy. This is compounded by reducing the statin dose (de-escalation of therapy), e.g., when adding another non-statin drug, as confirmed by the KOS-LIPID study [19]. It is also all too common to make the mistake of reducing the dose or discontinuing therapy once the therapeutic goal has been achieved [33]. This is a dangerous phenomenon because, especially in high- and very high-risk patients, discontinuation increases the risk of a repeat cardiovascular event [11, 30].

It is therefore necessary to closely monitor adherence, especially in patients after a cardiovascular or cerebrovascular event. Strict adherence to statins of more than 90%, compared with adherence <50% (assessed using the drug possession rate), has been shown to be associated with a 30% reduction in the risk of death, at less than 3-year follow-up [34]. Patient education and effective prevention programs in this area are important.

To increase adherence, the Polish Cardiac Society and the Polish Lipid Society are proposing recording in the discharge chart of myocardial infarction patients which drugs should be used and what LDL-C values should be achieved (Supplementary material). Then, if target LDL-C levels are not achieved, patients can be referred to a lipid disorder treatment program (drug program B.101).

Hypolipemic treatment in patients with ACS — summary of the 2021 PolA/CFPiP/PCS/PSLD/PSD/PSH guidelines [6]:

- In any ACS patient, the maximum tolerated dose of statin should be started as soon as possible to achieve the therapeutic goal.
- In any ACS patient, immediate combination therapy of a statin with ezetimibe, preferably in the form of a com-

bination formulation, can also be considered to achieve the therapeutic target for LDL-C as soon as possible.
- A saturating dose of a potent statin (atorvastatin, rosuvastatin) should be considered in any ACS patient before percutaneous coronary intervention.
- LDL cholesterol levels should be assessed in each patient 4–6 weeks after hospital discharge.
- In each ACS patient, the aim is to achieve, as soon as possible, an LDL-C level <1.4 mmol/l (<55 mg/dl), for effective prevention of subsequent incidents.
- In any patient who meets the definition of extreme cardiovascular risk, the aim is to achieve an LDL-C level <1.0 mmol/l (<40 mg/dl).
- In any ACS patient, hypolipemic treatment should be lifelong.
- A large percentage of ACS patients require combination therapy to achieve the therapeutic goal.
- Treatment with commercially available combination formulations helps improve patient cooperation.

Controlling LDL-C in the blood is a "team effort". It is necessary for the patient and the doctor to cooperate and for the patient to follow instructions and take medication regularly to achieve and maintain therapeutic goals. An important part of the cooperation is continuous, ongoing education of doctors and education of patients about the goals of therapy, how to achieve these goals, and about benefits of continuing treatment. Patients with high cardiovascular risk and patients who are not responding to treatment require special care and continuous control of LDL-C levels. In their case, abandonment or inadequate treatment can have particularly serious consequences [35].

Supplementary material

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

Article information

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Expert opinion of the Heart Failure Association of the Polish Cardiac Society, College of Family Physicians in Poland, and Polish Society of Family Medicine on the peri-discharge management of heart failure patients

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INTRODUCTION

Despite advances in the treatment of heart failure (HF), the rate of hospitalization for exacerbations of the disease remains high. One of the underlying reasons is that the recommended guidelines for HF management are still too rarely followed in daily practice. Disease exacerbation requiring inpatient treatment is always a factor that signals disease progression and thus worsens prognosis. This is also a key moment when therapy for HF exacerbation should be modified or initiated in the case of a newly diagnosed disease. Inpatient treatment and the peri-discharge period is the time when the etiology and mechanism of HF decompensation should be established. Therapy should be individualized based on etiology, HF phenotype, and comorbidities; it should take into account the possibilities of modern treatment. According to the recommendations of the European Society of Cardiology (ESC), HF patients should receive multidisciplinary management. Cooperation between various members of the multidisciplinary team taking care of HF patients improves the efficiency and quality of treatment. This expert opinion expands and details the information on the peri-discharge HF management recommended in the 2021 ESC guidelines and the 2022 American Heart Association (AHA)/ /American College of Cardiology (ACC)/Heart Failure Society of America (HFSA) guidelines.

HOSPITALISATION FOR HEART FAILURE — A MEDICAL, EPIDEMIOLOGICAL, AND PROGNOSTIC PROBLEM

Heart failure is a progressive condition with periods of exacerbations, which periodically also requires intravenous treatment and modification of medical management [1]. Hospitalization resulting from HF exacerbations significantly worsens patient prognosis. In Poland, current data on hospitalization for HF were obtained from an analysis conducted by the Ministry of Health (MoH), covering the entire adult population of Poland (41 532 268 people) from 2013 to 2018, focusing on people with a diagnosis of HF (1 686 861 people). In this group, almost half of the patients (817 432 people; 48.5%) were hospitalized. It was shown that between 2013 and 2018, the number of hospital admissions increased by as many as 33% (2013 — 198 881; 2018 — 264 808). Since 2008, the rate of hospitalization for HF in Poland has been the highest among Organization for Economic Cooperation and Development countries. The cost of hospitalization of HF patients increased by 125% between 2015 and 2020 in Poland. Expenditures of the National Health Fund (NHF) related to HF in Poland were estimated at 6.2 billion PLN in 2018, accounting for as much as 0.3% of GDP [2, 3]. The higher incidence of readmissions was seen primarily in women over 65 years of age, with comorbidities [4, 5].

Inpatient stay should be a key time for optimizing therapy and changing existing treatment. However, in daily practice, in most cases, medications prescribed on discharge are based on a pharmacotherapy regimen similar to that before hospitalization, which is a regimen that has proven ineffective in preventing cardiovascular destabilization [6]. Moreover, early initiation and intensification of pharmacotherapy do not occur in the peri-discharge period although numerous studies have shown that this is a safe procedure associated with improved patient prognosis [7–10]. Long-term observations have demonstrated that the post-discharge period, especially the first 30 days, is the time when cardiovascular events, exacerbation of HF, and the need for readmission are most common [11]. Hemodynamic destabilization and readmissions are factors that particularly worsen the prognosis of HF patients [1, 6, 11]. This is also indicated by the MoH data, according to which the chance of surviving 720 days from hospital discharge decreases significantly as the number of subsequent hospital admissions increases. With one hospitalization, the survival rate is 66.4%, and with four or more, it is only 43.9%.

BASELINE PHENOTYPE AND RESPONSE TO HOSPITAL TREATMENT AS DETERMINANTS OF POST-DISCHARGE MANAGEMENT

Clinical knowledge shows that in patients with acute heart failure (AHF), the quality of treatment in the period immediately after hospital discharge fundamentally affects short- and long-term morbidity and mortality [12]. Factors to be considered include individualized escalation of therapy, monitoring of its effectiveness and possible side effects of drugs, as well as rehabilitation carried out early after hospitalization. In practice, the implementation of HF treatment recommendations is not sufficient. The reasons for this may depend on both the patient and the healthcare system and may also be conditioned by the social environment and psychological profile of the patient. The sum of these factors is called the patient's clinical phenotype; its identification during hospitalization significantly modifies the possibilities of implementing, escalating, and sustainably continuing the recommended treatment [13].

According to an individual HF natural history, the patient's phenotypic features can be grouped according to the chronology of treatment, from the first clinical presentation and contact with the healthcare system to the patient's discharge from the hospital. For each hospitalization, the cycle of events is similar, and several groups of factors can be mentioned:

- the patient's historical data known at the time of admission;
- the clinical presentation of HF, including its etiology and the cause of decompensation;
- inpatient response to treatment and adverse events;
- individual determinants of patient cooperation after discharge.

The medical records and taking a thorough history from the patient and his/her family are irreplaceable sources of information. An effort should be made to gather as much data as possible, not only on cardiovascular risk factors and comorbidities but also on the chronology of events. Non-medical data, including social, psychological, and other issues, are also useful in planning patient care. The information obtained makes it possible to identify barriers to implementation, escalation, and maintenance of recommended therapy after discharge. Among the most significant factors are [14]:

- HF etiology, if already established;
- age of the patient, considering differences between chronological and biological age;
- number of previous hospital stays for cardiovascular decompensation;
- duration and complications observed during previous hospital stays;
- time from onset of the first concerning symptoms to the patient's contact with a physician and initiation of treatment (for previous and current hospital admissions);
- presence of comorbidities, especially atrial fibrillation (AF), type 2 diabetes mellitus (T2DM), chronic obstructive pulmonary disease (COPD), cancer, chronic kidney disease (CKD), liver failure, anemia, and neurological conditions, including progressive dementia;
- changes in "edema-free" body weight during HF (losses and gains after hospital stays), with determination of weight-loss percentage compared to the pre-HF period;
- frailty syndrome;

- presence of right ventricular dysfunction in previous hospital stays;
- left ventricular ejection fraction (LVEF) during previous hospital stays.
- treatment used to date, in particular, the type and doses of drugs recommended in the guidelines and the doses of diuretics;
- problems with patient adherence known from previous hospital stays (non-compliance, abandonment of medications, lack of conscious control of fluid supply, diuresis, body weight, etc.);
- mood disorders, depression, and other mental illnesses.

