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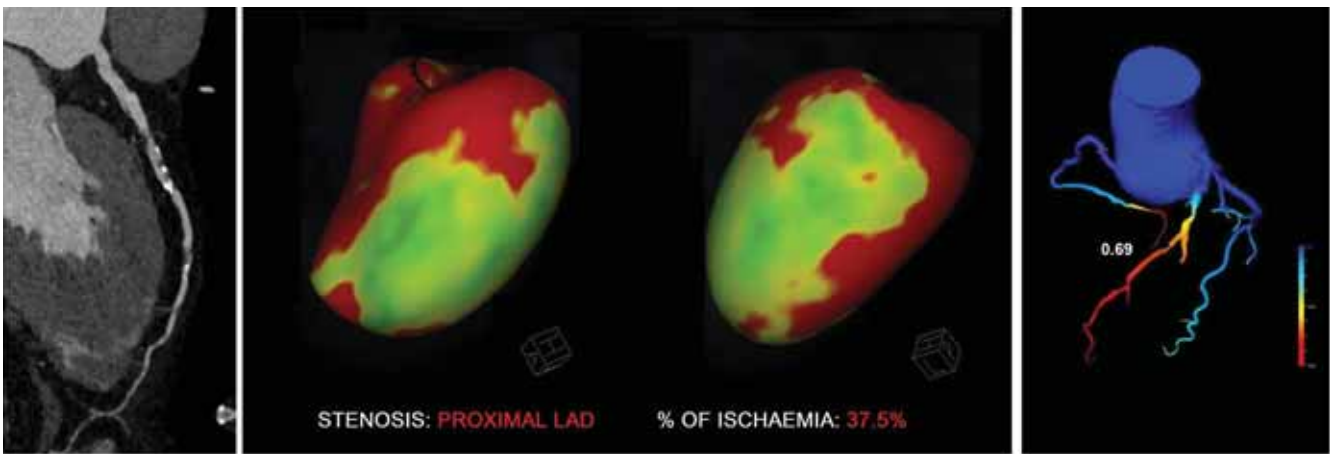

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Adult congenital heart disease and the coronavirus disease 2019: How to deal with uncertainty

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Related article
by Lipczyńska et al.

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In the early stages of the COVID-19 pandemic, pre-existing cardiovascular diseases were identified as important predictors for a dismal disease course in case of infection with the novel SARS-CoV-2 [1, 2]. Initially, it was unclear whether mostly young and otherwise healthy adults with congenital heart disease (ACHD) were at similar risk from severe COVID-19 as patients with acquired cardiovascular disease.

To err on the safe side, first experts' opinion-based recommendations on risk stratification for ACHD patients considered an important proportion of patients to be at moderate or high risk. Attention was mainly paid to the anatomical complexity of the congenital heart lesion [3, 4].

In October 2020, Lewis et al. [5] were the first to report outcomes among a single-center cohort of 53 children and adults with congenital heart disease (CHD) suffering from COVID-19. They were also the first to propose that physiological stage rather than cardiac anatomy was predictive of outcomes among ACHD patients in the case of COVID-19. Soon thereafter, this single-center experience was followed by a European multicenter registry addressing risk stratification of ACHD patients in the current pandemic [6]. In this registry, general risk factors (such as age, obesity, and multiple co-morbidities) were associated with an increased risk of complicated COVID-19 course, and patients with cyanotic heart disease, independent of the underlying anatomy, were deemed to be at the highest risk. The importance of the patients' physiological state in predicting COVID-19 risks in ACHD patients was again confirmed by Broberg et al. [7] in the largest so-far worldwide multicenter study. Again, general risk factors such as diabetes, male sex, increasing body mass index (BMI), and age were found to independently predict poor outcomes among ACHD patients with COVID-19. As reported before, cyanosis, but not cardiac anatomy *per se*, was an independent predictor of death.

In this issue of the *Kardiologia Polska* (*Kardiol Pol*, *Polish Heart Journal*), Lipczynska et al. [8] report COVID-19 cases among 1197 ACHD patients followed at a tertiary care center in Poland. A severe COVID-19 course was defined as either hospitalization requiring oxygen supply, non-invasive or invasive ventilation or circulatory support, or death. This retrospective analysis of patients attending the ACHD outpatient clinic in Warszawa between September 1, 2020 and March 31, 2021 identified 104 patients with COVID-19 confirmed with a positive test (n = 89) or a suspected SARS-CoV-2 infection (n = 15). Overall, five patients had a severe COVID-19 course, two of whom died. Decreased ventricular systolic function and significant valvular stenosis were frequently encountered in ACHD patients with a severe course, but the low number of outcome events preclude a meaningful statistical analysis. None of the general risk factors previously associated with dismal outcomes in the case of COVID-19 in both the general population and ACHD patients (such as older age, male sex, BMI, or comorbidities) predicted the outcome of interest. This result

Table 1. Predictors for poor COVID-19-related outcome outcome [5–8]

Risk factor	Lewis et al. COVID-19 cases: n = 53 [a]Outcome events: n = 9	Schwerzmann et al. COVID-19 cases: n = 105 [a]Outcome events: n = 13	Broberg et al. COVID-19 cases: n = 1044 [a]Outcome events: n = 24	Lipczyńska et al. COVID-19 cases: n = 104 [a]Outcome events: n = 5
General				
Age	Univariable OR: 0.98; *P* = 0.39	Per 5 years Univariable OR: 1.3; *P* = 0.02	Per year Univariable OR: 1.03; *P* = 0.03	Univariable OR: 1.00; *P* = 0.98
Male sex	Univariable OR: 1.51; *P* = 0.87	Univariable OR: 2.5; *P* = 0.13	Univariable OR: 5.4; *P* = 0.002	Univariable OR: 0.26; *P* = 0.26
Comorbidities	—	≥2 co-morbidities Univariable OR: 7.1; *P* = 0.002 Multivariable OR: 6.7; *P* = 0.03	Diabetes Univariable OR: 6.8; *P* <0.001 eGFR <60 ml/min/1.73 m^2 Univariable OR: 5.1; *P* = 0.004	Univariable OR: 2.63; *P* = 0.30
BMI	Obesity Univariable OR: 7.34; *P* = 0.046	>25 kg/m^2 Univariable OR: 7.2; *P* = 0.004 Multivariable OR: 16.4; *P* = 0.001	Univariable OR: 1.08; *P* = 0.001	Univariable OR 0.93; *P* = 0.52
ACHD-specific				
CHD-PAH	Univariable OR: 15.25; *P* = 0.01		Univariable OR: 5.9; *P* <0.001	OR: 4.44; *P* = 0.11
Cyanotic CHD	—	Univariable OR: 13.2; *P* = 0.002 Multivariable OR 60.0; *P* <0.001	Univariable OR: 8.9; *P* <0.001	—
Physiological stage	Physiologic Stage C Univariable OR: 19.38; *P* = 0.002	—	Physiological stage C or D Univariable OR: 6.4; *P* = 0.001 Previous heart failure admission Univariable OR: 7.4; *P* <0.001	Decreased systemic EF OR: 20.75; *P* = 0.02 Significant valvar stenosis OR: 20.75; *P* = 0.02

Abbreviations: ACHD, adult congenital heart disease; BMI, body mass index; CHD, congenital heart defect; EF, ejection fraction; eGFR, estimated glomerular filtration rate; OR, odds ratio

[a]A poor COVID-19-related outcome was defined as follows:
– Lewis et al: death or need for hospitalization, or new or increased respiratory support;
– Schwerzmann et al: hospitalization for COVID-19 requiring non-invasive or invasive ventilation and/or inotropic support, or death;
– Broberg et al: death;
– Lipczyńska et al: either hospitalization requiring oxygen supply, non-invasive or invasive ventilation or circulatory support, or death

was, most likely, another consequence of the small number of outcome events reported in this population.

Remarkably, of 1197 ACHD patients followed during the defined period, 28% had a telemedicine consultation only. In the current pandemic times, this is an important technical help to minimize the number of patients lost to follow-up, and the ACHD healthcare providers of the participating center must be congratulated for this innovative effort.

A comparative overview of previously defined predictors for poor COVID-19-related outcomes including the work by Lipczynska et al. [8] and other studies is depicted in Table 1. There are important discrepancies between the results. This might be partially attributable to different pandemic waves and virus strains but certainly also to the challenges of collecting a sufficient number of events. When looking closely at the reported severe cases in the present study [8], the two deceased patients had either general risk factors (systemic hypertension and being overweight in the 51 years-old female with repaired tetralogy of Fallot) or both general and ACHD-specific risk factors (cyanotic heart disease and obesity in the 36-year-old female with the unrepaired common arterial trunk). All one can say at this time is that in ACHD patients COVID-19 risks are related to the general health and the physiological state and not the complexity of the defect. The physiological state can be expressed by functional class or, as in the present study, by quoting ventricular ejection fraction or quantifying valvular disease. Both approaches seem to predict COVID-19 outcomes.

The COVID-19 pandemic has taught the ACHD community two important lessons: single-center efforts, like the present study, are the first and most important step for guiding ACHD patient management. Due to the variety of congenital cardiac defects and repair strategies, ACHD patients are a very heterogeneous population, and in the end, only collaboration among different centers from different countries will facilitate the collection of a sufficiently large number of ACHD cases to make meaningful conclusions. Collaboration is, therefore, the key to success. Secondly, ACHD patients' management that is mainly based on theoretical reasoning might be tempting but is not necessarily the right way to go. In the case of COVID-19 patients, we have realized that the young age of many of our patients is a very protective factor, independent of the underlying defect complexity. Declaring all ACHD patients with complex lesions to be at high risk for COVID-19 complications creates an unnecessary psychological burden to younger patients, some of whom are already struggling with the challenges of living with a congenital cardiac defect. As for other disciplines in cardiology, also ACHD management should be built on evidence whenever possible.

Article information

Conflict of interest: None declared.

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The right ventricle after cardiac surgery: Hypotheses, evidence, and the role of advanced echocardiography modalities

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Related article
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For decades, the right ventricle (RV) was considered not essential for cardiac function and therefore it was virtually ignored [1]. The RV, contrarily to the left ventricle, works under low-pressure high-volume physiology, with a wide degree of adaptation to altered preload. The RV comprises three compartments, the inlet, the trabeculated apex, and the outlet allowing contraction to occur with a peristaltic-like motion from the inflow to the outflow chamber [2].

The relation of the RV function to symptom occurrence and prognosis in a wide variety of cardiac conditions emphasizes the usefulness of comprehensive RV assessment. Notably, isolated RV dysfunction is associated with a significantly poorer prognosis as compared to left ventricular dysfunction [3, 4]. The evaluation of the RV is largely carried out by conventional 2D echocardiography in daily clinical practice; however, RV assessment might be difficult owing to its complex morphology, structure, and function. Recent modalities in echocardiography such as myocardial deformation, three-dimensional imaging, or exercise echocardiography are needed to overcome the potential limitations inherent in two-dimensional imaging [5]. In addition, cardiac magnetic resonance imaging provides a valuable opportunity to image the RV without the limitation of echogenicity.

In the present issue of the *Kardiologia Polska* (*Kardiol Pol*, *Polish Heart Journal*), Paulina Wejner-Mik et al. [6] describe interesting echocardiographic observations regarding alterations of RV morphology and function after cardiac surgery, with emphasis on speckle tracking and 3D echocardiography benefit in this context. The authors observed reversible changes in the geometry of the RV, reduced longitudinal right ventricular function after uncomplicated cardiac surgery, and a simultaneous compensatory increase in other components of RV function, namely the RV shortening fraction.

When RV dysfunction occurs during the postoperative phase of cardiac surgery, it represents a significant clinical challenge because of the high prevalence of morbidity and mortality [7]. Cardiac imaging by echocardiography during the postoperative phase is often restricted owing to mediastinal air, drains, dressings, patient noncompliance with supine position along with possible artificial ventilation. In addition, echocardiography examinations in the postoperative period are sometimes performed as point-of-care ultrasound (POCUS), sometimes via a portable or handheld ultrasound machine. Accordingly, RV dysfunction in the postoperative phase after cardiac surgery might well be underdiagnosed [7].

Shortening fraction is an echo parameter classically applicable for assessment of left ventricular function. It was used by Paulina Wejner-Mik et al. [6] to document a compensatory increase in the non-longitudinal component of the RV function. RV shortening fraction in the paper was calculated as the percentage shortening of the mid-cavity linear dimension of the RV in the 4-chamber apical view. Reduction in RV longitudinal function post-cardiac surgery was already reported, and a compensatory increase in transverse

strain also was documented in this context [8, 9]. The authors showed that global RV function was not affected, using 3D RV ejection fraction, RV indexed stroke volume, and fractional area change.

The micro-anatomy of the RV shows that myocytes are predominantly oriented in the longitudinal direction in the subendocardial layer, whereas circumferentially oriented myocytes are found in the thinner subepicardium; accordingly, the RV contraction pattern is predominantly longitudinal [10]. As a consequence, the RV output is mostly engendered by longitudinal contraction in physiological conditions.

Wejner-Mik et al. [6] used the RV shortening fraction as a simple surrogate of transverse strain to assess the non-longitudinal component of RV function, and this is a noteworthy approach when transverse and radial strain imaging is not pertinent (the authors mentioned in the Limitation section that transverse strain was not performed).

Mechanisms of RV dysfunction after cardiac surgery are multifactorial, ranging from per-operative myocardial depression to factors affecting afterload or preload, along with potential effects of inflammatory cytokines on endothelial function, etc. [10]. Nevertheless, in uncomplicated cardiac surgery, like in the studied population presented by Wejner-Mik et al. [6], we estimate that the impact of these factors is absent or minimal. Possible hypotheses that explain the reduction in RV longitudinal performance include the postoperative geometrical changes of the RV chamber related to the interventricular septal paradoxical motion and the drop in ventricular interdependence [11].

The so-called ventricular interdependence is explained by the basic concept that the size, morphology, and function of one ventricle affect the other and vice versa, both in systole and diastole. Notably, diastolic ventricular interdependence is mainly due to the pericardium, and systolic interdependence is mainly mediated by the interventricular septum [12]. For example, left ventricular stroke volume ultimately matches with RV preload; in this regard, it is estimated that 20%–40% of RV stroke volume is dependent on left ventricular contraction [13]. This interdependence is related to the pericardium that embraces both ventricles, the continuity between RV and LV myocardial fibers and muscular layers, the pulmonary and systemic circulation, the shared blood supply, and the interventricular septum [12].

In the article authored by Paulina Wejner-Mik et al. [6], the causes of change in the RV architecture and morphology were not quite elucidated. The 3D echocardiography did not show any change in RV volume in the postoperative phase, therefore, the change in RV geometry was not related to any change in preload a priori. Because of that, we hypothesize that changes in RV geometry are correlated with the drop in ventricular interdependence, namely the architectural changes consequent on the paradoxical septal motion and the reduced pericardial constraint after cardiac surgery [12].

The message reinforced by Paulina Wejner-Mik et al. [6] is that the assessment of RV function post-cardiac surgery should not rely only on parameters for longitudinal assessment (e.g., tricuspid annular longitudinal excursion, the systolic velocity of the tricuspid annulus, free wall longitudinal strain). Relying exclusively on longitudinal contraction after cardiac surgery might lead to overdiagnosis of global RV dysfunction. Moreover, after cardiac surgery, the RV should be regarded differently, consequent on the drop in ventricular interdependence, and therefore should be assessed differently.

Article information

Conflict of interest: None declared.

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REVIEW

Optimal anticoagulation in elderly patients with atrial fibrillation: Which drug at which dose?

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ABSTRACT

Aging is an important risk factor for adverse events in elderly patients with atrial fibrillation (AF) and complicates the management of anticoagulation. Underuse of oral anticoagulants (OACs) is common in elderly patients because of comorbidities, the altered physiological function of multiple organs, frailty, risk of falls, and the lack of randomized controlled trials (RCTs) specifically for elderly patients. Nevertheless, current data still support OACs use for reducing ischemic stroke with positive net clinical benefits. Sub-analyses of RCTs and real-world cohort studies showed that non-vitamin K antagonist OACs (NOACs) would be more favorable choices compared to warfarin for stroke prevention in the elderly. This review will discuss important data on stroke prevention and the use of NOACs in elderly AF patients.

Key words: anticoagulation, atrial fibrillation, elderly, NOAC, stroke

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia worldwide and the prevalence has been increasing with the aging of the population worldwide [1, 2]. AF increases the risks of ischemic stroke and systemic embolism (IS/SE), and the CHA_2DS_2-VASc score is recommended to guide the use of oral anticoagulant (OAC) for stroke prevention [3–6]. Age itself is one of the components of the CHA_2DS_2-VASc score, with 1 score assigned for age 65–74 years and 2 scores for age ≥75 years. The analysis of the Atrial Fibrillation Investigators database observed a 45% increase of risk of ischemic stroke per decade in age (hazard ratio [HR], 1.45; 95% confidence interval [CI], 1.26–1.66) [7]. Even in patients aged ≥65 years, a gradual increase of ischemic stroke with an increase of aging is still evident (Figure 1) [10–13]. Aging also increases the risk of intracranial hemorrhage (ICH) and major bleeding and contributes to the HAS-BLED score [8, 9] together with other risk factors (Figure 1) [10–13]. Besides, aging alters the physiological functions of multiple organs and might affect medication concentrations and exposure [14]. Therefore, OAC use in elderly AF patients, especially those aged ≥75 years, is a complex issue involving the balance between efficacy and safety.

"Old age" should not be the only reason to withhold oral anticoagulants for AF patients

In real-world practice, underuse of OAC is common in elderly AF patients because of the fear of bleeding and the lack of specific guidelines. However, a nationwide cohort study by Chao et al. demonstrated a decreased risk of stroke (HR, 0.69; 95% CI, 0.49–0.96) and a similar risk of ICH with warfarin compared to no antithrombotic treatment in AF patients aged ≥90 years. Warfarin was still associated with a positive net clinical benefit compared

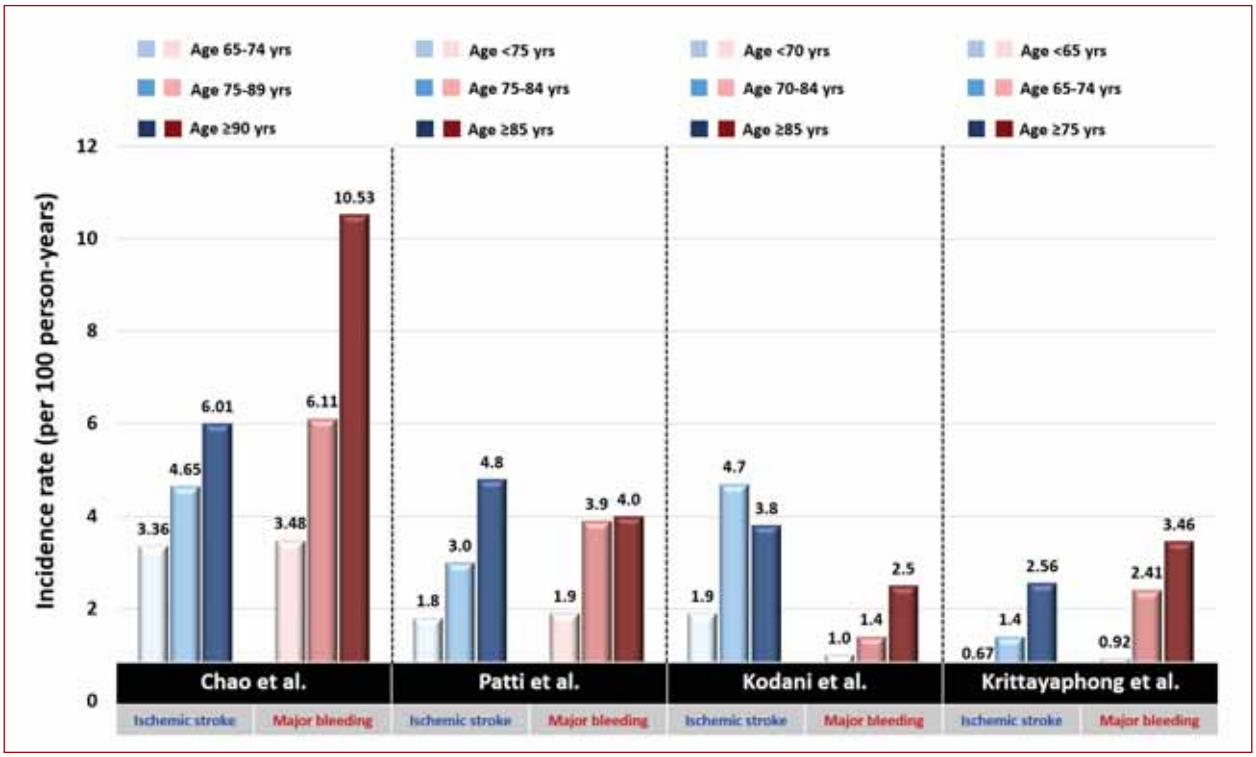

Figure 1. Risks of ischemic stroke and major bleeding in elderly patients with AF. Elderly patients are at increased risks of ischemic stroke and major bleeding, and the risks continues to rise at even advanced age. Data used in the figure were adapted from the papers by Chao et al., Patti et al., Kodani et al., and Krittayaphong et al. [10–13]

Abbreviations: AF, atrial fibrillation

to antiplatelet treatment [15]. The sub-analysis from the prospective PREFER in AF study (PREvention oF Thromboembolic Events-European Registry in Atrial Fibrillation) reported the presence of a significant gradient of net clinical benefit according to age strata with warfarin use, with the oldest patients deriving the greatest advantage [11]. Even among the very elderly (>90 years) AF patients perceived to be at high risk for bleeding, for example, those with a history of ICH, gastrointestinal (GI) bleeding, or chronic kidney disease, non-vitamin K antagonist OACs (NOACs) were associated with a lower composite risk of ischemic stroke, ICH, major bleeding, or mortality (HR, 0.763; 95% CI, 0.702–0.830) compared to non-OACs [16]. Therefore, old age should not be the only reason not to prescribe OAC in patients with AF.

NOACs would be more favorable choices over warfarin in elderly AF patients

Although NOACs are recommended over warfarin as the preferred choice for stroke prevention in AF in current guidelines [3–6], randomized controlled trials (RCTs) specifically comparing NOACs to warfarin in elderly AF patients are lacking. In landmark trials of NOACs, patients ≥75 years accounted for 30%–40% of all study population [17–20], and patients ≥85 years were even fewer. A meta-analysis including 5 phase-III RCTs reported higher risks of IS/SE and major bleeding in elderly (≥75 years) patients compared to non-elderly patients despite the treatment, but the beneficial effects of NOACs compared with warfarin in reducing IS/SE and major bleeding remained in the elderly group [21]. Sub-analyses from other landmark trials demonstrated a lower (apixaban and edoxaban) or similar (dabigatran and rivaroxaban) risks of major bleeding with NOACs compared to warfarin for AF patients aged ≥75 years (Figure 2) [22––25]. However, it should be emphasized that the enrollment criteria differ in various NOAC trials, and, therefore, these observations should not be interpreted as an indication that one NOAC is better than others for stroke prevention in the elderly with AF.

Real-world cohort studies might partly make up for the paucity of RCTs regarding NOACs use in elderly AF patients (Table 1) [10, 15, 26–31]. A nationwide cohort study showed that NOACs were associated with a lower risk of ICH and a similar risk of ischemic stroke compared to warfarin in AF patients aged ≥90 years [15]. Subgroup analysis at different age strata (age 65–74, 75–89, ≥90 years) in elderly AF patients supported the overall beneficial roles of NOACs compared to warfarin, but there was heterogeneity in treatment effects in different age strata (Figure 3) [10]. Aging seems to be a more dominant factor for ischemic stroke than types of OACs (NOACs or warfarin), but NOACs remained associated with a lower risk of ischemic stroke in patients aged ≥90 years compared to warfarin. In terms of ICH, NOACs behaved better than warfarin irrespective of age strata. Even for patients aged ≥90 years treated with NOACs, their risk of ICH (0.86%/year) was lower than

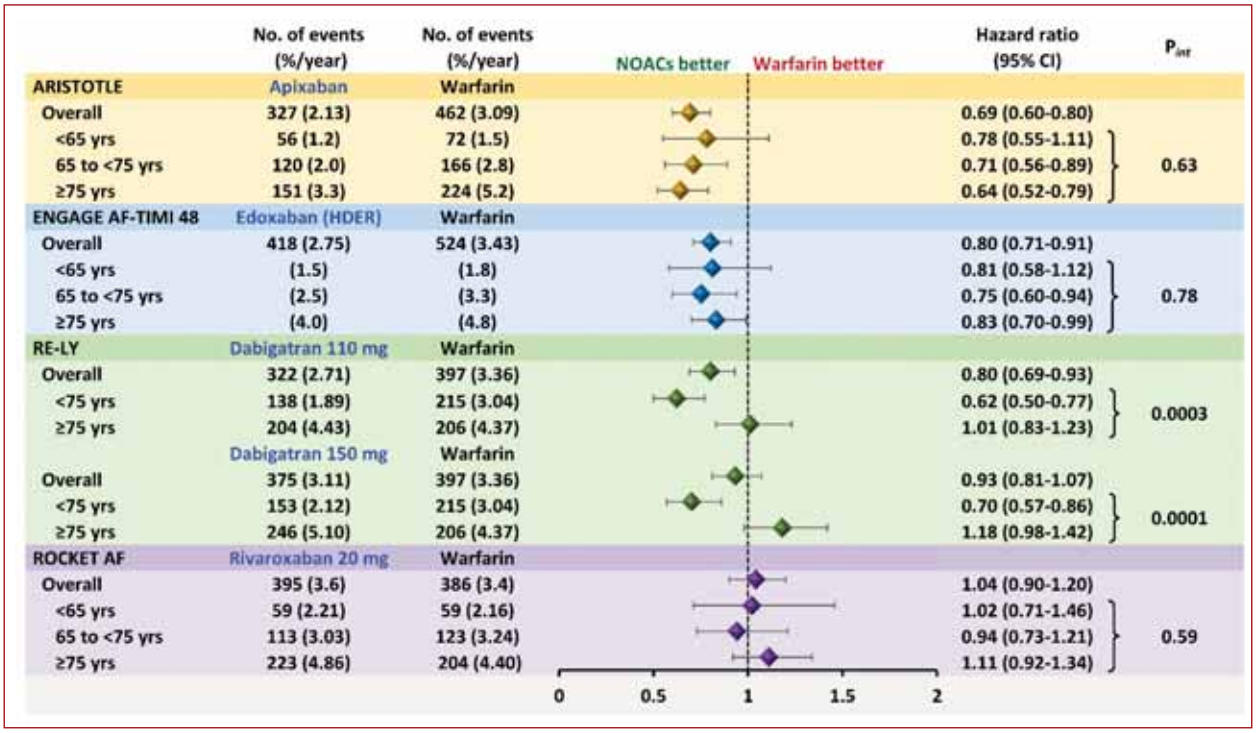

Figure 2. Risks of major bleeding of NOACs compared to warfarin across different age strata in landmark RCTs. Sub-analyses from landmark trials demonstrated a lower (apixaban and edoxaban) or similar (dabigatran and rivaroxaban) risks of major bleeding with NOACs compared to warfarin for AF patients aged ≥75 years. Data used in the figure were adapted from the papers by Kato et al., Eikelboom et al., Halvorsen et al., and Goodman et al. [22–25].

Abbreviations: CI, confidence interval; HDER, higher-dose edoxaban regimen; NOACs, non-vitamin K antagonist oral anticoagulants; P_{int}, P for interaction; RCTs, randomized controlled trials

Table 1. Real-world cohort studies in elderly patients with atrial fibrillation: NOACs compared to warfarin

Studies	Year	Country	Definition of elderly	NOACs	Warfarin	IS or IS/SE HR (95% CI)	Major bleeding HR (95% CI)	ICH HR (95% CI)
Lai et al. [26]	2018	Taiwan	≥85 years	Dabigatran (n = 1180)	n = 1180	1.25 (0.75–2.09)	(GI bleeding) 1.21 (0.76–1.91)	0.31 (0.10–0.97)
				Rivaroxaban (n = 1207)	n = 1207	1.02 (0.64–1.65)	(GI bleeding) 0.81 (0.47–1.38)	0.47 (0.17–1.26)
Tsai et al. [27]	2020	Taiwan	≥85 years	Dabigatran (n = 3893)	n = 3893	0.932 (0.811–1.114)	0.906 (0.769–1.031)	0.496 (0.357–0.688)
				Rivaroxaban (n = 3913)	n = 3913	0.781 (0.649–0.941)	0.868 (0.753–1.001)	0.453 (0.309–0.663)
				Apixaban (n = 574)	n = 574	0.540 (0.277–1.054)	0.874 (0.526–1.456)	0.182 (0.022–1.475)
Chao et al. [15]	2018	Taiwan	≥90 years	NOACs (37% Dabigatran; 57% Rivaroxaban; 6% Apixaban) (n = 978)	n = 768	1.16 (0.61–2.22)	0.95 (0.63–1.44)	0.32 (0.10–0.97)
Chao et al. [10]	2020	Taiwan	75–89 years	NOACs (50% Dabigatran; 5% Apixaban; 45% Rivaroxaban) (n = 28179)	n = 10609	0.825 (0.758–0.897)	0.857 (0.796–0.923)	0.564 (0.474–0.670)
Chan et al. [28]	2019	Taiwan	≥75 years	Edoxaban		0.65 (0.44–0.96)	0.47 (0.29–0.76)	0.40 (0.18–0.88)
				Apixaban		0.56 (0.39–0.79)	0.30 (0.19–0.49)	0.35 (0.17–0.69)
				Rivaroxaban		0.70 (0.51–0.97)	0.56 (0.39–0.82)	0.44 (0.24–0.81)
				Dabigatran		0.71 (0.51–0.98)	0.68 (0.47–0.97)	0.52 (0.29–0.94)
Hanon et al. [29]	2021	France	≥80 years	Rivaroxaban (n = 995)	n = 908	0.44 (0.15–1.30)	0.53 (0.33–0.85)	0.26 (0.09–0.80)
Deitelzweig et al. [30]	2019	US	≥80 years	Apixaban (n = 18897)	n = 18897	0.57 (0.47–0.70)	0.53 (0.48–0.58)	0.44 (0.34–0.57)
				Dabigatran (n = 6698)	n = 6698	0.87 (0.65–1.16)	0.90 (0.77–1.05)	0.50 (0.33–0.77)
				Rivaroxaban (n = 25917)	n = 25917	0.73 (0.63–0.85)	0.81 (0.67–0.99)	0.77 (0.63–0.94)
Russo et al. [31]	2020	Italy	≥80 years	NOACs (n = 252)	n = 504	1.00 (0.46–2.19)	0.82 (0.50–1.34)	0.29 (0.07–1.25)

Abbreviations: AF, atrial fibrillation; GI, gastrointestinal; ICH, intracranial hemorrhage; IS/SE, ischemic stroke/system embolism; NOACs, non-vitamin K antagonist oral anticoagulants