A still underestimated factor that determines subsequent patient outcomes is a delay between the appearance of the first HF symptoms and exacerbation and medical intervention [15]. Investigations conducted in the first hours of hospitalization should provide answers to further relevant questions. In addition to the etiology of HF (if already established), the specific circumstances and factors that may be responsible for the current cardiovascular decompensation are crucial. It is essential to elucidate the non-etiological causes of disease exacerbation besides analyzing acute causes of HF according to the CHAMPIT algorithm (acute Coronary syndrome/Hypertension emergency/Arrhythmia/acute Mechanical cause/Pulmonary embolism/Infections/Tamponade) [13]. Determining the etiology, in the case of *de novo* HF presentation, and searching for the causes of decompensation of previously stable HF can reveal the clinical circumstances – a specific patient phenotype – that determine further management. Undertaking treatment appropriate to the identified problem can modify HF management after discharge [13].

Among the most important etiological factors are:

- acute coronary syndromes (ACS) with the need for invasive treatment (revascularization);
- valve diseases for which invasive treatment can be used;
- infections, especially those requiring surgical management and long-term antimicrobial treatment (infective endocarditis or lead-related endocarditis, infected bedsores, and others);
- dysfunctions of implanted cardiac devices;
- thromboembolism;
- central nervous system ischemic events:
- arrhythmia;
- discontinuation or inappropriate use of pharmacotherapy, side effects of drugs (especially nephrotoxic or leading to thyroid dysfunction), alcohol, and illegal drugs;
- clinically significant bleeding;
- malignant neoplasms and their treatment.

In parallel and independently of etiologic diagnosis and causes of cardiovascular decompensation, the clinical presentation of HF itself can also influence post-discharge treatment. Current guidelines distinguish four main AHF phenotypes: acute pulmonary edema, decompensated chronic heart failure (CHF), isolated right ventricular HF, and cardiogenic shock. However, it is important to note that overlap between these phenotypes is possible in individual patients. The most important phenotypic features identified at the time of admission that may impose serious limitations on recommended therapies after discharge are summarized below [11]:

- class IV according to New York Heart Association (NYHA);
- "cold/wet" and "cold/dry" hemodynamic profiles of AHF;
- low blood pressure (BP);
- high natriuretic peptide levels, elevated troponin levels, hyponatremia, high urea levels, and high urea/creatinine ratio;
- impaired glomerular filtration, especially in those with a documented high percentage loss of "edema-free" body weight;
- low (<50–70 mEq/l) urinary sodium level 3 hours after intravenous loop diuretic administration;
- increased multiorgan congestion, especially with the presence of exudative fluid in body cavities;
- no prior treatment with renin-angiotensin-aldosterone system (RAAS) blockers and beta-blockers.

In addition to etiological intervention and treatment of the cause of cardiovascular decompensation, elimination of congestion and/or organ hypoperfusion usually requires diuretics, in some phenotypes, vasodilators, and, in others, drugs that increase myocardial contractility and peripheral vascular resistance. Determining the target condition, which is complete resolution of congestion and/or hypoperfusion and initiation or escalation of therapy recommended in the guidelines, and tracking the clinical response to this treatment (based on daily examination and laboratory test results) allows defining four basic clinical courses:

- steady clinical improvement toward a defined goal;
- initial clinical improvement followed by stabilization without reaching the target;
- steady clinical improvement but with worsening clinical parameters and additional test results (hypotonia, bradycardia, hyponatremia, greater than expected deterioration of renal function, hyperkalemia, metabolic alkalosis), individually or in combination;
- clinical worsening.

Except for the first course, all of the above scenarios require management modifications and may affect post-discharge management. Of paramount importance is the effectiveness of eliminating congestion, especially using the current recommendations for diuretic treatment (this factor is critical in maintaining clinical stability) and adequate treatment of comorbidities [16, 17]. Post-discharge treatment tactics and strategies can also be influenced by clinical adverse events observed during therapy. The same factors that contribute to the initial HF exacerbation can also complicate treatment.

Individual determinants of patient cooperation after discharge are among the least appreciated factors determining the success of HF therapy. Measures to improve

this cooperation are not implemented often enough. The factors that have the greatest impact on the effectiveness of cooperation include:

- the patient's level of education and his/her occupation;
- place of residence with special attention to the possibility of effective contact with various levels of the healthcare system (primary healthcare, cardiac outpatient center, hospital emergency department/emergency room, hospital ward), laboratory, pharmacy;
- opportunities for the patient and his/her family to use telemedical technologies during treatment;
- economic status;
- family and neighborhood environment.

METHODS OF ASSESSING PROGNOSIS IN HEART FAILURE RISK STRATIFICATION FOR READMISSIONS AND DEATH AFTER DISCHARGE AND THEIR UTILITY IN PRACTICE

There are many factors that are associated with particularly poor prognosis in HF patients [18]. These include disease progression expressed as consecutive stages A to D, NYHA classes I to IV, and, in the group with severe HF, the INTERMACS scale of 7 to 1. The risk is particularly high in patients after multiple hospital admissions for cardiovascular decompensation and in patients with CKD and other comorbidities [19, 20]. The prognosis is worse with decreasing LVEF, in patients with spherical left ventricular (LV) geometry (sphericity index >0.7) and with concomitant, hemodynamically significant valve diseases (especially mitral and/or tricuspid regurgitation) [21]. There is also an increased risk of decompensation or death in patients with a restrictive LV filling profile and significantly reduced LV longitudinal fiber function (reduced mitral annular velocities and longitudinal strain) [22]. A higher risk is observed in patients with right ventricular enlargement and dysfunction and pulmonary hypertension (tricuspid regurgitation velocity >2.8 m/s, mean pulmonary artery pressure >30 mm Hg) [23]. Patients >65 years of age, males, non-compliant patients, patients with depression, low body weight (cachexia) and nutritional deficiencies (including iron), ongoing infections, and high natriuretic peptide levels also have a worse prognosis [24].

Prognosis in HF is unfavorable in terms of both life expectancy and risk of hospitalization. According to data from the ESC Heart Failure Long-Term Registry, the prognosis is significantly worse in patients who were hospitalized than in outpatients. The annual overall mortality rate in the first group was 23%, while in the second group, it was 6.4%; the composite endpoint (overall mortality or HF hospitalization) in the first group was 35% and in the second 23% [25]. A huge problem is the need for frequent readmissions, especially in the first 30 days after discharge. According to Spanish data from 2003–2011, the rate of readmissions increased by 1.36% per year, from 17.6% to 22.1% [26]. The majority of hospital readmissions had a cardiovascular cause (60%), with HF in the first place. However, in recent years, attention has been drawn to the fact that conditions other than HF are responsible for a large proportion of hospital readmissions [20]. These data indicate the need for appropriate treatment of comorbidities in patients with HF. It is noteworthy that 1 in 6 patients discharged after cardiovascular decompensation is readmitted urgently to the hospital within 30 days of discharge [27]. The association of repeated hospital stays due to HF exacerbation with long-term prognosis has also been pointed out in other works. In one of them, the 30-day mortality rate was determined to be 7.4%, and the one-year mortality rate was 27.3% after hospitalization [28]. Each subsequent hospitalization was associated with shorter survival. Average survival after the first hospital stay for HF was 2.6 years, 1.8 years after the second, 1.5 years after the third, and only 1.3 years after the fourth hospitalization. However, the authors point out that this does not show that reducing readmission frequency would reduce mortality [28]. Further studies are needed to better understand the impact of readmissions on HF progression.

There is no single ideal prognostic indicator in HF. Such assessment is always multifactorial, depending, in addition to the above-mentioned determinants, also on the etiology of HF and the assessment of the reversibility of its cause (e.g., successful revascularization of the coronary arteries in patients with ischemic cardiomyopathy, successful treatment of a valve disease). Only a holistic view of these factors allows an experienced clinician to estimate the risk of serious complications and select patients for whom special care should be provided. Such analysis is not entirely accurate — despite a small number of risk factors, early disease progression does not mean that a given patient's prognosis is good [24]. In recent years, the MAGGIC scale, constructed from an analysis of data from 39 372 HF patients with preserved (HFpEF) and reduced ejection fraction (HFrEF) from 30 clinical trials, has been increasingly used; the scale includes 13 prognostic parameters [29]. These easily available scored indices include age, male sex, LVEF, NYHA class, creatinine level, not using beta-blockers, not using angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), systolic blood pressure (SBP), body weight, time from HF diagnosis, smoking, presence of T2DM and COPD. In the MAGGIC study, the median score was 23. Low risk, defined as <17 points, was associated with 3-year risk of death of 10%. In contrast, very high risk (>33 points) was associated with 3-year risk of death of 70%. A calculator to determine the 1-year and 3-year risk of death in HF can be found at www.heartfailurerisk.org. Analysis of data from the above-mentioned ESC Heart Failure Long-Term Registry showed that fewer than 1% of practicing physicians assessed the prognosis of their HF patients using the available scales [30]. Such patient assessment is not simple but very useful. The finding of a worse prognosis based on the calculation of a composite index, such as the MAGGIC score, is an indication for more intensive treatment, more

Table 1. Recommended non-pharmacological interventions in patients with heart failure (HF) [24]

Recommendations	Class	Level
It is recommended that HF patients are enrolled in multidisciplinary HF management programmes to reduce the risk of HF hospitalization and mortality	I	A
Self-management strategies are recommended to reduce the risk of HF hospitalization and mortality. Outpatient or inpatient care programmes are recommended to reduce the risk of HF hospitalisation and mortality	I	A
Influenza and pneumococcal vaccinations should be considered to prevent HF and hospitalization	II	A