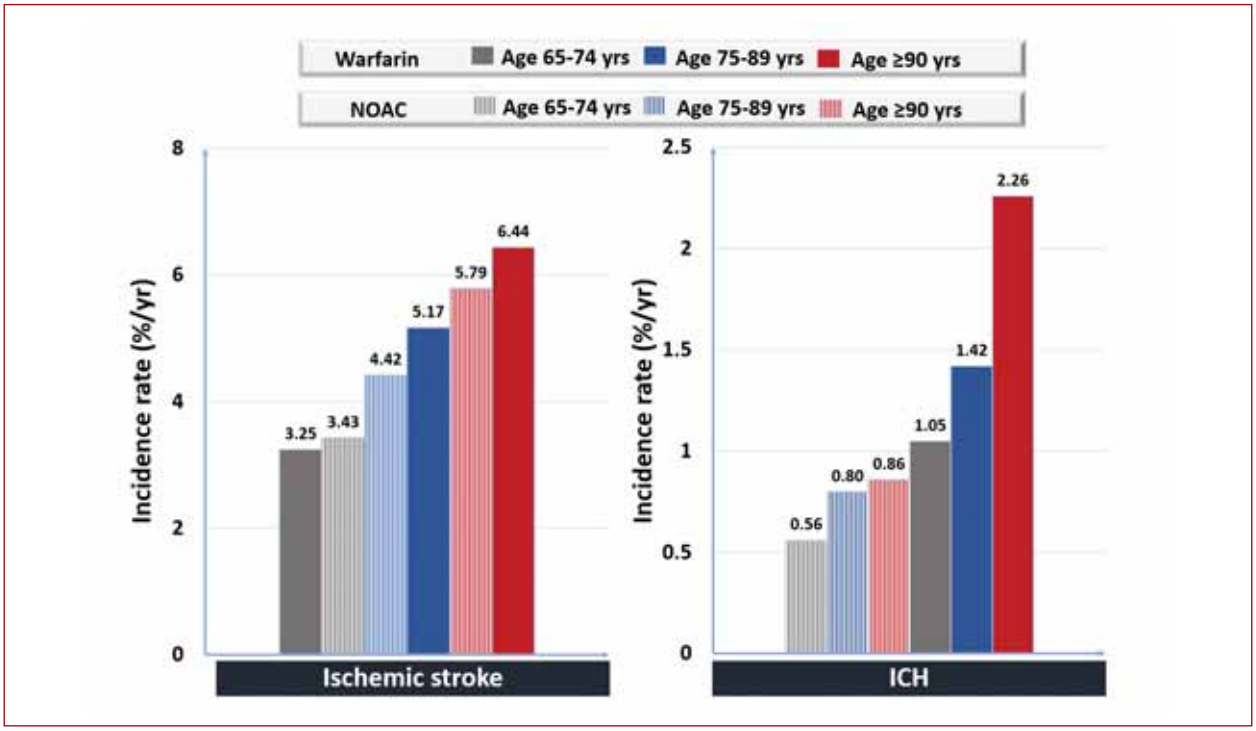

Figure 3. Annual risks of ischemic stroke and ICH in patients treated with NOACs or warfarin in different age strata. Aging seems to be a more dominant factor of ischemic stroke than types of OACs (NOACs or warfarin), but NOACs remained associated with a lower risk of ischemic stroke in patients aged ≥90 years compared to warfarin. In terms of ICH, NOACs behaved better than warfarin irrespective of age strata. Even for patients aged ≥90 years treated with NOACs, their risk of ICH (0.86%/year) was lower than in "younger" patients, aged 65–74 years, receiving warfarin (1.05%/year). Data used in the figure were adapted from the papers by Chao et al. [10]

Abbreviations: ICH, intracranial hemorrhage; OAC – oral anticoagulants; other — see Figure 2

"younger" patients aged 65–74 years receiving warfarin (1.05%/year) (Figure 3) [10]. The patterns of the associations between the risk of ICH and age seem to be different for warfarin and NOACs (Figure 4) [10]. For warfarin, the risk of ICH increased in parallel to the increase in age, while the curve of ICH risk seemed to be relatively flat with NOACs when age increased. Therefore, the absolute risk reduction in ICH with NOACs, compared with warfarin, would be more evident in the elderly AF population. Results from the meta-analysis of 11 RCTs and observational studies also favored NOAC use over VKAs in patients aged >75 years based on improved overall outcomes [32].

In daily practice, the introduction of NOACs did change the landscape of stroke prevention in the elderly AF population. In a recent nationwide report from Taiwan, the introduction of NOACs increased the initiation rates of OACs in elderly AF patients, which were related to the lower risk of ischemic stroke and mortality over time (Figure 5) [33].

DOSING OF NOACS IN THE ELDERLY

There are different dose reduction criteria for each NOAC. Although age had not been a dose reduction criterion in RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) [17], dabigatran 150 mg is not recommended for patients aged ≥80 years in Europe, and a lower dose (110 mg) should be considered for patients aged 75–79 years. In the ROCKET AF trial (Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) [18], dose reduction is mainly driven by renal function, and age had not been a dose-reduction criterion. Nevertheless, renal function is more often impaired in elderly patients in whom a reduced dose might be justified. Like in the ROCKET AF trial, old age was not a dosage-reduction criterion for edoxaban in the ENGAGE AF-TIMI 48 trial (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48) [20]. In the ARISTOTLE trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in AF) [19], age directly influenced apixaban dosing as age ≥80 years was one of the three dose-reduction criteria, and the dose of apixaban should be reduced once another dosage reduction criterion was present.

Since renal function is a crucial factor to determine NOAC dosing under most circumstances, accurate evaluation of renal function is important. The most commonly used formulas for estimating renal function include the Cockcroft-Gault (CG) formula, Modified Diet in Renal Disease (MDRD) formula, and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. The CG formula is adopted in most RCTs while the MDRD and CKD-EPI formulas are usually applied in real-world practice. Chao

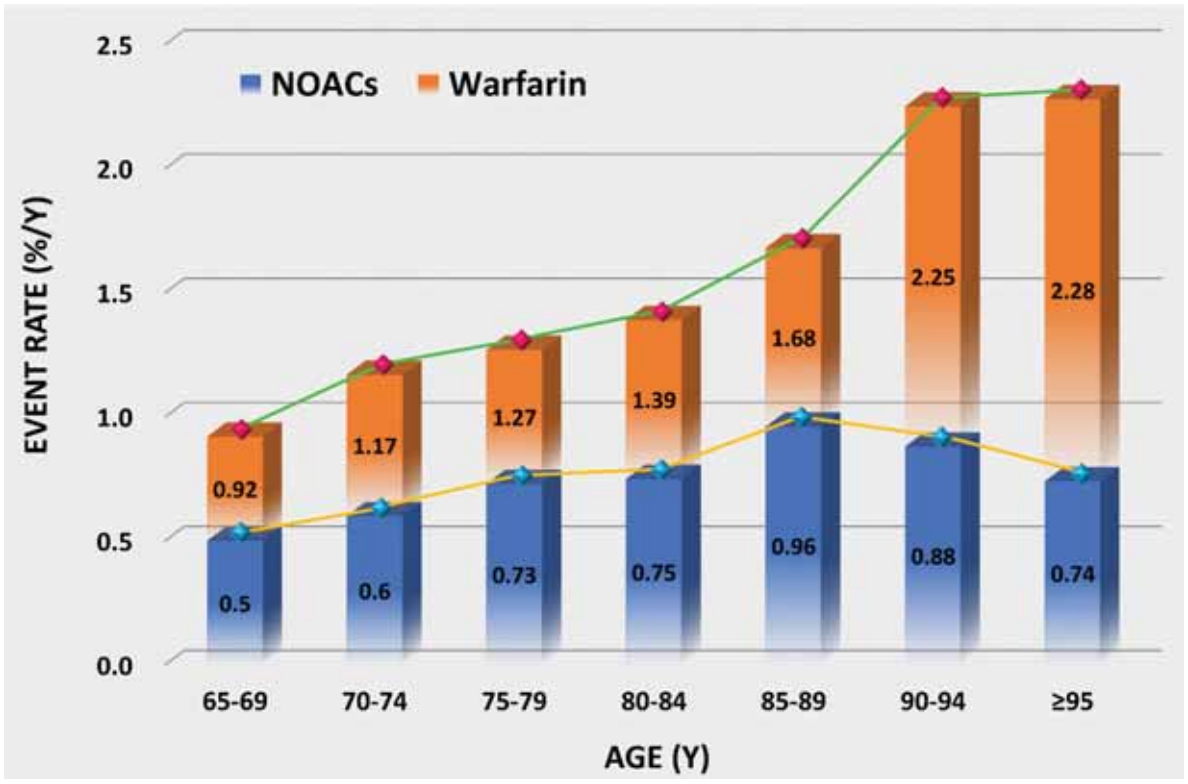

Figure 4. The differences of the risk of ICH between NOACs and warfarin in different age strata. The patterns of the associations between risk of ICH and age seem to be different for warfarin and NOACs. For warfarin, the risk of ICH increased in parallel to the increase in age, while the curve of ICH risk seemed to be relatively flat with NOACs when age increased. Therefore, the absolute risk reductions in ICH with NOACs, compared with warfarin, would be more evident in the elderly AF population. Data used in the figure were adapted from the papers by Chao et al. [10]

Abbreviations: see Figures 2 and 3

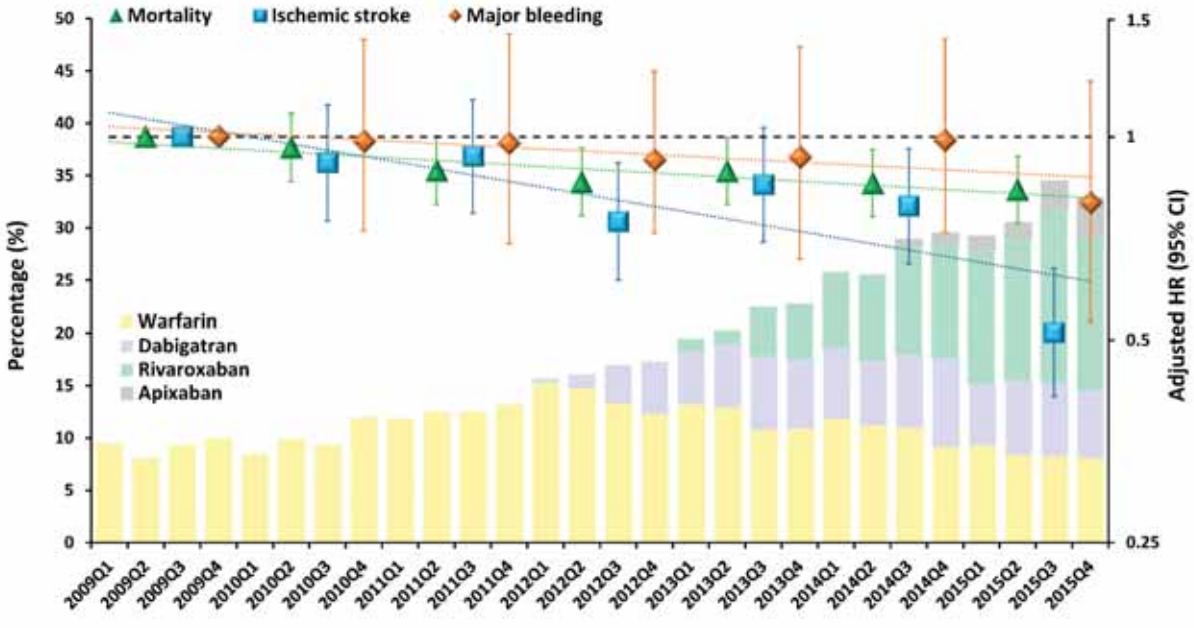

Figure 5. Temporal trends of OACs prescription in elderly AF patients in relation to risks of adverse events. The introduction of NOACs increased the initiation rates of OACs in elderly AF patients which were temporally related to the lower risk of ischemic stroke and mortality over time. The figure was redrawn, and data were adapted from the paper by Cheng et al. [33]

Abbreviations: see Figures 1–3

et al. [34] found the estimated glomerular filtration rate (eGFR) was overestimated in older patients (>75 years) and low body weights (<50 kg) using the MDRD and CKD--EPI compared to the CG equation, which might result in inappropriate dosing (mainly overdosing) of NOACs. Importantly, the overdosing may attenuate the benefits of NOACs regarding the risk of major bleeding compared to warfarin [35]. Therefore, the CG equation should be the preferred equation to calculate eGFR and determine the dosing of NOACs. This issue is particularly important for elderly AF patients.

WHAT IS THE OPTIMAL CHOICE AND DOSE OF NOACS IN ELDERLY AF PATIENTS?

Head-to-head comparisons among different NOACs in elderly patients with AF are still lacking, and only some indirect comparisons are available. A meta-analysis including 5 phase-III RCTs (ARISTOTLE, ENGAGE AF-TIMI48, Japanese-ROCKET AF [J-ROCKET AF], RE-LY, ROCKET AF) showed that standard-dose NOAC exhibited superior efficacy in the elderly (≥75 years) group, whereas low-dose NOACs showed equivalent efficacy compared to warfarin [21]. The efficacy of NOACs was consistent after excluding results from the edoxaban 30 mg-based regimen and the J-ROCKET AF trial. With regard to safety issues, although the overall major bleeding rate was significantly lower in the NOAC group than in the warfarin group, the benefit is observed mainly in non-elderly patients in whom both standard-dose and low-dose regimens of NOACs exhibited superior safety. In the elderly group, NOACs and warfarin exhibited equivalent safety, regardless of the NOAC dosage. The risk of ICH was significantly lower in the NOAC group than in the warfarin group, regardless of age or NOAC dosage. Moreover, the risk of GI bleeding was significantly higher in the standard-dose NOACs group than in the warfarin group in both elderly and non-elderly groups; low-dose NOACs showed a similar risk of GI bleeding in the elderly group and a lower risk in the non-elderly group. NOACs exhibited better net clinical outcomes than warfarin for both elderly and non-elderly patients in standard-dose, but not in elderly patients in low-dose regimens. Further analysis in extremely old patients (aged ≥80 years) demonstrated that standard-dose NOACs, but not low-dose NOACs, reduced IS/SE compared to warfarin [21]. Briefly, in elderly patients, standard-dose NOACs showed better efficacy and similar safety as compared to warfarin except for a trend toward more GI bleeding, whereas low-dose NOACs exhibited similar efficacy, and equivalent or better safety than warfarin. For the trend toward more GI bleeding with certain NOACs, some studies suggest avoiding concomitant antiplatelet treatment and probably considering proton pump inhibitor in elderly anticoagulated patients [36].

Some indirect comparisons among different NOACs in elderly patients were reported. A nationwide cohort study including 15361 patients aged ≥85 years showed a lower risk of ICH, mortality, and composite adverse events with dabigatran; a lower risk of ischemic stroke, ICH, mortality, and composite adverse events with rivaroxaban; and a lower risk of mortality and composite adverse events with apixaban when compared to warfarin [27]. Alnsasra et al. [37] reported the greatest net clinical benefit in elderly AF patients treated with warfarin with time in therapeutic range ≥60% or high dose NOACs (dabigatran 150 mg twice a day, apixaban 5 mg twice a day, rivaroxaban 20 mg once a day). Schäfer et al. [36] calculated the net clinical benefit of 4 landmark trials of NOACs using the annualized rate of thromboembolic events prevented minus the annualized rate of major bleedings induced, along with ICH multiplied by different weighting factors in AF patients aged ≥75 years. Compared to warfarin, the highest and most significant benefit was demonstrated in the case of apixaban, followed by edoxaban, whereas rivaroxaban or either dose of dabigatran only provided a slight numerical benefit. They reported that the higher benefit of apixaban and edoxaban was mainly driven by fewer events of major bleeding compared to warfarin. Furthermore, the increased bleeding risks with dabigatran and rivaroxaban, compared to warfarin, were mostly limited to extracranial bleeding [38].

The ELDERCARE-AF trial included elderly AF patients (≥80 years of age) who were ineligible for OAC use at doses approved for stroke prevention and showed that edoxaban 15 mg once daily was superior to placebo for preventing IS/SE without significant increase of major bleeding [39]. Subsequently, Chao et al. [40] performed a cohort study including 15 183 elderly AF patients aged ≥80 years with enrollment criteria similar to the ELDERCARE-AF trial. They showed that use of NOACs at either the full dose or reduced dose lowered ischemic strokes by 23%, all-cause mortality by 61%, and composite outcomes by 58%, while the risks of ICH and major bleeding were similar as compared to the non-OAC group. In this cohort study, 40% of patients were taking dabigatran, 49% rivaroxaban, and 11% apixaban.