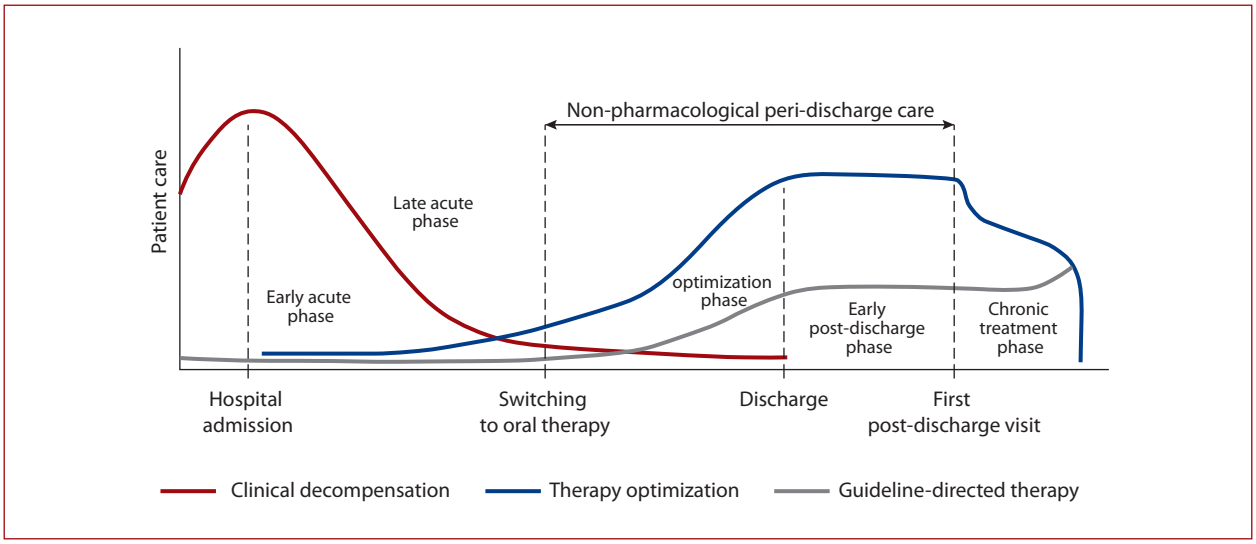

Figure 1. The clinical course of heart failure and the place of non-pharmacological management in the peri-discharge period [14]

frequent monitoring of HF course, and possibly referral to a transplantation center or palliative care.

NON-PHARMACOLOGICAL MANAGEMENT IN THE PERI-DISCHARGE PERIOD

Non-pharmacological management is a very important aspect of therapy. The current guidelines devote considerable attention to non-pharmacological interventions that should be implemented during hospitalization (Table 1) [24].

With regard to peridischarge treatment tasks and goals, non-pharmacological management involves three phases: the pre-discharge optimization phase, discharge, and early post-discharge phase (Figure 1) [14].

The essential tasks of the team coordinating HF treatment include [31]:

- HF diagnosis and monitoring disease progression;
- prescribing treatment, optimizing and monitoring HF therapy;
- patient and caregiver education about the disease and treatment;
- lifestyle education and recommendations (regarding diet, physical activity, and stimulants, among others);
- assessing the need for psychological and social support;
- coordination of comorbidity care;
- counseling and end-of-life palliative care.

The ESC guidelines support multidisciplinary-team care for HF patients. In the pre-discharge phase, the team should provide clinical assessment, therapy optimization, patient education, and a post-discharge care plan. Clinical evaluation of the patient, in the hospital, should include daily measurements of the following parameters: BP, heart rate (HR) and respiratory rate, body weight, and fluid retention levels. Periodically, it is also advisable to measure levels of biomarkers of myocardial overload and damage (B-type natriuretic peptide [BNP]/N-terminal pro-B-type natriuretic peptide [NT-proBNP], troponin) and assess renal function (creatinine/estimated glomerular filtration rate [eGFR], urea, electrolytes) [13].

In the peri-discharge period, patient education is a very important aspect affecting therapy effectiveness. This period should be used to comprehensively discuss with the patient issues such as their general knowledge of HF and prognosis, monitoring of vital signs, symptoms of fluid overload, and fluid intake. Implementing education and teaching patients to self-manage their symptoms reduces the risk of both HF and all-cause hospitalization (by 34% and 27%, respectively) [32]. Nurse-led face-to-face education is the most commonly chosen strategy in educating HF patients.

Education should include the following topics discussed in a comprehensible manner with the patient:

- basic information about the definition, cause, and course of HF (including prognosis);
- basic knowledge of pharmacotherapy (drugs, dosage, side effects, contraindicated drugs);
- essential information on implantable devices and percutaneous or surgical intervention;
- information on diet and use of stimulants (alcohol, cigarettes, use of psychoactive substances);

Table 2. Follow-up visits in patients with chronic heart failure

Clinical condition	Follow-up visits	Parameters evaluated	Specialist
Stable patient	Every 6 months	Signs of cardiovascular decompensation in patient history and on physical examination, other symptoms, BP, HR, complete blood count, electrolytes (sodium and potassium), creatinine, other[a]	Cardiologist/PCP
Patients discharged from hospital	Preferably 1–2 weeks after discharge, then as needed	Signs of cardiovascular decompensation in patient history and on physical examination, other symptoms, BP, HR, complete blood count, electrolytes (sodium and potassium), creatinine, other[a]	Cardiologist/PCP
Patients in the course of therapy escalation	As needed (to optimize therapy)	Signs of cardiovascular decompensation in patient history and on physical examination, other symptoms, BP, HR, complete blood count, electrolytes (sodium and potassium), creatinine, other[a]	Cardiologist/PCP

[a]Other — ECG once a year to assess the duration and morphology of the QRS complex and identify conduction and rhythm abnormalities (especially atrial fibrillation); echocardiography in case of clinical deterioration and 3–6 months after optimization of standard therapy for HFrEF to determine indications for possible modification of pharmacotherapy and/or implantation of devices (ICD, CRT)

Abbreviations: BP, blood pressure; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; ICD, implantable cardioverter-defibrillator; PCP, primary care physician

- knowledge about engaging in sexual activity;
- information on prophylactic vaccination;
- information on safe traveling.

Observations have shown that the rate of readmission within 30 days of the last hospital stay was significantly lower in the group of HF patients educated by a nurse (20.4%) compared to the group without education (50.0%) [33, 34]. It is also important to remember the need to educate family members and relatives of HF patients. Education and family support contribute to better adherence to pharmacological and dietary recommendations, and patients show better motivation and self-confidence [35, 36]. Special attention should be given to diuretic treatment with practical education on both diuretic dosage and fluid intake, as well as monitoring for symptoms of fluid overload. Symptom monitoring is an important aspect of patient-physician collaboration and should include assessment of breath shortness, fatigue, BP, HR, and body weight. These observations should be kept in the form of a diary/passport. It is important to teach the patient which symptoms are cause for concern (e.g. increased shortness of breath and/or edema or rapid weight gain of more than 2 kg in 3 days) and how to contact medical staff if there is an increase in symptoms that may indicate incipient cardiovascular decompensation. Cooperating patients can be taught to modify diuretic treatment and potassium supplementation depending on the severity of their symptoms, to control their renal function (creatinine/eGFR) and electrolyte levels. Patient involvement in self-management of symptoms and modification of diuretic treatment reduces the risk of HF hospitalization and mortality [13]. The Polish Cardiac Society has launched an educational portal for HF patients (www.slabeserce.pl) where they can improve their knowledge of the disease through accessible and understandable content. This portal can also be used to help educate patients. The Heart Failure Patient Passport can be downloaded from: https://niewydolnosc-serca.pl/sprawozdanie/paszport-pacjenta_z%20NS.pdf. A certified nursing education program is also available for nurses who would like to expand their competencies regarding the care of HF patients and become specialized HF educators.

The onset of HF is accompanied by the onset of depressive symptoms, loneliness, anxiety, and withdrawal [37, 38], so it is advocated that psychosocial support be provided to patients, their families, and/or caregivers. In recent years, cognitive behavioral therapies based on mindfulness techniques, applied in a group of HF patients, have confirmed the significant effect of this type of intervention on reducing depressive symptoms [39–41].

Patients admitted to the hospital for HF exacerbation can be discharged home if [42]:

- they are clinically stable (no signs of cardiovascular decompensation — in extreme HF this condition not always can be met) and hemodynamically stable;
- are in euvolemia, and their renal function parameters have been stable for >24 hours;
- have been properly educated in the context of both self-monitoring and HF itself.

The patient, when leaving the hospital, should receive [43]:

- a discharge letter with details of his/her hospital stay;
- recommendations for prevention and monitoring of symptoms;
- information specifying the course of rehabilitation;
- recommendations for post-discharge management regarding both the patient and his/her primary care physician (PCP).

It is also advisable to schedule a follow-up visit within 1–2 weeks after discharge from the hospital (Table 2). Such early outpatient follow-up (preferably on day 7) is primarily aimed at assessing signs of fluid overload, tolerability of pharmacotherapy, and the possible need to change the treatment, including doses of disease-modifying drugs and diuretics. The introduction of a follow-up visit on day 7 after discharge reduces the rate of 30-day readmission by 30% [13, 44–47]. In the early post-discharge phase, it is extremely important for patients to perform consciously and responsibly self-monitoring with regard to the presence of clinical symptoms, BP, heart rate, body weight, periodic assessment of clinical chemistry parameters (in PCP or cardiac center setting) as well as adhere to diet and physical activity recommendations [48]. It is recommended that HF patients

undergo regular medical checks, whose frequency depends on the treatment stage of the disease in a given patient. When planning care after HF exacerbation requiring hospital treatment, follow-up visits should be more frequent and scheduled at the time of patient discharge from the hospital. During post-hospital follow-up, indications for electrotherapy (implantable cardioverter-defibrillator, cardiac resynchronization therapy) should also be verified after a >3-month period of optimal pharmacotherapy. In the period between exacerbations, once the patient's condition is stabilized and all planned interventions have been carried out, outpatient check-ups may occur less frequently, but no less than every 6 months. These visits should take place regardless of the presence/severity of symptoms to optimize the pharmacotherapy and detect asymptomatic disease progression early. Patients with a history of HF exacerbation and significant modification of pharmacotherapy should be monitored more frequently, but the guidelines do not specify at what intervals. Recommendations for the frequency of follow-up visits in CHF — according to the ESC guidelines — are shown in Table 2 [13].