Notably, the optimal choice and dose of NOACs in elderly AF patients remain undetermined yet because of the absence of head-to-head comparisons in RCTs. Besides, the currently available trials differ in terms of inclusion and exclusion criteria, as well as of underlying stroke risks of study populations [38]. Therefore, it is too early to draw a robust conclusion regarding the choice of certain NOACs, and shared decision-making remains the most important step before NOACs are prescribed for elderly AF patients.

IMPORTANT CLINICAL FACTORS ABOUT THE ANTICOAGULATION MANAGEMENT IN ELDERLY PATIENTS WITH AF

Aging is usually accompanied by a gradual decline of renal function [41] and might influence the decision of OAC use. Khan et al. [42] observed that in the 36% of patients aged ≥75 years with eGFR <59 ml/min/1.73 m^2 at the time of NOAC initiation, all major bleeding episodes were associated with a decline in eGFR compared to baseline. Thus,

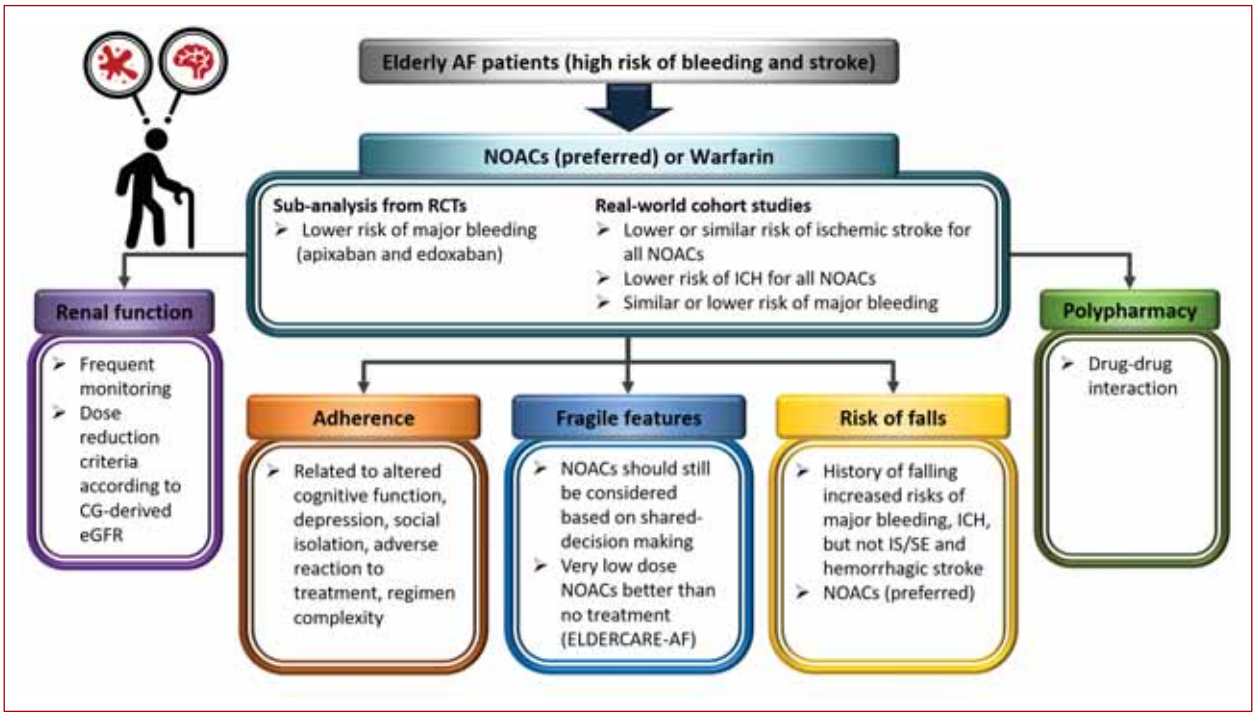

Figure 6. Considerations about the anticoagulation management in elderly patients with AF

Abbreviations: CG-derived eGFR, estimated glomerular filtration rate derived from the Cockcroft-Gault formula; IS/SE, ischemic stroke/system embolism; other — see Figures 1–3

regular monitoring of renal function is recommended in elderly anticoagulated patients to adjust the dosages of NOACs once indicated by dosage reduction criteria of each NOAC and to correct modifiable causes for patients whose renal function declines rapidly [42, 43]. A meta-analysis showed that in elderly patients, both NOACs without dose reduction in patients with creatinine clearance (CrCl) ≥50 ml/min and reduced-dosed NOACs meeting appropriate dose reduction criteria in those with a CrCl <50 ml/min behaved equivalently to warfarin for safety endpoints, which highlights the importance of following dose reduction criteria even for patients with impaired renal function [21]. The risk of falls with consequent bleeding is a common reason for not prescribing OACs in elderly AF patients [44]. In the subgroup analysis from the ARISTOTLE trial, about 5% of patients had a history of falling, and they had a more than the three-fold increased risk of fall and a more than the two-fold increased risk of any bone fracture during the trial period. Patients with a history of falling had higher rates of major bleeding and ICH, but similar rates of IS/SE and hemorrhagic stroke compared to those without a history of falls. The superiority of apixaban over warfarin in relation to efficacy and safety was consistent, irrespective of the history of falls [45]. In a secondary analysis of the ENGAGE AF-TIMI 48 trial, in patients with an increased risk of falling (but not specifically a history of falls), treatment with edoxaban resulted in a greater absolute risk reduction in severe bleeding events and all-cause death as compared to warfarin [45]. Therefore, NOACs might be an attractive choice for stroke prevention in elderly patients at risk of falling.

In a meta-analysis including patients aged 63.8–85.9 years from 20 observational studies, frailty was associated with decreased OAC prescription on hospital admission, but not at discharge. It was also associated with the increased risk of stroke, all-cause mortality, symptom severity, and length of hospital stay [47]. Polypharmacy is frequent in elderly patients, and drug-drug interactions, although less common with NOACs, should be considered. Drugs affecting the P-glycoprotein transport system may potentially interact with NOACs, and dose reductions are sometimes recommended in elderly patients [48]. Adherence to therapy is an issue in elderly patients and possibly relates to altered cognitive function, depression, social isolation, adverse effects of treatment, and regimen complexity [49, 50]. Furthermore, physiological organ changes, malnutrition, and hypoalbuminemia with heterogeneous binding to proteins may be present in a proportion of elderly patients, thus affecting the pharmacokinetics of NOACs [14]. All these risk factors should be comprehensively assessed and taken into consideration when prescribing NOACs for elderly patients (Figure 6).

CONCLUSIONS

Aging increases the risk of adverse events in elderly AF patients, but OAC use provides clinical benefits, with the oldest patients deriving the greatest advantage. Thus, the age and fear of bleeding should not be the reasons for withholding OACs. Sub-analyses and real-world cohort studies generally favor the use of NOAC over warfarin in elderly patients, but the optimal choice and dose of NOACs

have not been determined yet. Therefore, dose adjustment according to the dose reduction criteria of each NOAC is crucial. Other risk factors potentially affecting anticoagulation treatment should be assessed carefully, such as renal function impairment, risk of falls, frailty, nutritional status, adherence to therapy, etc. More data from RCTs are urgently needed for optimal stroke prevention strategies in elderly AF patients.

Article information

Conflict of interest: None declared.

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REVIEW

Optimal anticoagulation in patients with atrial fibrillation and bioprosthetic heart valves

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ABSTRACT

The antithrombotic management of patients after surgical or transcatheter bioprosthetic heart valves (BHVs) replacement is still challenging. Our review aims to describe the current evidence on the best antithrombotic strategy among patients undergoing BHVs replacement (surgical or transcatheter) and/or valve repair, with particular attention to those with atrial fibrillation.

Key words: anticoagulation, antithrombotic therapy, bioprosthetic valves, atrial fibrillation

INTRODUCTION

The general increase in life expectancy leads to a more frequent association between atrial fibrillation (AF) and valvular heart disease (VHD) in clinical practice [1]. It is well established that non-vitamin K antagonist oral anticoagulants (NOACs) represent the first-line therapy for stroke prevention in patients with non-valvular atrial fibrillation (NVAF) [2, 3], whereas vitamin K antagonists (VKAs) are the only treatment option in patients with mechanical heart valves (MHVs) [4, 5]. Moreover, NOACs show a better net clinical benefit vs. VKAs among the elderly with AF in a real-world setting [6–10].

The antithrombotic management of patients after bioprosthetic heart valves (BHVs), both surgical and transcatheter, is still challenging. Among patients in need of long-term oral anticoagulation therapy (OAC), such as those with AF, there is little evidence from randomized control trials (RCTs) about the best treatment between NOACs or VKAs in those with BHVs [11–13] or transcatheter aortic valve implantation (TAVI) [14, 15]. Currently, both the European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) and American College of Cardiology/American Heart Association (ACC/AHA) guidelines apply few class-I recommendations or level of evidence A to OAC therapy among patients with BHVs [4, 5]. This review aims to present the current evidence on the best antithrombotic strategy among patients who underwent BHVs replacement (surgical or transcatheter) and/or valve repair, with particular attention to those with AF.

OPTIMAL ANTITHROMBOTIC MANAGEMENT AFTER BHV REPLACEMENT IN THE GENERAL POPULATION

Surgical mitral and tricuspid BHVs replacement

Following surgical BHVs replacement, antithrombotic therapy is needed to avoid thromboembolic events, thrombosis of the valve, and subclinical organized valve thrombus complications, which are presumably related to suture material and a sewing ring that is not yet covered with biofilm and endothelialized [16, 17]. Furthermore, it has been shown that the risk of valve thrombosis and cerebral ischemia is higher in the 180 days after mitral surgery [16, 18, 19]. According to the most re-

Table 1. Characteristics of the studies exploring the best antithrombotic management after aortic bioprosthetic valve replacement in the general population

Author/ /reference	Study design	Enrolled patients, n	Outcomes measured	FU	OAC therapy, n (%)	Antiplatelet therapy, n (%)
Sundt et al. [23]	Retrospective, VKA vs. no-VKA	1151	Stroke, bleeding	90 days	Warfarin 624 (54.2)	OAC group 336 (53.9) no-OAC group 304 (57.7)
Moinuddeen et al. [24]	Retrospective, VKA vs. no-VKA	185	Stroke, bleeding, RO, HS, SR	>3 months	Warfarin 109 (58.9)	N/A
Brennan et al. [25]	Retrospective, VKA vs. ASA and retrospective, VKA + ASA vs. ASA	25656	Death, TE[a], bleeding[b]	3 months	Warfarin 2999 (11.7)	ASA 12457 (48.6) Warfarin + ASA 5972 (23.3)
Rafiq et al. [26]	Prospective, RCT — BHV-only subgroup VKA vs. ASA and BHV + CABG subgroup VKA + ASA vs. ASA	370	TE[c], bleeding, death	3 months	BHV subgroup Warfarin 105 (50.2) BHV + CABG subgroup Warfarin 63 (52.9)	BHV aubgroup ASA 104 (49.8) BHV + CABG subgroup ASA 56 (47.1)
Mérie et al. [27]	Retrospective, VKA vs. no-VKA	4075	Stroke, TE, CVM, bleeding[d]	Time periods (days) 30–89 90–179 365–729 >730	Warfarin[e]	N/A

[a]Cerebrovascular accident, transient ischemic attack, and noncerebral arterial thromboembolism; ASA, acetylsalicylic acid; [b]Hemorrhagic stroke, gastrointestinal bleeding, other bleeding; [c]Myocardial infarction, stroke, transitory cerebral ischemia, pulmonary embolism, deep vein thrombosis, peripheral arterial embolism, intra-cardiac thrombus formation; [d]Gastrointestinal, intracranial, urinary tract, and airway bleeding; [e]Number of patients on warfarin varies for each time period
Abbreviations: BHV, bioprosthetic heart valve; CABG, coronary artery by-pass graft; CVM, cardiovascular mortality; FU, follow-up; HS, hospital stay; n, number; N/A, not available; OAC, oral anticoagulants; RO, repeat operation; SR, survival rate; TE, thromboembolic events; VKA, vitamin-K antagonist

cent guidelines, when there are no other indications for OAC (e.g AF), VKAs therapy is recommended for 3 up to 6 months after mitral and tricuspid BHV surgical replacement [4, 5].

Surgical aortic BHVs replacement

The optimal antithrombotic strategy after surgical aortic BHV replacement is still uncertain [20, 21] – because of the low incidence of thromboembolic events following aortic surgery most studies are underpowered to highlight differences between treatment groups [22–24].

While the association therapy with warfarin and aspirin is clearly associated with an increased risk of bleeding [21, 22], comparing OAC monotherapy with single antiplatelet therapy (SAPT) has yielded controversial results.

In an observational study including 25 656 patients ≥65 years receiving aortic BHV, Brennan et al. [25] showed that warfarin-only therapy seems to have a similar risk of death, embolic events, and bleeding in the 3 months after surgery compared to aspirin-only treatment. On the other hand, in a recent prospective single-center RCT, aspirin was found to be as effective as warfarin in preventing thromboembolic events after BHVs replacement, but with less major bleeding [26].

In a retrospective observational study from the Danish National Patient Registry, including 4075 patients with aortic BHVs replacement discharged on VKA, the discontinuation of warfarin treatment within 6 months after BHVs surgery was associated with increased cardiovascular death and with differences in stroke and bleeding events [27]. This result supports the hypothesis of good effectiveness of prolonged (till 6 months) OAC therapy among aortic BHV patients. Tables 1 and 2 summarize the characteristics and results of the above-mentioned studies.

Considering the currently available literature, the 2021 ESC/EACTS guidelines recommend OAC with VKA or aspirin alone for 3 months after the procedure (class IIa B) [4]. In addition, ACC/AHA guidelines suggest lifelong therapy with aspirin in such patients (class IIa B) even if they were treated with VKA for the first 3 to 6 months after surgery (suggested specifically for low bleeding risk patients, class IIa B) [5].

Transcatheter mitral or aortic BHVs replacement

Mitral valve

Little is still known about the optimal antithrombotic strategy among patients undergoing transcatheter mitral BHV replacement, and no RCTs including these patients are available. Some retrospective observational studies suggest that dual antiplatelet therapy with aspirin plus clopidogrel (DAPT) might be insufficient to avoid post-procedural thrombotic complications [28, 29].