INDIVIDUALIZATION OF THERAPY — AN IMPORTANT ASPECT OF DISCHARGE MANAGEMENT

According to the 2021 ESC guidelines, optimizing therapy after hospitalization for AHF reduces the risk of readmissions, cardiovascular death and improves quality of life. Individualization of HF therapy is one of the areas of emphasis in the current guidelines, and it is based on clinical profiles that take into account the following data [13, 49]:

- BP;
- HR;
- heart rhythm type (especially the presence of AF);
- renal function and/or hyperkalemia;
- fluid overload.

The individualization of therapy should also take into account the patient's preferences and abilities. The guidelines place particular emphasis on careful assessment of fluid overload features in patients before discharge and optimization of oral diuretic treatment. In fact, the presence of fluid overload features in a patient discharged after HF exacerbation is associated with high risk of death and readmissions [50, 51]. For patients not previously treated with beta-blockers, but who show fluid overload features, these drugs should not be the first line of therapy, as they may lead to clinical deterioration.

In the pre-discharge period (once acute cardiovascular decompensation is under control), HFrEF patients must receive oral medications to improve their prognosis. This stage is possible in those patients who have achieved hemodynamic stability and have no significant fluid retention. The introduction of these drugs into therapy requires consideration of both the clinical profile and form of AHF (*de novo*, CHF exacerbation), as highlighted above. Primary medications for HFrEF that modify the course of the disease include beta-blockers, ACEI/ARB/angiotensin receptor neprilysin inhibitors (ARNI), mineralocorticoid receptor antagonists, (MRA), and sodium-glucose co-transporter 2 (SGLT2) inhibitors [13, 52, 53]. The TRANSITION and PIONEER-HF trials confirmed the clinical benefits of ARNI therapy in patients hospitalized for acute manifestation of HFrEF, both *de novo* and as CHF exacerbation [9, 10]. On the other hand, the PERSPECTIVE study — presented during the recent 2022 ESC congress in Barcelona — showed that ARNI does not impair cognitive function compared to valsartan in patients with HF with mildly reduced EF (HFmrEF) or HFpEF, although there was a reduction in the deposition of β-amyloid in the brain in patients treated with ARNI, which requires further research. The results of the studies showed that initiating ARNI therapy in the predischarge period is safe and is associated with early and sustained improvements in reducing the risk of major cardiovascular events and lowering biomarkers (NT-proBNP, troponin). It is noteworthy that patients with *de novo* HF benefited most from ARNI therapy introduced in the pre-discharge period. ARNI treatment can be started if SBP is not <100 mm Hg, eGFR is >30 ml/min/1.73 m^2, and potassium is <5.4 mmol/l. In persons previously receiving ACEI, 36 hours must elapse from the last dose of the drug. Given the current state of knowledge, in the opinion of the experts of the Heart Failure Association of the Polish Cardiac Society, ARNI (sacubitril/valsartan) should be the preferred drug over ACEI/ARB in HFrEF patients. This is supported by the recommendations in the latest 2022 AHA/ACC/HFSA guidelines.

The clinical benefits of beta-blocker treatment in HFrEF have been confirmed in a number of studies. Moreover, retrospective analyses have documented that dose reductions of these drugs or their discontinuation in patients hospitalized for HF exacerbation were associated with a worse prognosis [54]. The inclusion or continuation of MRA and SGLT2 inhibitor therapy, on the other hand, can be safely carried out even in patients with low SBP values (<90 mm Hg), except those with coexisting chronic coronary syndrome (CCS) for whom SBP >120 mm Hg is recommended [13]. The EMPA-RESPONSE-AHF trial in AHF patients treated with empagliflozin reported a reduction in the risk of a composite endpoint consisting of worsening HF, readmissions, and cardiovascular death at 60-day follow-up [55]. On the other hand, in the SOLOIST-WHF study in patients with T2DM and HF exacerbation, treatment with sotagliflozin, initiated before or shortly after discharge, resulted in a significantly lower total number of cardiovascular deaths and HF hospital admissions and urgent visits compared to placebo [56]. The latest EMPAG-HF study shows that early inclusion of empagliflozin in standard diuretic therapy increases the effectiveness of diuresis without adversely affecting renal function in AHF patients. These results somewhat accord with the EMPULSE study mentioned below, which showed, among others, the safety of empagliflozin therapy in stable patients just after an AHF episode.

It is worth recalling that high HR is an unfavorable prognostic factor on discharge. Reducing HR is an important therapeutic goal in the treatment of HFrEF. This strategy is beneficial for patients with sinus rhythm and HR greater than or equal to 70 bpm. The ETHIC-AHF trial and the Optimize Heart Failure Care program have demonstrated that intensification of treatment before discharge with concomitant administration of beta-blockers and ivabradine to patients stabilized after decompensated HFrEF resulted in benefits as early as in the first month of therapy (higher percentage of patients with HR <70 bpm) and after one year of followup [8, 57, 58]. For patients treated with beta-blockers and ivabradine, improved LVEF, reduced risk of death and readmission for HF, and better quality of life have been reported after 12-month follow-up [57, 58]. Although according to the latest ESC guidelines, it is optimal to use representatives of all four drug groups (beta-blockers, ACEI/ARB/ARNI, MRAs, and SGLT2 inhibitors), even at the expense of possibly not reaching target doses, this is not always possible in daily practice [13]. Table 3 shows the clinical profiles for each drug group. The therapy established before discharge is the starting point for further optimization in the outpatient setting. The pre-discharge period usually does not allow for achieving optimal doses of the listed HF course-modifying drugs, so after the patient is discharged from the hospital, it is necessary to gradually increase them until the target or maximum drug doses tolerated by the patient are reached. Such information should be included in the hospital discharge letter and in the information for the family doctor.

While for main HFrEF pharmacotherapy, the current ESC and AHA/ACC/HFSA guidelines are convergent (the use of beta-blockers, ACEI/ARB/ARNI, MRAs, and SGLT2 inhibitors has a class I recommendation), except for the positioning of ARNI versus ACEI/ARB, some important differences emerge for patients with LVEF >40%. For patients with HFmrEF, the ESC guidelines recommend the use of beta-blockers (to reduce the risk of HF hospitalization and death), ACEI/ARB/ARNI, MRAs, and SGLT2 inhibitors (recommendation class IIb), without specifying recommendations for pharmacotherapy to improve prognosis in HFpEF patients (beyond treatment of concomitant diseases and control of risk factors). In part, this was because the guidelines were published before the results of recent studies on treatment options for HFpEF [13]. The more recent AHA/ACC/HFSA guidelines from this year recommend the use of SGLT2 inhibitors as first-line therapy for both HFmrEF and HFpEF (class IIa), before beta-blockers, ACEI/ARB/ARNI, MRAs (class IIb) [53]. This is largely due to the results of studies such as EMPEROR-Preserved and DELIVER. The EMPULSE trial evaluated empagliflozin versus placebo in patients hospitalized for AHF regardless of LVEF. For patients receiving empagliflozin during 90 days of follow-up, it was shown

Table 3. Pharmacological treatment of heart failure depending on the patient's clinical profile [49]

Patient with low BP (<90/60 mm Hg)	
HR 60–70 bpm	**HR >70 bpm**
MRA SGLT2 inhibitor ↓ beta-blocker ↓ diuretic ↓ ACEI/ARB/ARNI	MRA SGLT2 inhibitor ↓ beta-blocker ↓ diuretic ↓ ACEI/ARB/ARNI **Ivabradine**
Patient with high BP (>140/90 mm Hg)	
ACEI/ARB/ARNI SGLT2 inhibitor Beta-blocker MRA Diuretic **Vericiguat** **Hydralazine/isosorbide dinitrate**	
Patient with low heart rate (<60 bpm)	
BP >90/60 mm Hg	**BP <90/60 mm Hg**
ACEI/ARB/ARNI SGLT2 inhibitor MRA diuretic ↓ beta-blocker **Vericiguat**	SGLT2 inhibitor MRAs ↓ beta-blocker ↓ ACEI/ARB/ARNI ↓ diuretic
Patient with increased heart rate (>70 bpm)	
ACEI/ARB/ARNI SGLT2 inhibitor Beta-blocker MRA Diuretic **Ivabradine**	
Patient with AF	
QRS complex frequency >60 bpm	**BP <90/60 mm Hg**
Beta-blocker ACEI/ARB/ARNI SGLT2 inhibitor MRAs Diuretic **Digoxin** **Oral anticoagulant (NOAC of choice)**	SGLT2 inhibitor ACEI/ARB/ARNI MRAs ↓ beta-blocker ↓ diuretic **Oral anticoagulant (NOAC of choice)**
Patient with CKD	
eGFR <30 ml/min/1.73 m^2	**eGFR >30 ml/min/1.73 m^2**
SGLT2 inhibitor Beta-blocker Diuretic **Vericiguat** Hydralazine/isosorbide dinitrate	SGLT2 inhibitor Beta-blocker ACEI/ARB/ARNI MRA Diuretic **Vericiguat** Hydralazine/isosorbide diazotate
Patient with hyperkalaemia (K^+ >5.5 mEq/l)	
SGLT2 inhibitor Beta-blocker Diuretic ↓ ACEI/ARB/ARNI ↓ MRA **Potassium-binding products** (e.g., polystyrene sulfonate, Resonium A) **vericiguat**	

↓ Dose reduction or drug discontinuation

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, heart rate; MRA, mineralocorticoid receptor antagonist; NOAC, non-vitamin K antagonist oral anticoagulant; SGLT2, sodium-glucose co-transporter 2

that they were 36% more likely to experience a clinical benefit in terms of reduced risk of cardiovascular death, hospitalization for HF, and improved quality of life. The drug was started once clinical stability had been achieved, usually on the 3rd day of hospitalization [59, 60]. The benefit of treating HF without significantly reduced ejection fraction (LVEF >40%) has also been demonstrated for another SGLT2 inhibitor, dapagliflozin. The DELIVER study confirmed that in patients with HFpEF/HFmrEF (LVEF >40%), dapagliflozin significantly reduces the risk of cardiovascular death or HF exacerbation [61].