Table 2. Results of the studies analyzing the optimal antithrombotic management after aortic bioprosthetic valve replacement in the general population

Author/reference	Results		
Sundt et al. [23]	Stroke, n (%)	VKA vs. no-VKA	16 (2.5) vs. 9 (1.9) P = N/A (NSD)
	Bleeding, n (%)	VKA vs. no-VKA	Mediastinal 32 (5.0) vs. 42 (7.4) Other bleeding 7 (1.1) vs. 4 (0.8) P = N/A (NSD)
Moinuddeen [24]	Stroke, n (%)	VKA vs. no-VKA Time points <24 hours; 24 hours — 3 m ;> 3 m	5 (4.6), 3 (2.8), and 12 (11) vs. 5 (4.6), 3 (2.8) and 12 (11) P = N/A (NSD)
	Bleeding, n (%)	VKA vs. no-VKA	10 (9.2) vs. 7 (9.2) P = N/A (NSD)
	Repeat operation, n (%)	VKA vs. no-VKA	6 (5.5) vs. 7 (9.2) P = N/A (NSD)
	Hospital staying (mean)	VKA vs. no-VKA	12 months both groups P = N/A (NSD)
	Survival rates (mean%)	VKA vs. no-VKA Time points 1, 5, and 7 years	93%, 84%, and 62% vs. 87%, 74%, and 67% *P* = 0.60
Brennan [25]	Death ARR (95% CI)	Warfarin vs. ASA	1.01 (0.80–1.27)
		Warfarin + ASA vs. ASA	0.80 (0.66–0.96)
	TE ARR (95% CI)	Warfarin only vs. ASA only	0.95 (0.61–1.47)
		Warfarin + ASA vs. ASA-only	0.52 (0.35–0.76)
	Bleeding ARR (95% CI)	Warfarin vs. ASA	1.23 (0.85–1.79)
		Warfarin + ASA vs. ASA	2.80 (2.18–3.60)
Rafiq et al. [26]	TE BHV subgroup	Warfarin vs. ASA	4 (3.8%) vs. 3 (2.9%) *P* = 0.721
	TE BHV + CABG subgroup	Warfarin + ASA vs. ASA	7 (11.1%) vs. 9 (16.1%) *P* = 0.592
	Bleeding BHV subgroup	Warfarin vs. ASA	3 (2.9%) vs. 2 (2.9%) *P* = 0.683
	BHV + CABG subgroup	Warfarin + ASA vs. ASA	6 (9.5%) vs. 1 (1.8%) *P* = 0.117
	Death BHV subgroup	Warfarin vs. ASA	4 (3.8%) vs. 3 (2.9%) *P* = 0.721
	Death BHV + CABG subgroup	Warfarin + ASA vs. ASA	4 (6.3%) 3 (5.4%) *P* = 0.800

Table 2 (cont.). Results of the studies analyzing the optimal antithrombotic management after aortic bioprosthetic valve replacement in the general population

Author/reference	Results		
Mérie et al. [27]	Stroke Event rate (95% CI)	No-VKA vs. VKA Time period (days) 30-89	7 (4.07–12.06) vs. 2.69 (1.49–4.87) AIRR (95% CI) 2.46 (1.09–5.55) *P* = 0.03
	TE events Event rate (95% CI)	No-VKA vs. VKA Time period (days) 30–89	13.07 (8.76–19.50) vs. 3.97 (2.43–6.48) AIRR (95% CI) 2.93 (1.54–5.55) *P* <0.001
		No-VKA vs. VKA Time period, days, 90–179	5.04 (3.43–7.40) vs. 1.87 (0.84–4.16) AIRR (95% CI) 2.65 (1.08–6.51) *P* = 0.03
	CV mortality Event rate (95% CI)	No-VKA vs. VKA Time period, days, 30–89	31.74 (24.69–40.70) vs. 3.97 (2.43–6.48) AIRR (95% CI) 7.61 (4.37–13.26) *P* <0.001
		No-VKA vs. VKA Time period, days, 90–179	6.50 (4.67–9.06) vs. 2.08 (0.99–4.36) AIRR (95% CI) 3.51 (1.54–8.03) *P* = 0.003
		Time period, days, 180–364	3.07 (2.27–4.16) vs. 0.65 (0.16–2.61) AIRR (95% CI) 4.57 (1.09–19.13) *P* = 0.04
	Bleeding Event rate (95% CI)	No-VKA vs. VKA Time perio, days, 30–89	11.86 (7.81–18.01) vs. 5.37 (3.54–8.16) AIRR (95% CI) 2.32 (1.28–4.22) *P* = 0.006

Abbreviations: AIRR, adjusted incidence rate ratio; ARR, adjusted relative risk; CI, confidence interval; NSD, non-significant difference; other — see Table 1

A state-of-the-art review by Pagnesi et al. [30] suggests considering an anticoagulation-based antithrombotic strategy to prevent the risk of valve thrombosis and thromboembolic events after any transcatheter mitral valve replacement procedure (valve-in-valve or valve-in-ring).

The current guidelines are limited by these uncertainties; however, they suggest a VKA prescription for 3 months following the transcatheter mitral intervention as it is the most common strategy applied in clinical practice [4].

Aortic valve

In the historical trials evaluating TAVI for severe aortic stenosis, a 6-month DAPT strategy following the procedure was used [31, 32]; so, until 2017, this approach was recommended by guidelines (IIa, level of evidence C) [33]. Several observational studies [30–34] and RCTs [35–37] demonstrated a better clinical safety profile of SAPT compared to DAPT, with no significant differences in terms of efficacy among TAVI patients.

In a pooled cohort of 4832 patients discharged with or without OAC after aortic BHV implantation (3889 TAVI and 943 surgical aortic BHV) [42], Chakravarty et al. showed a lower incidence of increased mean valvular gradient, over the first year after the procedure, among patients on OAC (mainly warfarin), with no significant differences in the stroke rate. In patients without an established indication for OAC after successful TAVI, a treatment strategy with aspirin and rivaroxaban 10 mg daily was associated with a higher risk of death or thromboembolic complications and a higher risk of bleeding than with the DAPT strategy [41].

The latest European and American guidelines recommend lifelong SAPT with aspirin after TAVI in patients with no baseline indications for OAC (Class I A and IIa B, respectively) [4, 5]. Moreover, American guidelines approve DAPT or VKA strategy in low bleeding risk patients (class IIb B) [5].

Table 3. Results of the studies analyzing the clinical performance of non-vitamin K oral anticoagulants after bioprosthetic valve implantation in the general population

Author/reference	Study design	Results				
Ball et al. [43]	Retrospective Observational Apixaban in BHV	Hospital readmission, n (%)	18 (33)			
		Mortality, n (%)	3 (6)			
		Major bleeding, n (%)	1 (2)			
		Minor bleeding, n (%)	3 (6)			
		MBV vs. ABV (readmission), n (%)	10 (48) vs. 8 (24), $P = 0.07$			
		AF vs. SR (mortality), n (%)	(14) vs. (3), $P = 0.14$			
Pasciolla et al. [44]	Retrospective cohort study VKA vs. NOACs NOACs included apixaban rivaroxaban dabigatran	Thromboembolic events, n (%) (events per drug)	VKA	API	RIVA	DABI
			0	1(2.5)	2 (5)	0
		Thromboembolic events, n (%) (NOACs vs. VKA)	3 (2.4) vs. 0 $P = 0.20$			
		Major bleeding, n (%) (events per drug)	VKA	API	RIVA	DABI
			2(2.9)	7(8.1)	2(5)	0
		Major bleeding, n (%) (NOACs vs. VKA)	9 (7.1) vs. 2 (2.9); $P = 0.22$			
Shim et al. [45]	Prospective Randomized Edoxaban vs. VKA		Efficacy outcomes (Edoxaban vs. VKA)			
		Death, n (%)	0 in both groups			
		Thromboembolic events, n (%)	0 vs. 1 (0.92)			
		Asymptomatic intracardiac thrombus, n (%)	0 vs. 3 (2.75)			
		Subcl. leaflet thrombosis, n (%)	0 vs. 1 (0.92)			
		Thrombus within cardiac chambers, n (%)	0 vs. 1.83			
		Composite of all efficacy outcomes, n (%)	0 vs. 4 (3.67) RD (95% CI), 0.0367 (0.0720–0.0014); $P \leq 0.001$			
			Safety outcomes (Edoxaban vs. VKA)			
		Major bleeding, n (%)	3 (2.75) vs. 1 (0.92) RD (95% CI), 0.0183 (0.0172–0.0539); $P = 0.013$			
		CRNMB	1 (0.92) vs. 1 (0.92) RD (95% CI), 0 (0.0253–0.0253); $P = 0.002$			
		Major bleeding + CRNMB, n (%)	4 (3.67) vs. 2 (1.83) RD (95% CI); 0.0183 (0.0250–0.0617); $P = 0.018$			
Dangas 2020 [46]	Prospective Randomized Rivaroxaban10 mg+ASA vs. ASA+Clopidogrel	Primary efficacy outcome[a], n (%)	105 (12.7) vs. 78 (9.5) HR (95% CI), 1.35 (1.01–1.81)			
		Primary safety outcome[b], n (%)	46 (5.6) vs. 1 (3.8) HR (95% CI), 1.50 (0.95–2.37)			
Collet et al. [15]	Prospective Randomized Stratum 2[c]: Apixaban 5 mg BID Versus SAPT or DAPT	Primary endpoint[d], n (%)	89 (16.9) vs. 101 (19.3) HR (95% CI), 0.88 (0.66–1.17)			

[a]Composite of death from any cause or thromboembolic events, including any stroke, myocardial infarction, symptomatic valve thrombosis, systemic embolism (not involving the central nervous system), deep-vein thrombosis, or pulmonary embolism; [b]Composite of life-threatening, disabling, or major bleeding; [c]Patients with no indication to oral anticoagulation; [d]Composite of all-cause death, stroke, heart attack, valve thrombosis, pulmonary or systemic embolism, deep vein thrombosis or major bleeding

Abbreviations: ABV, aortic bioprosthetic valve; AF, atrial fibrillation; CRNMB, clinically relevant non-major bleeding; HR, hazard ratio; MBV, mitral bioprosthetic valve; NOACs, non-vitamin K antagonist oral anticoagulants; Subcl, subclinical; RD, risk difference; SR, sinus rhythm; other — see Tables 1 and 2

NOACs after surgical or transcatheter BHV replacement

Surgical BHV replacement

Current guidelines do not recommend the use of NOACs over VKAs when OAC is the preferred antithrombotic strategy after surgical BHVs replacement, especially in patients without AF [4, 5]. However, some data are being collected on the clinical performance of NOACs in patients with BHVs or previous valve repair, irrespective of the presence of a long-term indication for OAC (Table 3).

In a small single-center retrospective study [43] including 54 patients undergoing a BHV replacement (61% aortic, 39% mitral), the standard dose of apixaban was safe and well-tolerated with low incidences of major/minor bleeding and thrombotic events. The subgroup analysis comparing patients with and without AF showed a trend toward increased mortality in patients with AF, but results did not reach statistical significance (14% vs. 3%; $P = 0.135$).

In a small exploratory study including 197 patients undergoing BHV replacement (68% aortic, 21% mitral, 11% both aortic and mitral), Pasciolla et al. [44] evaluated the efficacy and safety of NOACs (n = 127, 64%) vs. warfarin (n = 70, 35.5%). Eighty-six patients received apixaban, 40 rivaroxaban and 1 dabigatran. More than half (51.8%) of the study population had a history of AF (NOACs, n = 57 and

VKAs, n = 45). The authors found a similar rate of thromboembolic complications (2.4% vs. 0%; *P* = 0.20) and major bleeding events (7.1% vs. 2.9%; *P* = 0.22) in the two groups.

The favorable results of observational studies were recently confirmed in the Explore the Efficacy and Safety of Edoxaban in Patients after Heart Valve Repair or Bioprosthetic Valve Replacement (ENAVLE) study [45], a prospective RCT exploring the effectiveness and safety of edoxaban for the first 3 months after surgical aortic and mitral BHV implantation and mitral repair. The study enrolled 218 patients (109 per group). Edoxaban was non-inferior to warfarin for preventing thromboembolism (risk difference –0.0367; *P* <0.001) and potentially comparable for the risk of major bleeding (risk difference 0.0183; *P* = 0.013) during the first 3 months after surgical BHV implantation or valve repair.

TAVI

Among patients undergoing TAVI, the results of RCTs do not favor a NOAC treatment-based strategy over the antiplatelet therapy. In the Global Study Comparing a rivAroxaban-based Antithrombotic Strategy to an antipLatelet-based Strategy After Transcatheter aortIc vaLve rEplacement to Optimize Clinical Outcomes (GALILEO) trial, rivaroxaban 10 mg daily plus aspirin was compared to DAPT in TAVI patients with no indication to long-term OAC treatment. The study was prematurely terminated because of safety concerns. Indeed, after 17 months of follow-up, the composite endpoint of death or thromboembolic events (hazard ratio [HR], 1.53; *P* = 0.04), as well as major bleeding events (HR, 1.50; *P* = 0.08), were found higher in the rivaroxaban group [46].

Similar results were shown by the Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis (ATLANTIS) trial which compared apixaban 5 mg twice daily to aspirin alone or DAPT after TAVI (stratum 2 — no indication for long term OAC) [15]. At one year follow-up, no significant difference in the primary efficacy endpoints was shown (Table 3). However, the authors found higher numbers of secondary endpoints including death, stroke, heart attack, or systemic embolism in the apixaban group.

In summary, among patients undergoing surgical BHV replacement, NOACs can be at least as effective and safe as warfarin. However, in the clinical setting of patients with TAVI, due to the unfavorable results of the GALILEO and ATLANTIS trials, the ESC/EACTS guidelines contraindicated the routine use of OAC in TAVI patients without baseline indication to long term OAC (class III B) and the American guidelines specifically warrant the use of NOACs in these patients [4, 5].

ORAL ANTICOAGULATION IN AF PATIENTS WITH BHVS REPLACEMENT

Patients with AF and BHVs have a non-significantly higher risk of thromboembolic events compared to those with AF only. However, in BHV patients with AF, the VKA use is independently associated with a lower risk of thromboembolic events (HR, 0.83; *P* = 0.03) [47]. The optimal OAC therapy in AF patients with BHVs is still debated. According to the current guidelines [4], life-long therapy with OAC is recommended for AF patients undergoing BHVs replacement (class IC). Moreover, NOACs may be used as an alternative to VKA only after 3 months from the BHV replacement among AF patients with different classes of recommendation [4, 5]. Considering the results of the RIvaroxaban for Valvular heart diseasE and atRial fibrillation (RIVER) trial [13], according to the ESC/EACTS guidelines, NOACs may be considered over VKA also in the first three months following surgical BHV implantation in mitral position in patients with AF (class IIb C) [4].

NOACs in AF patients with BHVs replacement: preliminary studies

Two preliminary studies [44, 45] reported the clinical performance of NOACs in AF patients with BHVs replacement or valve repair.

In a retrospective single-center cohort study including 73 AF patients undergoing aortic (n = 61) or mitral (n = 12) BHV replacement, Yadlapati et al. [48] collected data on thromboembolic and major bleeding events during NOAC therapy (dabigatran, n = 44; rivaroxaban, n = 25; apixaban, n = 4). During the follow-up period of 511.8 ± 400.8 days, they recorded 1 transient ischemic attack (TIA; 1.4%), 5 major bleeding (6.9%), and 6 minor bleeding (8.2%) events, 1 hemorrhagic stroke, and 3 deaths (4.1%). Based on these results, the authors concluded that NOACs therapy appears effective in the prevention of thromboembolic events, albeit at the expense of increased bleeding. However, it is worth mentioning that 72% of the study population was taking concomitant aspirin treatment [48].

In a retrospective multicenter observational study including 122 AF patients with a prior BHV replacement or valve repair, Russo et al. [49] investigated the incidence of thromboembolic and major bleeding events with NOAC treatment. Patients were treated with apixaban (53.1%), dabigatran (31%), or rivaroxaban (15.5%). During a follow-up of 835 ± 203 days, 2 patients (1.7%) experienced thromboembolic events, and 4 patients (3.3%) had major bleeding events. The authors concluded that NOACs seem to be an effective and safe alternative therapy in patients with BHVs replacement or valve repair. Notably, only 20% of patients were under concomitant antiplatelet therapy. Table 4 shows details of the abovementioned studies.

NOACS vs. VKAs in AF patients with BHVs replacement

Of the 4 major clinical trials comparing NOACs to warfarin in patients with AF for the prevention of stroke and systemic embolism [50–53], only the Effective Anticoagulation with Factor Xa Next Generation in AF-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial and the Apixaban

Table 4. Clinical performance of non-vitamin K antagonist oral anticoagulants after bioprosthetic heart valve replacement

First author/ /reference	Study design	Number of patients	Follow-up, days	NOAC, n (%)	Procedure, n (%)	Results	
Yadlapati et al. [48]	Obs. Rtsp SC	73	511.8 400.8	Dabigatran 44 (60.3) Rivaroxaban 25 (34.2) Apixaban 4 (5.5)	ABV 61 (83.6) MBV/MVR 12 (16.4)	TE events Bleeding events Mortality	1 TIA (1.4) 5 MB (6.9) 6 MB (8.2), 2 ICH (2.7) 3 (4.1)
Russo et al. [49]	Obs. Rtsp MC	122	835 203	Dabigatran (31) Rivaroxaban (15.5) Apixaban (53.1)	ABV 52 (43) MBV 24 (20) MSR 41 (34) AVR 5 (4)	TE events Bleeding events Mortality	2 (1.7) M.A.I: 0.8% 4 (3.3) M.A.I: 1.3% 0 (0)

Abbreviations: AVR, aortic valve repair; M.A.I, mean annual incidence; MC, multicenter; MB, major bleeding, mB, minor bleeding; MVR, mitral valve repair; Obs, observational; Rtsp, retrospective; SC, single-center; TIA, transient ischemic attack; other — see Tables 1 and 3

for Reduction in Stroke and Other Thromboembolic Events in AF (ARISTOTLE) trial included AF patients with BHV replacement [51, 53].