IMPACT OF COMORBIDITIES ON INPATIENT COURSE AND OUTPATIENT CARE PLANNING

Heart failure is often accompanied by other cardiovascular conditions and diseases of other organs and systems. According to the ESC Pilot Survey registry, 74% of HF patients have at least one non-cardiovascular concomitant disease, which translates into a significant increase in mortality in this patient population [62]. The current guidelines devote a great deal of attention to treatment of comorbidities as important causes of readmissions when they are not recognized and/or not treated effectively [13]. Particularly noteworthy in the peri-discharge period are:

- among cardiovascular conditions: CCS, AF, arterial hypertension (AH);
- beyond cardiovascular conditions: iron deficiency (ID), T2DM, CKD.

Chronic coronary syndromes

The most common cause of HF in our population is coronary artery disease, which can lead to significant abnormalities in LV contractility, size, and shape. Myocardial ischemia should therefore be considered whenever patients are hospitalized for AHF, especially if a reduction in LVEF is observed *de novo*. Documenting ischemia using non-invasive exercise tests can be difficult in HF patients due to often poor exercise tolerance and chronically elevated LV end-diastolic pressure. Coronary angiotomography or invasive coronary angiography can be performed to determine the presence and severity of CCS, which will be critical in determining possible indications for coronary revascularization if stenocardial symptoms persist despite optimal pharmacotherapy [63]. Beta-blockers, which are one of the main groups of drugs in the treatment of HFrEF patients, are also recommended in CCS, primarily for their antianginal effects. Ivabradine, on the other hand, should be considered as an alternative to beta-blockers (if contraindicated) or as an additional treatment to reduce ischemia in patients with HR >70 bpm [63]. Other antianginal drugs (primarily calcium antagonists, nicorandil, ranolazine, and nitrates) can also be effective in treating angina symptoms. Moreover, the addition of trimetazidine, which improves LV function and exercise tolerance in patients with HFrEF and CCS already treated with chronic beta-blockers, may be considered. In HF patients, short-acting nitrates should be used with caution because they can cause hypotension. It is also important to note that diltiazem and verapamil are contraindicated in HFrEF patients [13].

Atrial fibrillation

Atrial fibrillation is the most common type of arrhythmia in HF patients (15%–30%), especially those >65 years old. The risk of AF is particularly high in HFpEF patients (40%), and it is an independent factor for a worse prognosis in this group of patients (increased risk of stroke, thromboembolic complications, hospitalization for HF, and death) [13]. The finding of AF in an HF patient requires first and foremost:

- identifying and treating the causes and triggers of cardiac arrhythmias;
- treatment of HF;
- prophylaxis of thrombotic complications;
- choosing a strategy for sinus rhythm control or ventricular rate control.

In all patients with HF and paroxysmal, persistent, or permanent AF, chronic oral anticoagulant treatment is recommended unless contraindicated. Non-vitamin K oral anticoagulants are preferred for preventing thromboembolic incidents because they have similar efficacy to vitamin K antagonists and a lower risk of bleeding [64]. However, this applies to patients with AF without significant mitral valve stenosis or the presence of a mechanical valve prosthesis. In patients with a contraindication to oral anticoagulant therapy, left atrial appendage closure may be considered.

The cornerstone of AF treatment is symptom control through HR control. In cases of significant irreversible myocardial impairment with obviously enlarged cardiac cavities (especially the left atrium), a strategy of ventricular rate control rather than rhythm type control may be recommended. This is due to the low probability of both restoring and maintaining sinus rhythm in this group of patients. Pharmacological control of the ventricular rate can be achieved by using primarily beta-blockers and digoxin [64]. The choice of drugs depends on the HF phenotype, symptoms, comorbidities, and potential side effects. Dronedarone, diltiazem, and verapamil are contraindicated in HFrEF patients while amiodarone, due to its numerous side effects, can usually be used only for a short period (<6 months) [13]. The acceptable resting ventricular rate in patients with permanent AF is 110 bpm, although some experts suggest that it should be in the range of 60–100 bpm [65, 66].

Hypertension

Hypertension is one of the main risk factors for the development of HF, and nearly two-thirds of HF patients have a history of AH. Hypertension causes LV hypertrophy, thereby impairing its diastolic function; it is also a strong predictor of HF development (even with preserved LVEF), thus playing a special role in HFpEF etiopathogenesis. AH treatment significantly reduces the risk of developing

HF and hospitalization for HF, especially in people over >65 years of age. It must be remembered that inadequately controlled AH can lead to episodes of acute cardiovascular decompensation manifesting as pulmonary edema. The most important recommendations for the treatment of AH in patients with HF are as follows [13, 67]:

- in HFrEF patients, ACEI/ARB, beta-blockers, diuretics, and/or MRAs are recommended. With inadequate BP control, treatment with dihydropyridine calcium antagonists (amlodipine or felodipine) can be added to therapy;
- in HFpEF patients, treatment is based on ACEI/ARB, beta-blockers, diuretics, and calcium antagonists. BP thresholds for starting treatment and therapeutic goals should be the same as those for HFrEF patients.

ARNIs are also effective in lowering BP; moreover, they significantly improve the prognosis of HFrEF patients. Drugs in this group are, therefore, recommended as an alternative to ACEI/ARB for the treatment of AH in HFrEF patients. Non-dihydropyridine calcium antagonists (diltiazem, verapamil), alpha-blockers, and centrally acting drugs, such as moxonidine, are not recommended in HFrEF patients [13].

Iron deficiency and anemia

ID is an important comorbidity in HF patients. There is evidence that ID is associated with greater severity of HF symptoms, more frequent HF hospital stays, and increased risk of death [68, 69]. Clinical trials have indicated that intravenous iron supplementation (in the form of iron carboxymaltose) has significant benefits in HF patients [70–72]. It should be emphasized that oral iron supplementation in HF patients is ineffective and not recommended [73]. In the latest ESC recommendations for HF diagnosis and treatment, the place of intravenous iron supplementation is as follows [13]:

1. The use of intravenous ferric carboxymaltose should be considered in patients with stable symptomatic HFrEF (LVEF <45%, so also in patients with HFmrEF) and ID to improve the quality of life, exercise capacity, and to reduce the severity of HF symptoms [70, 71].
2. Intravenous ferric carboxymaltose should be considered in patients with HFrEF and HFmrEF (LVEF <50%) clinically stabilized after an AHF episode (current or recent hospitalization) and ID to reduce the risk of subsequent unplanned hospitalization for HF progression [72].

Given the aforementioned benefits, all HF patients, regardless of hemoglobin levels, renal function, and LVEF values, should be periodically screened for ID, also during hospitalization for AHF. Iron deficiency in HF patients is diagnosed based on ferritin levels <100 µg/l or ferritin level 100–299 µg/l (in this case, if accompanied by transferrin saturation <20%). If ID is found during hospitalization for AHF, the first dose of ferric carboxymaltose should be given in the hospital. In addition, intravenous iron supplementation can (and should!) be continued and carried out on an outpatient basis. In the CONFIRM-HF and AFFIRM-AHF studies, patient body weight and hemoglobin levels were taken into account when dosing intravenous ferric carboxymaltose in patients with HF and ID. The drugs are given at baseline and at 6 weeks. A total dose of 0.5–2.0 g of ferric carboxymaltose is given in a regimen of up to 1.0 g at baseline and the remaining dose at 6 weeks [72, 73]. If the hemoglobin level is >15 g/dl, intravenous iron should not be administered. Abnormal renal function, BP, and HR values are not contraindications to the administration of intravenous ferric carboxymaltose. Patients on intravenous iron should be re-evaluated for iron status after 3–6 months and, if required, supplemented again. It should also be mentioned that no allergy tests need to be performed before the first intravenous administration of ferric carboxymaltose.

Type 2 diabetes mellitus

Data from the literature indicate that up to 30% of HF patients have comorbid T2DM, and as many as two-thirds of the HF patient population have carbohydrate metabolism disorders (diabetes or pre-diabetes) [13]. Type 2 diabetes mellitus significantly increases the risk of developing HF and is one of the leading causes of CHF along with CCS and AH. T2DM patients have a 2–5 times higher risk of developing HF compared to those with normal glucose metabolism. In cases where T2DM and HFrEF are established, it is recommended that SGTL2 inhibitors (empagliflozin or dapagliflozin) be used first and foremost, which, in addition to their hypoglycemic effects, are, as already mentioned, one of the four groups of drugs included in the fundamental therapy of HFrEF [74, 75]. Metformin is a safe drug in HF patients; however, it should not be used in patients with eGFR <30 ml/min/1.73 m^2 and those with liver failure because of the risk of developing lactate acidosis. Glucagon-like peptide-1 (GLP-1) analogs and dipeptidyl peptidase 4 (DPP-4) inhibitors (except saxagliptin which increases the risk of hospitalization for HF) are not currently recommended in HF patients due to their neutral effects on the risk of death and hospitalization for HF [13, 76]. The use of sulfonylurea derivatives and thiazolidinediones (glitazones) is associated with increased risk of HF and/or hospitalization for HF and hence is not indicated for T2DM therapy in patients at risk of HF or those already diagnosed with CHF [13, 76].

For type 1 diabetes mellitus, insulin remains the drug of choice. Its use leads to sodium retention in the body, which can result in increased fluid retention and consequent cardiovascular decompensation in HF patients. Therefore, initiation of insulin therapy in HF patients and diabetes requires close monitoring of the patient's condition for early detection of possible fluid retention and incipient exacerbation of HF [13, 76]. It should be emphasized that a patient with diabetes mellitus and HF requires special monitoring (PCP, cardiology, diabetes) in the outpatient setting.

Renal impairment

Heart failure and CKD share common risk factors, such as T2DM and AH. CKD is one of the major independent determinants of increased mortality and morbidity in HF. In the course of CHF, especially when the disease is exacerbated, renal function often deteriorates. One reason for the increase in plasma creatinine levels is the use of diuretics in combination with ACEI/ARB/ARNI, MRAs, SGLT2 inhibitors, and nephrotoxic drugs, which include iodine contrast agents, certain antibiotics (gentamicin, trimethoprim), and non-steroidal anti-inflammatory drugs (NSAIDs). It should also be remembered that patients with impaired renal function may accumulate renally excreted drugs such as digoxin, insulin, and low-molecular-weight heparin. It is therefore very important to adjust the dosage of these drugs appropriately according to the degree of kidney damage.

Patients with HF and coexisting CKD are at higher risk of cardiovascular incidents. In the presence of renal impairment or in people over >65 years of age with good baseline renal function after inclusion of RAAS, ARNI, or SGLT2 inhibitors, the initial drop in glomerular filtration pressure may lower eGFR and increase serum creatinine. These changes generally resolve during long-term treatment. An increase in serum creatinine by <50% above baseline (as long as it is <266 µmol/l), or a decrease in eGFR by <10% compared to baseline (as long as it is >25 ml/min/1.73 m^2), may be considered acceptable. Transient deterioration of renal function during initiation of therapy should not lead to its discontinuation, as the new drugs recommended for the treatment of HFrEF (ARNIs, SGLT2 inhibitors) show a nephroprotective effect [77, 78]. ARNI, compared to enalapril, has been shown to reduce the rate of renal function deterioration [79]. A similar benefit has been indicated for the use of SGLT2 inhibitors (dapagliflozin, empagliflozin) compared to placebo, both in patients with HFrEF and those with CKD [77, 80].

With regard to diuretic treatment, small and transient increases in serum creatinine levels during treatment of acute HF are also not associated with a worse prognosis. In patients with very low eGFR, the effectiveness of diuretics (thiazide and loop diuretics) may be reduced. Diuretics should, therefore, be used in properly adjusted doses, as often a similar effect can be achieved with smaller and safer doses.

MONITORING A PATIENT WITH HEART FAILURE — THE ROLE OF TELEMEDICINE

The current ESC guidelines indicate that home telemonitoring of HF patients can be considered to reduce the risk of cardiovascular death, hospitalization, and HF exacerbation [13]. This form of patient care is associated with a 20% reduction in overall mortality and a 37% reduction in HF hospitalization. Telemonitoring turned out to be a particularly valuable tool during the COVID-19 pandemic. Monitored parameters such as symptoms, body weight, heart rate, and BP can be collected and stored in an electronic health record as part of medical record keeping and used to optimize therapy or provide medical advice remotely [75]. Teleconsultation is a relatively new tool in patient care in Poland. Teleconsultation was officially introduced into the National Health Fund's catalog in March 2020 in connection with the COVID-19 pandemic, as procedure no. 89.0099 — medical advice via ICT or communication systems.

The simplest form of teleconsultation is telephone advice, which allows for monitoring of the patient's condition, reminds of the need to take medication, and makes sure the patient is using the appropriate dosage. Telephone advice permits therapy optimization if the physician knows the patient and has seen him/her recently at the medical facility. During the phone call, the patient should be asked about his/her current well-being as well as any recent changes, the presence of peripheral edema, body weight changes, and modifications in treatment. The patient should also provide values of regular home BP and heart rate measurements, as well as the results of previously ordered laboratory tests. During such a telephone consultation, the doctor provides the patient with further recommendations, and may also suggest the need to visit a medical facility in person or, in exceptional urgent cases, to go to the hospital.

Ideally, the first follow-up visit after discharge from hospitalization for HF exacerbation should be a personal visit. However, this was not always possible, especially during the COVID-19 pandemic. If such a visit is to have the form of telephone consultation, then during such a consultation the physician should, first of all:

- assess the patient's general condition and degree of cardiovascular compensation (NYHA class, possible severity of symptoms indicative of decompensation);
- analyze and, if necessary, modify drug treatment;
- continue to educate the patient about HF (including self-management of symptoms) and related lifestyle modification, in which the Heart Failure Patient Passport is a great help;
- define and discuss the essential goals of treatment with the patient again;
- assess the compensation and treatment of comorbidities;
- make an assessment on the need for a personal visit at the office or readmission.

Many implanted therapeutic devices can wirelessly and remotely provide information about the device itself (generator and electrode function), rhythm disturbances, or the patient's clinical data (heart rate, activity, heart tone volume, bioimpedance). There is strong evidence that remote monitoring can detect device malfunctions earlier than conventional monitoring and may be useful in detecting cardiac arrhythmias such as AF. However, there is little evidence that device monitoring reduces HF admissions or mortality.

INPATIENT AND OUTPATIENT CARDIAC REHABILITATION IN PATIENTS WITH HEART FAILURE — THE CHALLENGE OF MODERN TIMES

Numerous clinical studies and meta-analyses classify cardiac rehabilitation with physical training, whose importance has changed over the years, as one of the most important non-pharmacological management options for HF patients [81–84]. Physical training is safe and recommended for HF patients, and the benefits of systematic controlled exercises outweigh the associated risks [85]. However, in patients with advanced HFrEF combined with multimorbidity, a cardiac rehabilitation program based on supervised exercise should be considered [13]. Figure 2 shows a diagram of cardiac rehabilitation dedicated to HF patients, which indicates the various stages of rehabilitation depending on the patient's condition.

TELEREHABILITATION IN HEART FAILURE — OPPORTUNITIES IN THE 21ST CENTURY

HF patients diagnosed with COVID-19 or survivors, i.e. so-called convalescents, are a new challenge in cardiac rehabilitation. The individualized cardiac rehabilitation of these patients depends on both CHF severity, symptoms, and short- and long-term health consequences of COVID-19. Such rehabilitation invariably includes education of the patient and his/her family, as well as physical training (breathing, endurance, resistance exercises, relaxation). It is worth using the modified 10-point Borg dyspnea scale, especially in more severe clinical cases [86, 87]. Following consultation with a physician and analysis of risk factors, a return to recreational low- to moderate-intensity sports can be considered, in parallel, however, with a structured exercise program under specific supervision of a specialist regarding the type and intensity of exercise [13, 85]. Regular physical activity should always be individualized and well monitored as well as tailored to the patient's current needs and lifestyle, taking into account the factors that affect them [82, 88, 89].

It is emphasized that cardiac rehabilitation during the pandemic period should be carried out with the shortest length of stay in a facility in favor of monitored home rehabilitation, using new technologies and telemonitoring [13, 88–90]. In 2021, a consensus of four prestigious arrhythmology societies, the International Society for Holter and Noninvasive Electrocardiology, Heart Rhythm Society, European Heart Rhythm Association, and Asia-Pacific Heart Rhythm Society, was published on ambulatory electrocardiographic telemonitoring, outlining cardiac telerehabilitation as a dedicated procedure for patients with cardiovascular conditions [91]. The COVID-19 pandemic made telerehabilitation sometimes the only possible intervention, so the European Association of Preventive Cardiology was calling for action to widely implement cardiac telerehabilitation during the COVID-19 pandemic as the optimal way to conduct secondary prevention [92].

Hybrid telerehabilitation is one of the possible forms of implementing cardiac rehabilitation programs funded by the National Health Fund. Published data indicate that it is effective, safe, and accepted by patients, resulting in good interactive patient cooperation [93–95]. It also leads to improvement in the quality of life [96]. It may be of particular importance for patients discharged from the hospital. Telerehabilitation should be conducted by a team of trained specialists including a doctor, physiotherapist, nurse, psychologist, and nutritionist. It uses equipment that allows remote monitoring of symptoms, parameters (electrocardiogram, BP, body weight), and control of physical training.

Hybrid telerehabilitation consists of two stages:

- the first preliminary stage is carried out in inpatient or outpatient settings;
- the second basic stage is carried out at home (telemonitored training sessions).