In a *post hoc* analysis from the ENGAGE AF-TIMI 48 [53] including 191 AF patients with BHV replacement (68.6% mitral; 31.4% aortic), Carnicelli et al. [54] showed similar rates of stroke/systemic embolism (HR, 0.37; $P = 0.15$) and major bleeding (HR, 0.5; $P = 0.26$) compared to warfarin. Moreover, patients on edoxaban showed significantly lower rates of myocardial infarction, stroke, or cardiovascular death (HR, 0.36; $P = 0.03$). The authors concluded that edoxaban appears to be a reasonable alternative to warfarin in AF patients with previous BHV replacement.

No significant differences between apixaban and warfarin were found for any outcome analyzed in the *post-hoc* analysis of the ARISTOTLE trial [55] including 156 patients with AF and BHVs or valve repair (see Tables 5 and 6 for details).

Two multicenter observational studies [56, 57] showed a more favorable effect of NOACs over warfarin in AF patients with BHV replacement. In particular, Russo et al. [56] in a propensity score matching study including 260 AF patients with BHVs (130 patients in each treatment group) showed a low rate of major bleeding among the NOACs group leading to a positive (+1.87) net clinical benefit of NOACs over VKAs.

Among 2 672 AF patients with BHVs included in a large integrated health care delivery system in California, Duan et al. [57] did not find significant differences between NOACs-users and VKAs-users in terms of thromboembolic events (composite of ischemic stroke, transient ischemic attack, or systemic embolism). Moreover, a lower risk of major bleeding (HR, 0.69; $P < 0.001$) was shown in the NOAC group. These results were consistent across subgroups (dabigatran versus warfarin; aortic versus mitral valve replacement). Tables 5 and 6 show the characteristics and results of the studies. The preliminary results of the observational studies were confirmed in several RCTs [11–13].

The DAWA pilot study [11] was the first trial designed to compare the effectiveness and safety of dabigatran 110 mg twice daily vs. warfarin in patients undergoing mitral and aortic BHV replacement. The primary endpoint was the presence of a newly diagnosed intracardiac thrombus at 90 days; the secondary outcomes were the development of dense spontaneous echo contrast and the incidence of any stroke, myocardial infarction, valve thrombosis, and peripheral embolic events. The study was terminated prematurely because of the low enrollment (34 patients). During the 90 days of follow-up, no significant differences were found either for the primary or secondary outcomes between the groups.

In a recent small trial [12], 50 AF patients undergoing aortic BHV replacement were randomized to receive apixaban (n = 25 patients) or warfarin (n = 25 patients) in a 1:1 ratio for the first 3 months after surgery. At 3 months follow-up, no valvular dysfunction was recorded; major bleeding events occurred in 3 patients (12%) among the warfarin group and none in the apixaban group. The only death reported was in the warfarin group early after surgery (9 days) due to massive pericardial bleeding effusion. The authors concluded that apixaban was non-inferior to warfarin in the first 3 months after surgical aortic BHV replacement and safer with respect to major bleeding and death.

The RIVER trial [13] was a large multicenter RCT in which 1005 AF patients undergoing surgical mitral BHV replacement were enrolled and randomized to receive rivaroxaban or warfarin. At twelve months follow-up, no significant differences in the incidence of stroke (3% vs. 2.4%), major bleeding (1.4% vs. 2.6%), or death (4% vs. 4%) were reported between rivaroxaban and warfarin. This trial brought solid data on the non-inferiority of rivaroxaban compared to warfarin with respect to the mean time until the occurrence of death, major cardiovascular events, or major bleeding at 12 months in AF patients with mitral BHV replacement.

Tables 7 and 8 summarize RTCs evaluating NOACs vs. VKAs in AF patients with BHVs replacement.

Table 5. Overview of the studies characteristics comparing non-Vitamin K oral anticoagulants with Vitamin K antagonist oral anticoagulants in AF patients with bioprosthetic valves or prior surgical valve repair

Author/reference	Study design	Number of patients	Mean FU, years	NOAC, n (%)	Procedure, n (%)	Primary outcomes	
Carnicelli et al. [54]	Posthoc analysis phase III trial	191	2.8	Edox. 121 (63.4)	ABV 60 (31.4) MBV 131(68.6)	Efficacy outcome	S/SE
						Safety outcome	MB
						Other	Primary net clinical outcome (S/SE, MB, death)
Guimarães et al. [55]	Posthoc analysis phase III trial	156	1.8	Apix. 87 (55.8)	ABV 73 (46.8) MBV 26 (16.7) ABV +MBV 5 (3.2) MVR 50 (32.1) AVR 2 (1.3)	Efficacy outcome	S/SE ACS IS MI Death CVM
						Safety outcome	MB, MB/CRNMB ICH GI bleeding Any bleeding
Russo et al. [56]	Retrosp. Propensity S-matched	260 130 for each group	1.1	Apix. 72 (55.4) Rivarox. 39 (30.0) Dabig. 17 (13.1) Edox. 2 (1.4)	ABV 128 (49.2) MBV 132 (50.8) ABV +MBV 66 (25.4)	Efficacy outcome	S/SE TIA
						Safety outcome	MB
						Other	ICH
Duan et al. [57]	Retrosp. cohort study	2672	2.9	Dabig. 362 (13.5) Apix. 60 (2.2) Rivarox. 17 (0.6)	ABV 1,724 (64.5) MBV 943 (35.3) N/A 5 (0.2)	Efficacy outcome	Composite of IS TIA/SE
						Safety outcome	Composite of MB[a]

[a]Gastrointestinal bleeding, intracranial hemorrhage, and bleeding from other sites

Abbreviations: Apix, apixaban; ACS, all-cause stroke; Dabig, dabigatran; Edox, edoxaban; GI, gastrointestinal; ICH, intracranial hemorrhage; IS, ischemic stroke; MI, myocardial infarction; S-matched, score-matched; S/SE, stroke/systemic embolism; Rivarox, rivaroxaban; other — see Tables 1, 3 and 4

Oral anticoagulation in AF patients with TAVI

VKA

Results from studies evaluating the role of OAC alone or with an antiplatelet agent after TAVI are controversial. Early observational studies showed an increased bleeding risk with the association therapy of VKAs with SAPT or DAPT, with no differences in the occurrence of thrombotic events [58, 59].

A recent subanalysis of the Placement of Aortic Transcatheter Valve II (Partner II) trial and associated registries [60] showed that antiplatelet therapy with (HR, 0.43; $P = 0.015$) or without (HR, 0.32; $P = 0.002$) OAC reduced the 2-year risk of stroke among patients with prior AF undergoing TAVI, implicating multifactorial stroke mechanism in these patients.

The POPular TAVI [61] was a randomized trial of clopidogrel in patients undergoing TAVI who were taking oral anticoagulation (warfarin) for appropriate indications. Patients before TAVI were assigned in a 1:1 ratio into two groups: one not receiving clopidogrel (n = 157) and the other receiving clopidogrel (n = 156) for 3 months. Patients with OAC alone showed a lower incidence of serious bleeding (relative risk, 0.64; $P = 0.02$) than those on OAC plus clopidogrel. No significant differences in death from cardiovascular causes, non-procedure-related bleeding, stroke from any cause, or myocardial infarction were found.

Based on these results, when long-term OAC is indicated, the current guidelines suggest using life-long OAC alone in TAVI patients with AF (class of recommendation I B in the ESC guidelines and IIaB in the American guidelines). To date, VKAs are the first-line treatment within the first 3 months following TAVI; at the end of this period, NOACs can be evaluated as an alternative [4, 5].

NOACs

The role of NOACs in AF patients undergoing TAVI is still uncertain. In a large propensity score matching study involving 962 AF patients undergoing TAVI who were discharged

Table 6. Results of the studies comparing non-vitamin K oral anticoagulants with vitamin K antagonist oral anticoagulants in atrial fibrillation patients with bioprosthetic valves or surgical valve repair

Author/reference	Events		Statistics (NOACs vs. VKA)
Carnicelli et al. [54]	S/SE	Warfarin = 8 HDE = 3 LDE n = 4	HDE vs. warfarin: HR, 0.37; 95% CI, 0.10–1.42; $P = 0.15$ LDE vs. warfarin HR, 0.53; 95% CI, 0.16–1.78; $P = 0.31$
	MB	Warfarin = 9 HDE = 4 LDE = 1	HDE vs. warfarin: HR, 0.5; 95% CI, 0.15–1.67; $P = 0.26$ LDE vs. warfarin HR, 0.12; 95% CI, 0.01–0.95; $P = 0.045$
	Primary net clinical outcome	N/A	HDE vs. warfarin: HR, 0.46; 95% CI, 0.23–0.91; $P = 0.03$ LDE vs warfarin HR, 0.43; 95% CI, 0.21–0.88; $P = 0.02$
Guimarães et al. [55]	Efficacy outcomes		Efficacy outcomes
	S/SE	Warfarin = 2 Apixaban = 4	HR, 1.714; 95% CI 0.313–9.372; $P = 0.53$
	ACS	Warfarin = 2 Apixaban = 4	HR, 1.714, 95% CI 0.313–9.372; $P = 0.53$
	IS	Warfarin = 1 Apixaban = 4	HR, 3.286, 95% CI 0.37–29.4; $P = 0.29$
	MI	Warfarin = 1 Apixaban = 1	HR, 0.825, 95% CI 0.367–29.40; $P = 0.29$
	Death	Warfarin = 6 Apixaban = 7	HR, 1.017, 95% CI 0.341–3.037; $P = 0.98$
	CVM	Warfarin = 2 Apixaban = 2	HR, 0.827, 95% CI 0.123–6.201; $P = 0.89$
	Safety outcome		Safety outcome
	MB	Warfarin = 7 Apixaban = 7	HR, 0.882, 95% CI 0.309–2.519; $P = 0.82$
	MB/CRNMB	Warfarin = 10 Apixaban = 9	HR, 0.781, 95% CI 0.317–1.925; $P = 0.59$
	ICH	Warfarin = 2 Apixaban = 1	HR, 0.467, 95% CI 0.042–5.187; $P = 0.54$
	GI bleeding	Warfarin = 2 Apixaban = 3	HR, 1.244, 95% CI 0.208–7.448; $P = 0.81$
	Any bleeding	Warfarin = 28 Apixaban = 30	HR, 0.866, 95% CI 0.517–1.451; $P = 0.59$
Russo et al. [56]	S/SE TIA	VKA = 5 NOAC = 3	HR, 0.49, 95% CI, 0.19–1.22; $P = 0.14$
	MB	VKA = 12 NOAC = 6	HR, 0.59, 95% CI, 0.15–2.4; $P = 0.47$
	ICH	VKA = 3 NOAC = 1	HR, 0.33, 95% CI, 0.05–2.34; $P = 0.3$
Duan et al. [57]	Composite of IS TIA/SE	N/A	HR, 1.19, 95% CI, 0.96–1.48; $P = 0.106$
	Composite of MB[a]	N/A	HR, 0.69, 95% CI 0.56–0.85; $P < 0.001$

Abbreviations: HDE, high dose edoxaban; LDE, low dose edoxaban; a: composite of major bleeding including gastrointestinal bleeding, intracranial hemorrhage, and bleeding from other sites; other — see Tables 1, 3–5

on NOACs (n = 326; 53.7 % rivaroxaban, 39.2% apixaban, and 7.1% dabigatran) or warfarin (n = 626), Jochheim et al. [62] did not show any significant differences in the primary safety outcomes (bleeding according to the Bleeding Academic Research Consortium) or all-cause mortality between the two groups at 1-year follow-up. However, the incidence of the primary efficacy outcomes (all-cause mortality, myocardial infarction, and any cerebrovascular events) was higher in the NOACs group (21.2% vs. 15%; HR, 1.44; $P = 0.05$).

Conversely, in the prospective study of Seeger et al. [63], TAVI patients with AF treated with apixaban experienced a significantly lower rate of the safety endpoints (a composite of all-cause mortality, all stroke, life-threatening bleeding, acute kidney injury, coronary obstruction, major vascular complications, and valve dysfunction requiring re-intervention) at 30 days follow up (13.5% vs. 30.5%; $P < 0.01$). No significant differences were found in the rate of stroke at 30 days (2.1% vs. 5.3%; $P = 0.17$) and 12 months follow-up between treatment groups (1.2% vs. 2.0%; $P = 0.73$).

Among 2588 patients who underwent TAVI, enrolled in the prospective multicenter observational Optimized Transcatheter Valvular Intervention (OCEAN) study [64], 403 (15.6%) patients had AF on anticoagulation therapy

Table 7. Characteristics of randomized clinical trials comparing non-vitamin K oral anticoagulants with vitamin K antagonist oral anticoagulants in AF patients with bioprosthetic valves or surgical valve

Author/reference	Study design	Procedure	Study groups	Number of patients (NOACs/VKAs)	Primary outcomes
Durães et al. [11]	Phase 2 RCT Pilot study — FU At 90 days	ABV = N/A MBV = 20	Dabigatran 110 mg vs. Warfarin	Overall = 27 Dabigatran = 15 Warfarin = 12	New intracardiac thrombus (TEE)
Piepiorka-Broniecka et al. [12]	Prospective RCT — At 30 days And At 90 days	ABV	Apixaban vs. Warfarin	Overall = 50 Apixaban = 25 Warfarin = 25	Death Bleeding (1 and 3 months) BV function (3 months)
Guimarães et al. [13]	Multicenter RCT — FU 365 days	MBV	Rivaroxaban vs. Warfarin	Overall = 1005 Rivaroxaban = 500 Warfarin = 505	[a]Composite of Death MACE[b] MB — Bleeding events[c]

[a]Mean time until a primary-outcome event in days; [b]Ischemic attack, valve thrombosis, systemic embolism not related to the central nervous system, or hospitalization for heart failure; [c]According to the criteria of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF): Any bleeding; Major bleeding; Intracranial bleeding; Fatal bleeding; Clinically relevant nonmajor bleeding; Minor bleeding

Abbreviations: BV, bioprosthetic valve; RCT: randomized clinical trial; TEE: transesophageal echocardiography; other — see Table 1, 3 and 4.

Table 8. Results of the randomized clinical trials comparing non-vitamin K oral anticoagulants with vitamin K antagonist oral anticoagulants in AF patients with bioprosthetic valves or surgical valve

Author/reference	Results (n of events)		Statistics
Durães et al. [11]	New intracardiac thrombus (TEE)	Warfarin = 1 Dabigatran = 0	RR, 1.1; 95% CI, 0.9–1.3; *P* = 0.42
Piepiorka-Broniecka et al. [12]	Cumulative death	Warfarin = 1 Apixaban = 0	*P* = 0.31
	Cumulative bleeding	Warfarin = 3 Apixaban = 0	*P* = 0.07
	Valve dysfunction	Warfarin = 0 Apixaban = 0	N/A
Guimarães et al. [13]	Efficacy outcome		Efficacy outcome
	[a]Composite of Death MACE[b] MB[c]	Warfarin = 340.1 Rivaroxaban = 347.5	RMST difference, 7.4 days (–1.4–16.3) *P* <0.001 for noninferiority *P* = 0.10 for superiority
	Safety outcomes		Safety outcomes
	MB	Warfarin = 13 Rivaroxaban = 7	HR, 0.54; 95% 0.21– 1.35; *P* = N/A
	ICH	Warfarin = 5 Rivaroxaban = 0	N/A
	Fatal bleeding	Warfarin = 2 Rivaroxaban = 0	N/A
	CRNMB	Warfarin = 24 Rivaroxaban = 23	HR, 1.05; 95% CI, 0.60–1.87; *P* = N/A
	mB	Warfarin = 49 Rivaroxaban = 37	HR, 0.75; 95% CI, 0.49–1.15; *P* = N/A

[a]Mean time until a primary-outcome event in days; [b]Ischemic attack, valve thrombosis, systemic embolism not related to the central nervous system, or hospitalization for heart failure; [c]According to the criteria of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF): Any bleeding; Major bleeding; Intracranial bleeding; Fatal bleeding; Clinically relevant nonmajor bleeding; Minor bleeding

Abbreviations: RR, relative risk; RMST, restricted mean survival time; other — see Tables 1–5 and 7

(NOACs, n = 227; VKAs, n = 176). Compared with VKAs, NOACs were associated with a low incidence of all-cause mortality (10.2% vs. 20.6%; HR, 0.53; *P* = 0.036) during a median follow-up of 568 days. Similarly, Butt et al. [65] did not find differences in terms of 3-year incidence of arterial thromboembolism, bleeding, or mortality among 219 (29.8%) AF patients treated with NOACs and 516 (70.2%) treated with VKAs following TAVI.