The initial stage is aimed at assessing clinical condition, exercise capacity, education, planning, and conducting several training sessions. If it is carried out in an outpatient clinic, it begins with an initial visit, during which, in addition to standard examinations, the patient has an exercise test, which is the basis for a training plan. Over the following 5 days, the patient participates in educational meetings that include learning how to use the telerehabilitation equipment and exercise techniques, consultations with a nutritionist and psychologist, and lectures on pro-healthy lifestyles, diet, benefits of regular physical activity, and first aid. In the case of implementation of the initial stage during hospitalization, all the procedures described above take place during hospitalization, and after discharge, the patient implements the second stage of telerehabilitation at home. After the telerehabilitation cycle, a follow-up visit is scheduled with an exercise test, and further recommendations are given to the patient [97, 98].

During the pandemic period, to minimize the exposure of medical personnel and patients, a modification of the hybrid telerehabilitation procedure was prepared [99]. It was proposed to shorten the initial outpatient stage to 2 days and conduct further training using audio/video communicators, with the patient already at home. In addition, when the initial stage takes place during hospitalization, it has been proposed that it can be carried out by specialized teams (meeting the requirements for hybrid telerehabilitation outlined in the relevant protocols of the National Health Fund) in each center/department, and not, as is currently the case, only in rehabilitation centers/departments. In addition, in well-defined cases, the authors propose conducting the final visit using only ICT systems [99].

The increasingly common availability of hybrid telerehabilitation in HF provides an opportunity to involve a much larger number of patients in rehabilitation and to reduce regional disparities. Possible modifications make it optimal, and in the case of high-risk patients such as those

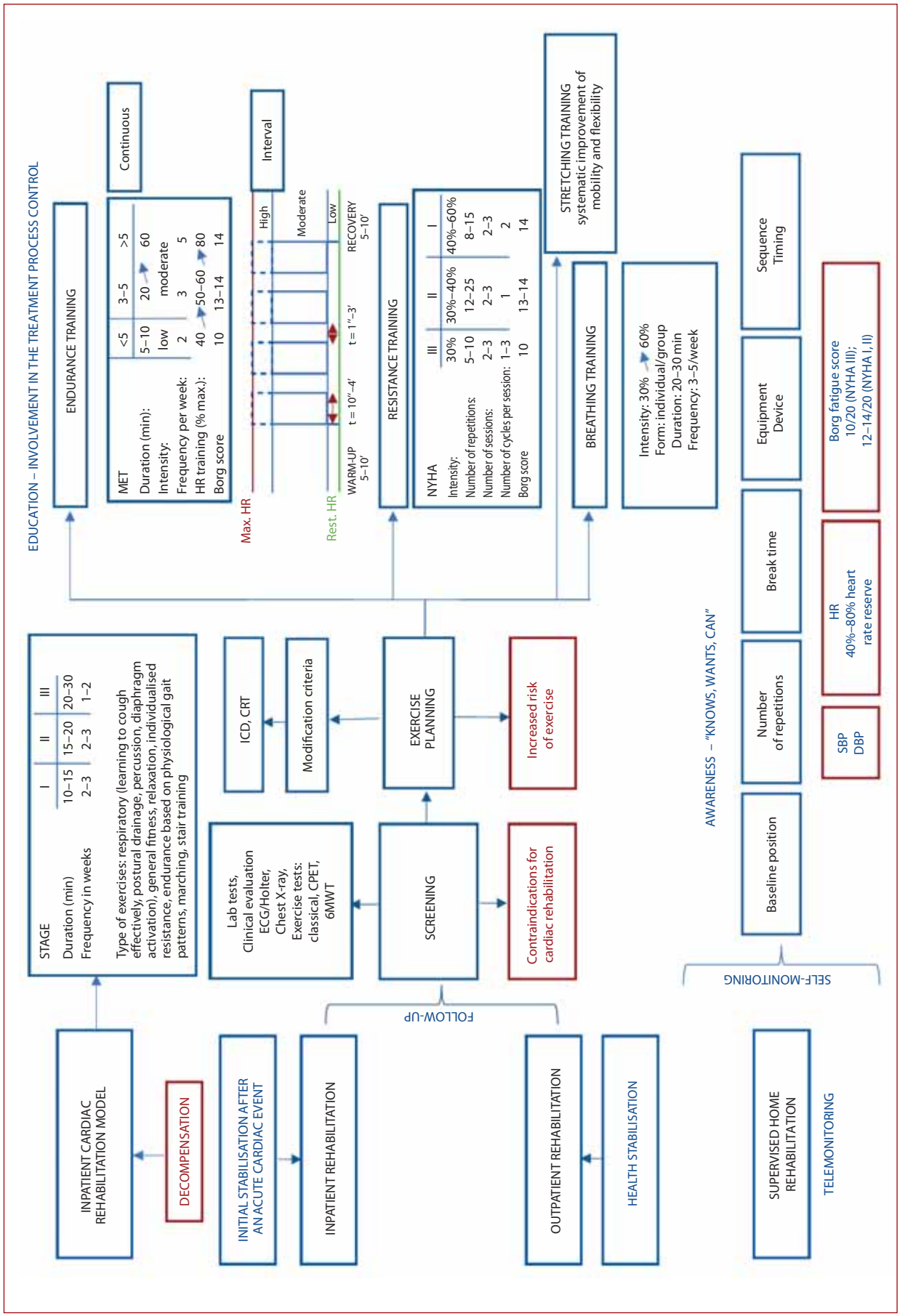

Figure 2. Cardiac rehabilitation scheme in patients with heart failure

Abbreviations: 6MWT, sixminute walk test; CPET, cardiopulmonary exercise test; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; HF, heart failure; HR, heart rate; ICD, implantable cardioverter defibrillator; MET, metabolic equivalent; SBP, systolic blood pressure

with HF, it sometimes becomes the only possible form of rehabilitation during infectious disease epidemics.

TASKS AND COMPETENCIES OF THE FAMILY PHYSICIAN IN THE TREATMENT OF PATIENTS WITH HEART FAILURE

A family physician provides medical care for a population of healthy and sick people of all ages who have chosen him or her as a primary care provider. Each family physician cares for an average of 12 to 24 HF patients [100, 101].

The tasks of the family physician in the care of HF patients have been described in detail in numerous international and national management recommendations [101–104]. They emphasize teamwork, including collaboration with an environmental/family nurse and a cardiology specialist. Intersectoral cooperation, especially with social welfare institutions, is also important with regard to the care of a portion of the HF patient population. In the period immediately following the discharge of a patient hospitalized for HF, the most important tasks of the family physician include [102]:

- Optimizing pharmacotherapy implemented in the hospital setting.
- Monitoring relevant clinical parameters and laboratory and imaging results.
- Identifying and treating comorbidities [105].
- Educational activities conducted jointly with the environmental/family nurse for both the patient and his/her caregivers and immediate family members.
- Implementing significant preventive measures and, if necessary, referring the patient for hospital treatment.
- Assistance in solving social problems [101].
- Implementing the immunization program, especially against influenza and *Pneumococcus*. Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is also of particular importance owing to the recent pandemic. As already emphasized, the first medical consultation should take place within 1–2 weeks (optimally 7 days) after the patient's discharge from the hospital [101]. An indication for readmission of an HF patient in the peri-discharge period is a significant exacerbation of the disease course.

In terms of pharmacotherapy, it is particularly important to increase the dosage of HF course-modifying drugs (beta-blockers, ACEI/ARB/ARNI, MRAs) to the target or maximum dose tolerated by the patient, and to include new drugs recommended in the guidelines if the patient has not received them before (e.g., SGLT2 inhibitors). Depending on the patient's profile and baseline cardiovascular risk, it is possible to apply different types of interventions to an individual patient with class II drugs (ivabradine, digoxin, ferric carboxymaltose, vericiguat). Family doctors should [104]:

- adjust the selection and dosage of diuretics according to the patient's current clinical condition (assessment of fluid overload, BP);
- periodically monitor renal function (creatinine/eGFR, urea) and electrolyte levels (sodium, potassium) in the HF patient, especially during the period of drug therapy modification;
- decide whether to include other drugs, such as ivabradine and digoxin, in the treatment;
- make decisions about discontinuing/replacing medications that can worsen HF (e.g., glitazones, NSAIDs, calcium antagonists, tricyclic antidepressants) [13].

The decision to reimburse (30% payment) SGLT2 inhibitors (dapagliflozin and empagliflozin) for HF patients as of 1 May 2022 in Poland will certainly increase the availability of this effective treatment. The reimbursement indications include patients with HFrEF (LVEF <40%), regardless of comorbid diabetes, who have persistent symptoms, in NYHA class II–IV despite therapy based on beta-blockers, ACEI/ARB/ARNI and, if such treatment is indicated, MRA [106]. Patients with diabetes and CKD will additionally benefit from the inclusion of SGLT2 inhibitors. Reimbursed treatment with SGLT2 inhibitors can be introduced by any physician in the system caring for an HF patient, not just a cardiologist.