In the multicenter, prospective, randomized, open-label ENVISAGE-trial [14], edoxaban was non-inferior to VKAs for the efficacy endpoints (composite of death from any cause, myocardial infarction, ischemic stroke, systemic thromboembolism, valve thrombosis) (HR, 1.05; *P* = 0.01) or major bleeding (HR, 1.05; *P* = 0.01). However, it was associated with a higher rate of major bleeding events (HR, 1.40; P = 0.93), mainly due to gastrointestinal bleeding.

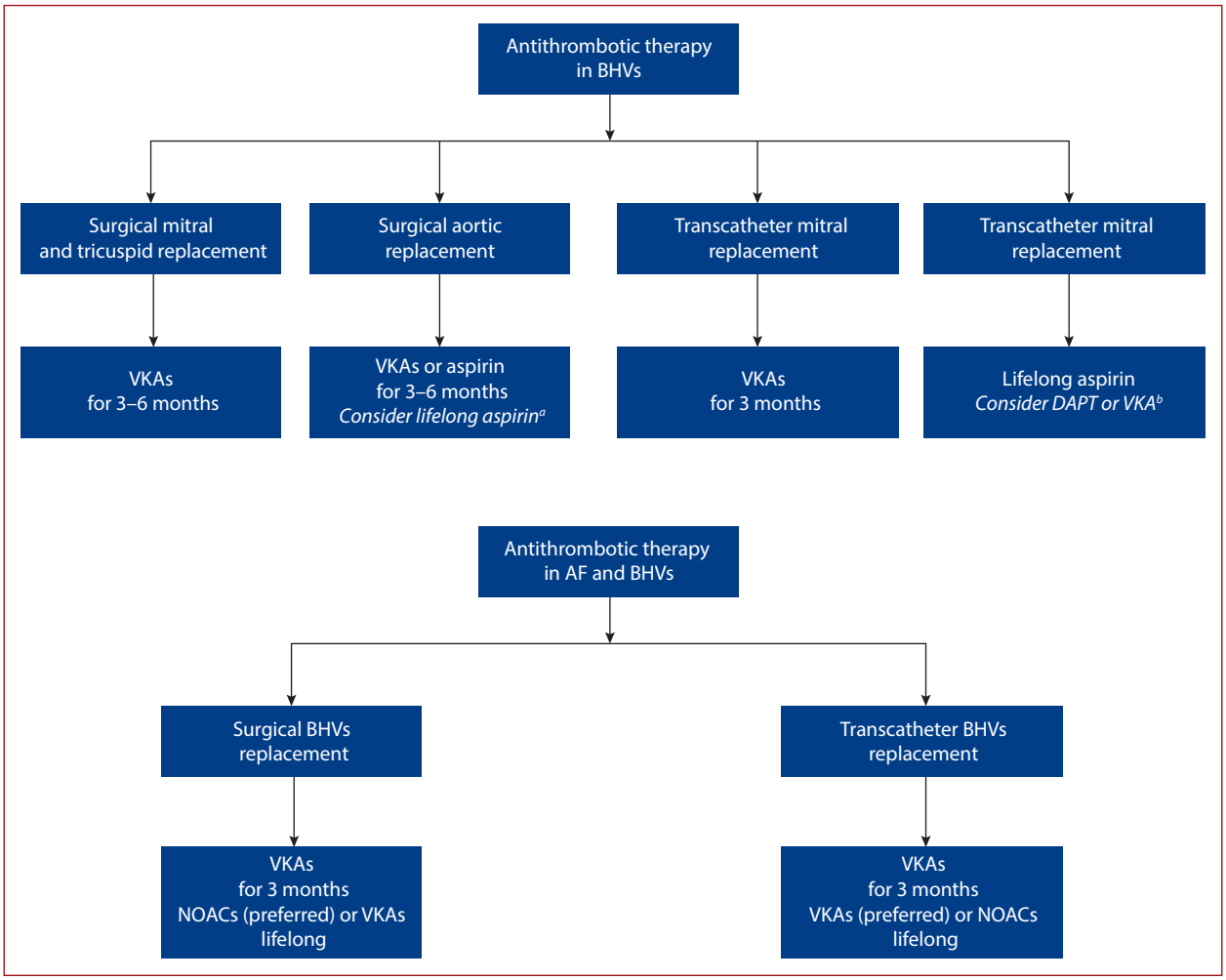

Figure 1. Proposed approach to antithrombotic therapy after bioprosthetic valve replacement
[a]Even in patients treated with VKAs in the first 3–6 months; [b]In low bleeding risk patients

Abbreviations: AF, atrial fibrillation, BHVs, bioprosthetic heart valves; DAPT, dual antiplatelet therapy (aspirin plus clopidogrel); NOACs, non-vitamin K antagonist and anticoagulants; VKA, vitamin K antagonist oral anticoagulants

On the other hand, in the AF cohort of the ATLANTIS trial (stratum 1) [15], apixaban 5 mg twice daily was found non-inferior for both the primary (composite of all-cause death, stroke, heart attack, valve thrombosis, pulmonary or systemic embolism, deep vein thrombosis or major bleeding; 21.9% vs. 21.9%; *P* = NS) and safety outcomes (0.9% vs. 1.3%; *P* >0.05) compared to warfarin.

Even if these preliminary results suggest that NOACs are comparable for the safety profile to VKAs in AF patients undergoing TAVI [47, 63–65], some concerns remain about the incidence of adverse ischemic and bleeding events [14, 62]. Finally, until more data are available, the VKA-based strategy should be preferred early after TAVI in AF patients.

DISCUSSION

There is increasing evidence that OAC therapy can play a key role in the prevention of early and late thrombotic complications in patients with BHVs, especially in those undergoing mitral or tricuspid replacement [4, 5, 16, 18, 19, 66]. The optimal duration of OAC therapy is still debated (three or six months). The life-long treatment with aspirin alone is still the standard of care for TAVI patients with no indication for long-term OAC [4, 5].

According to the international guidelines [4, 5], OAC-alone therapy is the favored strategy among AF patients undergoing BHVs replacement.

Several studies suggest a preference for NOACs over VKAs among AF patients undergoing surgical BHV replacement [7, 54, 57, 63–65]; however, most of them [48, 49, 54, 55, 57, 62–65] included patients with concomitant antiplatelet therapy leading to several biases both for thromboembolic and bleeding outcomes. Three recent metanalyses [67–69] support the use of NOACs over VKAs in AF patients with BHVs, however, the large heterogeneity of the study populations (especially for age and comorbidities) and the inclusion of different valve surgeries make it difficult to generalize the results [67]. Few data support the early use of NOACs even in the first three months [14,

54, 55]; however, the number of patients randomized in the first 3 months after the procedure is too small to draw definitive conclusions.

Among AF patients undergoing TAVI, the choice of the optimal oral anticoagulant therapy is still uncertain, due to heterogeneous results of the available studies [4, 15, 62–65]. Moreover, the conflicting results of the ENVISAGE [64] and ATLANTIS trials [46] suggest that comparative RCTs for each NOACs are needed to draw definitive conclusions since the clinical results can vary from one NOAC to another. Figure 1 shows our proposed approach for antithrombotic therapy after both surgical and transcatheter BHV replacement, in light of the data available in the literature.

CONCLUSION

Finding an optimal oral anticoagulant therapy among patients with BHVs and AF is still challenging. Despite the increasing data suggesting a preference to NOACs over VKAs among AF patients undergoing surgical BHVs replacement, further confirmatory studies are needed to clarify the clinical profile of NOACs among AF patients with BHVs in the first 3 months after intervention and among those with TAVI.

Article information

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Predictors of COVID-19 outcomes in adult congenital heart disease patients: Anatomy versus function

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Editorial
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ABSTRACT

Background: It is unclear whether patients with adult congenital heart disease (ACHD) should be considered as an increased risk population with poor outcomes when suffering from COVID-19.

Aims: This study aimed to collect clinical outcome data and to identify risk factors of a complicated course of COVID-19 among ACHD patients.

Methods: Among all outpatients who came to medical attention via telemedicine or direct physician contact at our institution between September 1, 2020 and March 31, 2021, we included all with a COVID-19 diagnosis. The incidence of COVID-19, a clinical course of the disease, and outcome were determined.

Results: One hundred and four (8.7%) out of 1 197 patients who were seen at our outpatient clinic for ACHD patients met the definition of COVID-19. Most of them reported a mild course of COVID-19 (99 [95.5%]). Five patients (4.5%) experienced severe symptoms and needed hospitalization. Two patients (1.9% of all with a confirmed diagnosis, 40% with severe infection) died. In the multivariable analysis, decreased systemic ventricular systolic function and any significant valve stenosis were predictors of a complicated disease course.

Conclusions: Our study confirmed previous results showing that a physiology-based model, rather than an anatomy-based model, better predicted COVID-19 outcomes among ACHD patients, which is of importance for patients and healthcare providers during the COVID-19 pandemic.

Key words: COVID-19, adult congenital heart disease, outcome

INTRODUCTION

The novel SARS-CoV-2 responsible for COVID-19 is known to damage the cardiovascular system, leading to increased morbidity and mortality in patients with underlying cardiovascular diseases [1]. It is unclear whether patients with adult congenital heart disease (ACHD) should be considered as an increased risk population with poor outcomes when suffering from COVID-19 as they are typically younger than those with acquired cardiac disease and are less likely to have comorbidities [2]. On the other hand, the heterogeneity of this population makes the prediction of their response to COVID-19 very challenging. In a patient with ACHD, the severity of the disease is determined not only by defective anatomy or surgical repair but also by the current physiology, as physiological variables may have a prognostic value. According to the American Heart Association/American College of Cardiology Adult Congenital Heart Disease Guidelines, the more advanced physiological stage is characterized by the presence of moderate or greater valvular heart disease (stenosis or regurgitation), moderate/severe ventricular dysfunction, hypoxemia, hemodynamically significant shunt, arrhythmias,

WHAT'S NEW?

It is unclear whether patients with adult congenital heart disease (ACHD) should be considered as an increased risk population with poor outcomes when suffering from COVID-19 as they are typically younger than those with acquired cardiac disease and are less likely to have comorbidities. We confirmed that anatomical complexity does not predict an adverse outcome. Decreased systemic ventricular systolic function and any significant valve stenosis were predictors of death or hospitalization. Our study showed that a physiology-based model, instead of an anatomy-based model, better predicts COVID-19 outcomes among ACHD patients. This information is important both for patients and medical care providers facing the next wave of COVID-19.

pulmonary arterial hypertension, Eisenmenger syndrome, or evidence of end-organ dysfunction [3]. Those with cyanotic lesions, genetic lesions, or an advanced physiological stage have been considered at the highest risk for moderate/severe COVID-19 [4, 5]. However, the results were based on small studies and need to be validated in a larger ACHD population. This study aimed to collect clinical outcome data and to identify risk factors of a complicated course of COVID-19 among ACHD patients.

METHODS

The study was conducted in a tertiary referral center for an ACHD as a retrospective registry of patients diagnosed with COVID-19. From all outpatients who had routine clinic appointments via telemedicine or direct physician contact at our institution between September 1, 2020 and March 31, 2021, we included all with a COVID-19 diagnosis (positive test for SARS-CoV-2 infection using a PCR test, antibody, and SARS-CoV-2 antigen-based ELISA or if someone had contact with an infected person in their household and developed typical symptoms).

The following variables of interest were demographic and historical medical data: body mass index (BMI), history of surgery for defects, a type of cardiac defect, the complexity of cardiac defect according to the European ACHD guidelines [6], New York Heart Association (NYHA) functional class before COVID-19, clinically relevant comorbidity, a clinical course, and an outcome of the COVID-19 disease. A severe COVID-19 was defined as death or the need for hospitalization requiring oxygen supply, non-invasive or invasive ventilation, or circulatory support. No need for hospitalization was defined as a mild course. Symptoms and infection duration were quantified and confirmed with the patient. A minimum temperature of ≥38.0°C was used to define fever. Echocardiographic data were collected from each patient's most recent echocardiogram within 12 months before infection. The following variables were assessed from standard transthoracic echocardiograms: significant (at least moderate) valvular stenosis or regurgitation (definition according to the ESC valvular heart disease guidelines), at least moderate systemic ventricular dysfunction (ejection fraction of systemic ventricular function at least 40%), or any subpulmonic ventricular dysfunction. The diagnosis of pulmonary arterial hypertension had to be confirmed by cardiac catheterization.

The local research ethics board approved the study (IK-NPIA-0021-19/1901/2021). For this type of retrospective study, formal patient consent was not required.

Statistical analysis

Continuous variables were presented as the mean (standard deviation [SD]), and categorical variables were expressed as numbers and frequencies. A univariate logistic regression model was used to determine the odds ratios (ORs) and 95% confidence intervals (CIs) for risk factors associated with hospitalization and/or death related to COVID-19. All variables with a significance threshold

Table 1. Characteristics of ACHD patients diagnosed with COVID-19

Parameters	N = 104
Age, years, mean (SD)	38.5 (12)
Male, n (%)	48 (46)
BMI, kg/m^2, mean (SD)	25.5 (4.2)
Complex CHD, n (%)	28 (26.9)
Prior intervention, n (%)	60 (57.6)
Genetic syndrome, n (%)	7 (6.7)
Baseline oxygen saturation, %, mean (SD)	95.1 (5.7)
CHD-associated PAH, n (%)	10 (9.6)
Decreased systemic ventricular systolic function, n (%)	10 (9.6)
Decreased subpulmonary ventricular systolic function, n (%)	9 (8.6)
Significant valvular regurgitation (any), n (%)	26 (25)
Significant valvular stenosis (any), n (%)	10 (9.6)
Acquired comorbidities, n (%)	39 (37.5)
Medications	
β-blockers, n (%)	44 (42.3)
ACE-I/ARB, n (%)	31 (29.8)
Diuretics, n (%)	21 (20.2)
Oral anticoagulation, n (%)	18 (17.3)
Antiplatelet therapy, n (%)	2 (1.9)
COVID-19 symptoms	
Fever, n (%)	53 (51)
Cough, n (%)	49 (47)
Shortness of breath, n (%)	18 (17)
Fatigue, n (%)	71 (68)
Anosmia, n (%)	48 (46)
Ageusia, n (%)	46 (44)
Gastrointestinal symptoms, n (%)	14 (13.5)
Hospitalization, n (%)	5 (4.5)
Death, n (%)	2 (1.9)
None, n (%)	11 (10.6)

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; CHD, congenital heart disease; PAH, pulmonary arterial hypertension; SD, standard deviation

Table 2. Characteristics of patients with severe COVID-19 infections

Age	Sex	Main diagnosis	Clinical background	SARS-CoV-2 infection course
19	Male	Repaired tetralogy of Fallot, Down syndrome	NYHA class II, decreased RV function, significant pulmonary stenosis, oxygen saturation at rest 94%, BMI 21 kg/m^2	Hospitalization due to SARS-CoV-2 bilateral pneumonia requiring non-invasive ventilation, fully recovered after 21 days after hospital admission
51	Female	Repaired tetralogy of Fallot	NYHA class II, systemic hypertension, BMI 28.1 kg/m^2	Death due to SARS-CoV-2 infection 14 days after admission (ARDS related to COVID-19 requiring intubation), renal failure
36	Female	common arterial trunk type IV (unrepaired)	NYHA class II, permanent atrial flutter/atrial fibrillation, severely reduced biventricular function, oxygen saturation at rest 76%, BMI 32.4 kg/m^2	Hospitalization due to heart failure exacerbation, SARS-CoV-2 infection during hospital stay worsening the clinical course of the disease, died suddenly on day 10 after hospital admission
31	Female	unrepaired cyanotic CHD: single ventricle, transposition of the great arteries, significant pulmonary stenosis	NYHA class II, moderate mitral regurgitation, oxygen saturation at rest 94%, BMI 17.5 kg/m^2	Hospitalization due to bilateral pneumonia requiring oxygen-therapy with a face mask fully recovered 14 days after hospital admission
51	Female	congenitally corrected transposition of the great arteries, history of ASD and VSD closure, and TV replacement	NYHA class II/III, severe systemic RV dysfunction, permanent atrial fibrillation BMI 22.5 kg/m^2	Hospitalization due to severe gastrointestinal symptoms of COVID-19 infection (gastritis) with subsequent HF exacerbation (patient required inotropic agents), fully recovered after 28 days

Abbreviations: ASD, atrial septal defect; NYHA, New York Heart Association class; TV, tricuspid valve; VSD, ventricular septal defect; other — see Table 1

of P <0.01 in the univariate model were included in the multivariable logistic regression analysis to identify independent predictors of a complicated SARS-CoV-2 infection course in ACHD patients. A two-sided P-value of <0.05 was considered statistically significant. All data were analyzed with an R software package version 4.0.0 (R Foundation, Vienna, Austria).