One of the most important considerations for making therapeutic decisions for patients after HF hospitalization is to monitor their body weight, hydration status, and signs of circulatory congestion (including increased sensation of fatigue/dyspnea, lower extremity edema ascites, and auscultatory features of pulmonary congestion), BP, HR, and respiratory rate. These parameters allow not only for the optimization of pharmacotherapy but also deciding on the timing of possible readmission of the patient [13, 103]. Laboratory parameters that may need to be monitored include peripheral blood count, iron deficiency markers, thyrotropic hormone, liver aminotransferases, glucose levels (or glycated hemoglobin), and lipid profile. A laboratory test of great utility is the determination of natriuretic peptide (BNP, NT-proBNP) levels. The listed goals of treatment and tasks related to the care of HF patients in primary healthcare will certainly improve coordinated care introduced to practices of family doctors in Poland. Within the entrusted budget, it is possible to perform an extended panel of diagnostic tests and carry out specialist consultations with the patient, without the need to refer the patient to outpatient specialist care. An HF patient within the framework of coordinated care in primary healthcare should be provided with:

- a comprehensive visit with the development of an individual medical care plan (once a year),
- individual follow-up visits (depending on the clinical condition),
- the possibility of consulting a cardiologist — directly (if the patient's condition requires it) or in the form of a medical consultation using telemedicine techniques (a primary care physician — cardiologist),
- educational advice (nursing and dietary),
- selected additional tests.

These tests include primarily: NT-proBNP, electrocardiographic stress test, transthoracic echocardiography, continuous Holter ECG monitoring, and continuous ambulatory blood pressure monitoring. These tests should be used in HF patient care, depending on indications, clinical assessment made by the family physician, and, in selected cases, also after consultation with a cardiologist. If it is necessary to extend the diagnosis or conduct specialist treatment, the patient, as indicated earlier, should be referred for outpatient specialist care [107].

THE ROLE OF THE NURSE IN CARING FOR HEART FAILURE PATIENTS

The current ESC guidelines invariably point to adherence to self-management as an important element in improving outcomes for HF patients, reducing mortality, and improving quality of life [13]. Therefore, most recommendations for HF management place a strong emphasis on promoting self-management behavior, such as lifestyle modifications and restrictions in fluid intake [108].

Nursing care is considered a very important part of the healthcare system for CHF patients [109, 110]. Nurses should conduct educational activities by identifying access to professional information, promoting patients' health awareness, and thereby empowering them [111, 112].

Many countries have programs in which HF nurses provide continuity of care, working closely with the family physician, cardiologist, patient, and his/her family/caregivers [113, 114]. The role of the nurse focuses on:

- educating the patient about his/her disease (definition, etiology, and risk factors of HF), symptoms that require a medical appointment, and factors that contribute to HF exacerbation;
- taking part in monitoring patient adherence to therapeutic recommendations (drug dosage, options for flexible supply of diuretics);
- providing advice and recommendations on diet, physical activity, fluid intake, recommended vaccinations, and more;
- education on techniques for measuring heart rate, BP, saturation, respiratory rate, and body weight, assessing peripheral edema and feeling of dyspnea, as well as monitoring for any adverse effects of the treatment, pointing out the possibility of modifying doses of certain drugs (primarily diuretics and BP-lowering drugs).

These activities aim to prepare the patient for self-management and self-care. Self-care can be assessed using standardized questionnaires [115–121]. This is of particular importance because, as already mentioned, the reasons for the high mortality rate of cardiac patients after hospital discharge are mainly: inappropriate lifestyle, irregular use of medications or interruption of prescribed pharmacotherapy, lack of control of risk factors, insufficient access to specialized cardiac care after hospitalization, and complications and comorbidities [119].

During the COVID-19 pandemic, the emphasis on social distancing and self-care for HF patients was greater than ever. Hospital stays were associated with higher risk of SARS-CoV-2 infection, and hospitalization for HF carries a poorer long-term prognosis. Medication adherence may be a differentiating factor in this regard. Careful attention to symptoms, as well as daily body weight, can alert patients, their families, and healthcare professionals about the onset of a CHF exacerbation. Introducing appropriate treatment modifications at this early stage of HF deterioration may save some of these patients from subsequent hospitalization. Nurses can play a key role in this process, for example, by maintaining telephone contact with patients, and thus promoting self-care [120].

HEART FAILURE DURING THE COVID-19 PANDEMIC

Due to the COVID-19 pandemic, HF patients faced difficulties in receiving scheduled services for primary and secondary care, in both inpatient and outpatient settings [122, 123]. This affected their safety and made it difficult to exercise proper monitoring. In the vast majority of patients (>80%), SARS-CoV-2 infection is asymptomatic or paucisymptomatic [124–128]. Severe disease develops in about 18% of confirmed cases of SARS-CoV-2 infection [129]. The so-called cytokine storm (3%–4% of patients with viral sepsis) leading to multi-organ failure can be one of the causes of the patient's death [126, 130, 131].

SARS-CoV-2 has high potential to cause multi-organ damage, including cardiac damage, both *de novo* (without prior heart disease), and as increased damage of the already diseased myocardium. Whether it occurs as a CHF exacerbation or develops in patients without prior heart disease, AHF is associated with a very high mortality rate of nearly 50% [132, 133].

Both the burden of cardiovascular disease and cardiovascular involvement in COVID-19 are associated with a worse prognosis, especially in patients over >65 years of age [134–136]. The most common burdens include AH (more than half of patients), obesity, and T2DM [137–140]. Some of the cardiovascular complications are due to inflammation and/or acute myocardial damage due to SARS-CoV-2 infection [122, 141–146], and they include

- thromboembolism;
- AHF *de novo* or as CHF exacerbation;
- Takotsubo syndrome;
- abnormal heart rhythm;
- ACS.

Confirmation of acute myocarditis is often possible with cardiac magnetic resonance imaging [146, 147]. It is noteworthy that in patients with confirmed COVID-19, cases of Takotsubo syndrome have also been reported, mainly affecting women [148, 149]. Cardiac arrhythmias (AF, ventricular tachycardia, and ventricular fibrillation) during hospitalization for COVID-19 have been reported

Table 4. Selected clinical data to help differentiate SARS-CoV-2 infection and HF exacerbation

	COVID-19	HF exacerbation
History of cardiovascular disease	+/–	+
Fever	+	–
Cough	+	+/–
Myalgia	+	–
Leg oedema	–	+
Leukocyte and CRP levels	Lymphocytopenia and increase in CRP, leukocytosis with secondary bacterial infection	Usually unchanged (unless the cause of the exacerbation is an infection)
Elevated NT-proBNP, BNP	In patients with a severe course of COVID-19	+
Troponin concentration	Elevated only in patients with severe COVID-19 and myocardial damage	Usually stably elevated
ECG	Sinus tachycardia (arrhythmia in severe infection)	Tachyarrhythmias (including AF), non-specific ST-segment changes
Echocardiography	Usually normal	Depending on the HF phenotype (reduced global left ventricular contractility, enlarged cardiac cavities, dilated inferior vena cava)
Lung imaging (X-ray, CT)	Subpleural consolidations, "ground glass" opacities, radiographic features of ARDS and diffuse consolidations ("white lung") in stage 4. COVID-19	Congestive changes, pleural fluid, pulmonary oedema in advanced exacerbation of left ventricular failure

Abbreviations: AF, atrial fibrillation; ARDS, acute respiratory distress syndrome; BNP, B type natriuretic peptide; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography; ECG, electrocardiogram; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

in a varying percentage of patients, from 7% of those who did not require intensive care unit care to as many as 44% of patients treated in these units [150–152].

Differentiating symptoms of SARS-CoV-2 infection alone from those of HF exacerbation can be problematic, especially since these conditions can co-occur (145). All available clinical data should be considered (Table 4) [132, 146]. Testing for SARS-CoV-2 should be considered in all HF patients suspected of having COVID-19, even if they have already undergone the infection or have been vaccinated, and those qualified for urgent hospitalization.

SUMMARY — A DECALOGUE OF PRE- AND POST-DISCHARGE RECOMMENDATIONS

The pre- and peri-discharge management of patients with HF and disease exacerbations is a great challenge not only for modern cardiology but also for the many specialists who provide care for these patients. The following are basic recommendations that, if followed, should help manage patients in the peri-discharge period:

1. Consideration of the inpatient course of AHF or exacerbated CHF in pre-discharge management. Determining the etiology, phenotype of HF, and clinical profile of the patient, enables implementation of personalized treatment.
2. Introducing drugs from the four fundamental groups that improve prognosis in HFrEF (beta-blockers, ACEI/ARB/ARNI, MRAs, and SGLT2 inhibitors) if possible before hospital discharge.
3. Careful evaluation of the patient's clinical condition in terms of the level of residual cardiovascular risk and fluid retention (including a decision on the intensity of diuretic treatment) and introduction of drugs from class II recommendations.
4. Recognizing and properly treating comorbidities (including ID).
5. Including, in the discharge letter, a treatment plan with follow-up appointments for a PCP, cardiologist, and other specialists as needed.
6. Continued therapy escalation in outpatient setting according to guidelines after hospital discharge (primarily increasing doses of the primary medications to the maximum tolerated dose in HFrEF treatment: beta-blockers, ACEI/ARB/ARNI, MRAs, inclusion of SGLT2 inhibitors if the patient had not previously received them).
7. Considering the role of cardiac rehabilitation in CHF treatment, both inpatient, outpatient, and hybrid telerehabilitation.
8. Incorporating new effective monitoring methods based on telemedical systems into HF patient care.
9. Continuous education of patients and their families about HF, especially symptoms, treatment, and self-care.
10. Cooperation and proper division of responsibilities during HF patient care among cardiologists, family physicians, nurses, and other specialists.

Modern medicine offers a range of treatment options for HF patients. Their use in this growing group of patients should translate into reduced hospital admissions and mortality as well as improved quality of life.

Article information

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XV Konferencja

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