RESULTS

During 6 months of observation, 1197 patients were seen by cardiologists (28% were consulted via telemedicine) at our outpatient clinic for ACHD. The mean age of the entire cohort was 38.5 ±14 years. In 243 (20.3%) patients, a complex congenital cardiac defect was diagnosed. We identified 104 (8.7%) patients who met our definition for a SARS-CoV-2 infection. Overall, 89 (86%) patients had a diagnosis confirmed with testing, while in 15 (14%) patients, the diagnosis was based on clinical grounds. Table 1 summarizes the baseline characteristics of ACHD patients diagnosed with COVID-19. Most patients reported a mild course of COVID-19 disease (99 [95.5%]). Five patients (4.5%) experienced severe symptoms and needed hospitalization. Two patients (1.9% of all with a confirmed diagnosis, 40% with severe infection) died.

Table 2 summarizes details on patient characteristics and clinical history of individuals with severe COVID-19.

In the univariable analysis, decreased systemic and subpulmonary ventricular systolic function, and any significant valvular stenosis were predictors of hospitalization and/or death. In the multivariable analysis, decreased systemic ventricular systolic function and any significant valve stenosis were predictors of a complicated disease course (Table 3).

Table 3. Uni- and multivariable analysis for COVID-19 — related hospitalization and/or death

Variable	OR (95% CI)	P-value
Univariable analysis		
Age, years	1.00 (0.93–1.08)	0.98
Male sex	0.26 (0.03–2.56)	0.26
History of intervention	1.11 (0.18–6.91)	0.96
Complex CHD (vs. moderate/mild)	4.44 (0.70–28.12)	0.11
Genetic disorder	3.88 (0.37–40.29)	0.26
Baseline oxygen saturation	0.95 (0.37–1.08)	0.41
BMI, kg/m^2	0.93 (0.74–1.16)	0.52
CHD-associated PAH	2.5 (0.25–24.83)	0.43
Acquired comorbidities	2.63 (0.42–16.45)	0.30
Decreased systemic ventricular systolic function	7.58 (1.10–52.23)	0.04
Decreased subpulmonary ventricular systolic function	8.76 (1.25–61.42)	0.03
Significant valvular regurgitation (any)	2.08 (0.33–13.21)	0.44
Significant valvular stenosis (any)	7.58 (1.10–52.23)	0.04
Multivariable analysis		
Decreased systemic ventricular systolic function	20.75 (1.69–254.74)	0.02
Significant valvular stenosis (any)	20.75 (1.69–254.74)	0.02

Abbreviations: OR, odds ratio; other — see Table 1

DISCUSSION

This is the first sizable single-center report on the outcome of COVID-19 among ACHD patients in Europe. The main finding of our study is that decreased systemic ventricular function and significant valvular stenosis identify patients with a severe course of COVID-19. Our results are in agreement with the real-world data, which has already been published and confirmed the thesis that anatomical complexity itself does not predict an adverse outcome. In the first publication by Lewis et al., the authors concluded that an ACHD Physiological Stage C or D was associated with a moderate/severe COVID-19. Moderate/severe ventricular dysfunction and at least moderate valvular stenosis were among the criteria that placed patients at Physiological Stage C or D. Similarly, Broberg et al. [7] found that reduced subaortic ventricular function was predictive of a severe course. In the work by Ruperti-Repilado et al. [8], more than 90% of ACHD experts pointed out that pulmonary arterial hypertension (PAH), cyanotic heart disease, and

Fontan palliation are the most important factors of an unfavorable outcome. In our analysis, neither baseline oxygen saturation, PAH, nor ACHD complexity were important as outcome predictors. These results provide important knowledge regarding our current perception of risks and shift us away from an anatomy- to a physiology-based model.

In the article by Schwerzmann et al. [4], the authors demonstrated that general risk factors (age, obesity, and multiple comorbidities) may predict a complicated course of COVID-19. Obesity is a well-known risk factor for a severe course of COVID-19, along with hospitalization, transferto the intensive care unit, being put on a ventilator, and, finally, dying [10]. This was not the case in our study as in our cohort the mean BMI was 25.5 kg/m^2 — much lower than reported by others [3, 7]. Acquired comorbidities (systemic hypertension, diabetes, atrial fibrillation, or ischemic heart disease) are infrequent in the ACHD population. We found them in 39 (37.5%) cases and did not demonstrate they influenced the COVID-19 outcome. Older age was a risk factor for COVID-related death in ACHD and the general population. In our population, it has not been shown to be an important prognostic factor. Although the mean age and the frequency of acquired cardiac risk factors were comparable with previously published reports, this phenomenon remains to be explained.

This is the first study in which an attempt was made to determine the rate of infection among the ACHD population. In a small series of patients with Fontan circulation from Italy, the authors estimated that the 1-year COVID-19 incidence was 11% [11]. During the autumn and winter of 2020/2021, our outpatient clinic treated 1 197 ACHD patients. Yet only 104 (8.7%) of them were COVID-19 positive. Of these, only 5 patients had a severe course and 2 died, resulting in an overall case/fatality ratio (in those tested) of 1.9%. Broberg et al. [7] reported a similar case/fatality ratio at the level of 2.3%. Our results concern the period before the common vaccination program and during the first year of the COVID-19 pandemic.

The ACHD patients are known to greatly benefit from prompt access to continuous expert care. Authors from Italy reported cancellation of all elective hospital procedures during the first year of the COVID-19 pandemic but stable the overall number of urgent hospital admission during that time [12]. Our center did not restrict access to medical care. In response to patients' requests, we implemented new alternative ways of communication. Twenty-eight percent of consultations were carried out using telemedicine.

The spectrum of COVID-19 symptoms in our population was like those described in other ACHD cohorts [13], with fatigue and fever being the most frequent (68% and 51%, respectively). Notably, 10.6% of patients were completely asymptomatic; diagnoses were made incidentally through COVID-19 PCR testing, after a known exposure, or through the SARS-CoV-2 antibody test. As the ACHD population is relatively young, the real proportion of patients who had COVID-19 may be higher.

Study limitations

The limitation of our study is its retrospective design. We did not test every patient treated at our outpatient clinic for SARS-CoV-2. As we know, some patients have asymptomatic infections; this implies that other asymptomatic carriers were likely to be among this population. The preceding limitations suggested that the true case/fatality ratio might be lower, and on the other hand, the rate of SARS-CoV-2 infections might be higher. Our study focused on short-term death and serious complications and did not address potential medium and long-term complications. Further studies on the longer-term consequences of COVID-19 in ACHD are needed. We are also aware that the logistic regression model performed for our dataset with few events involves some uncertainty, and the results should be interpreted with caution.

CONCLUSIONS

In conclusion, our study confirmed previous results showing that a physiology-based model, instead of an anatomy-based model, better predicts COVID-19 outcomes among ACHD patients. This information is important both for patients and medical care providers facing the next stage of the pandemic.

Article information

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Conflict of interest: None declared.

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Changes in right ventricular morphology and function in patients undergoing cardiac surgery: A 3D echocardiographic study

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ABSTRACT

Background: An impairment of standard echocardiographic parameters of right ventricular (RV) function is a known phenomenon in patients undergoing cardiac surgery, but its significance remains unclear.

Aims: This study aimed to assess changes in RV function in patients undergoing cardiac surgery using speckle tracking and 3D echocardiography.

Methods: The study population comprised 122 patients referred for cardiac surgery. Transthoracic echocardiographic (TTE) examinations were performed: before the surgery (TTE1), 1 week after surgery (TTE2), and 1 year after surgery (TTE 3). Parameters measured during these examinations included both standard and advanced indices of the RV size and function, as well as a new parameter introduced by our team — RV shortening fraction (RV SF).

Results: TTE1 was performed on average (standard deviation [SD]) 24 (15) hours before surgery, whereas TTE2 and TTE3 were performed on average 7.2 (3) days and 346 (75) days after the surgery, respectively. A postoperative impairment of parameters of RV longitudinal function was observed (P <0.001). However, neither the RV size assessed by both 2D and 3D techniques changed, nor the global RV function measured with the use of fractional area change and ejection fraction. Additionally, during the postoperative period, an increase in the value of an RV SF by 12.9% was observed. After 12 months we observed an improvement in the parameters of the longitudinal RV function.

Conclusions: Uncomplicated cardiac surgery causes transient impairment of the longitudinal systolic RV function, with no influence on the global RV function. The preservation of global function results from increased RV SF. After 12 months, an improvement of the longitudinal function can be observed.

Key words: 3D echocardiography, cardiac surgery, right ventricular function

INTRODUCTION

The right ventricular (RV) function is recognized as an important factor influencing the course of numerous cardiovascular pathologies. It has been proved that preoperative RV dysfunction is a strong risk factor for death in patients undergoing cardiac surgery; it is also associated with an increased risk of perioperative complications [1–4]. This underlines the importance of accurate preoperative assessment of RV function to improve risk stratification and the need for early accurate postoperative monitoring to optimize treatment [5, 6]. Currently, tricuspid annular longitudinal excursion (TAPSE) and RV S' (systolic velocity of the tricuspid annulus measured by tissue Doppler) are the most frequent echocardiographic parameters. Studies based

WHAT'S NEW?

An impairment of standard echocardiographic parameters of right ventricular (RV) function is a known phenomenon in patients undergoing cardiac surgery. However, little is known about the significance of these alterations for global RV function. In our study, we clarify this issue using novel echocardiographic techniques: 3D assessment of RV volume and function, as well as a speckle tracking technique. In the postoperative period after uncomplicated cardiac surgery, we observed transient changes in the geometry of the right ventricle, as well as impairment of its longitudinal function with a simultaneous compensatory increase in other components of the RV function, which enable to maintain global RV function at the unchanged level. This observation was possible owing to the introduction of a new parameter: RV shortening fraction (RV SF) by our team. In the follow-up examination, an improvement of parameters reflecting the function of the RV longitudinal fibers can be observed.

on these indices suggested RV functional impairment following cardiac surgery [1, 7, 8]. However, these parameters provide insight into the longitudinal function of the RV free wall and do not necessarily reflect global RV function [9]. The development of novel echocardiographic techniques, including 3D echocardiography, allows accurate evaluation of RV volume and function [10, 11].

The purpose of this study was to assess the impact of cardiac surgery on the morphology and function of the right ventricle assessed by both standard echocardiographic parameters, as well as advanced echocardiographic techniques including speckle tracking and 3D echocardiography.

METHODS

Study group

One hundred twenty-two consecutive adult patients (92 [75.4%] men), mean (standard deviation [SD]) age 65 (11) years with coronary artery disease and/or significant left-sided valvular disease referred for cardiac surgery in our center were included in this prospective study. The referrals were based on heart-team decisions.

The exclusion criteria included RV enlargement or dysfunction at baseline, a history of RV infarction, severe chronic disease significantly affecting prognosis, atrial fibrillation, previous cardiac surgery, planned tricuspid valve repair, pulmonary artery systolic pressures >40 mm Hg, perioperative myocardial infarction, poor quality of echocardiographic views excluding the possibility of analysis.

Concomitant diseases present in our study group were diabetes (26.2%), hypertension (73.8%), and hypercholesterolemia (79.5%). Twenty-six patients (21.3%) had a history of myocardial infarction.

Cardiac surgery

Coronary artery bypass surgery (CABG) was performed in 81 (66.4%) patients, out of whom 71 (58.2%) patients underwent bypass surgery on a beating heart (off-pump coronary artery bypass grafting, OPCAB). In the remaining group, isolated valve surgery was performed in 32 (26.2%) patients, whereas concomitant valvular surgery and CABG were performed in 9 (7.4%) patients.

Table 1. Surgical procedures in the studied group of patients (n = 122)

Procedure, %	Number of patients (n)	Prevalence
OPCAB	71	58.2
On-pump CABG	9	7.4
CABG + AVR	4	3.3
CABG + MV annuloplasty	2	1.62
CABG + aortic aneurysm surgery (Bentall procedure)	3	2.5
MV annuloplasty	2	1.62
MVR	6	4.92
AVR	22	18
AVR + aortic aneurysm surgery (Bentall procedure), aortic root/aneurysm surgery	2	1.62
AV + MV plastic surgery	1	0.82

Abbreviations: AVR, aortic valve replacement; CABG, coronary artery bypass grafting; MV, mitral valve; MVR, mitral valve replacement; OPCAB, off-pump coronary artery bypass grafting

The majority of surgeries were performed by a full midline sternotomy. Only 9 (7.4%) patients underwent minimally invasive surgery. More detailed characteristics for surgical procedures are presented in Table 1.

Study protocol

Transthoracic echocardiography (TTE) was performed before cardiac surgery (TTE1), 1 week after surgery (TTE2), and 1 year after surgery (TTE3).

The study protocol was approved by the local Ethics Committee, and all study participants signed written informed consent.

Echocardiography

Transthoracic echocardiographic studies were performed by a single experienced echocardiographer with the use of the GE Vivid 9 ultrasound system (General Electric Healthcare, Boston, MA, US). The imaging protocol included full echocardiographic examination according to current guidelines [12, 13].

Numerous RV dimensions listed in Table 2 were measured using 2- and 3-dimensional echocardiography (Figure 1). Moreover, the following parameters of RV function were measured: tricuspid annular longitudinal excursion (TAPSE), systolic tissue Doppler velocity of the tricuspid annulus (RV S'), and fractional area change (FAC)

Table 2. Right ventricular dimensions measured during echocardiographic examinations

Parameter	Echocardiography			*P* pre- vs. postoperative	*P* preoperative vs. follow-up
	Pre-operative mean (SD)	Post-operative mean (SD)	Follow-up mean (SD)		
RV D1, mm	35 (5)	34 (6)	36 (5)	0.03	0.08
RV D2 diast, mm	25.6 (4)	24.5 (5)	25.9 (4)	0.02	0.4
RV D2 syst, mm	18.4 (3.4)	17 (4)	18.2 (4)	<0.001	0.8
RV D3, mm	66.7 (7.5)	69 (8)	67.8 (7.6)	0.01	0.2
RVOT 1, mm	28 (3)	26.9 (3)	27.5 (3)	0.001	0.2
RVOT 2, mm	29.3 (4)	27.4 (3)	28.6 (3)	<0.001	0.6
RVOT 3, mm	23.7 (3.5)	21.6 (3)	23.4 (2.5)	<0.001	0.3
TV annulus, mm	29.3 (4)	28.9 (5)	31 (5)	0.3	0.08
RV wall thickness, mm	4.5 (0.6)	4.6 (0.8)	4.6 (0.8)	0.8	0.6
RV EDA, cm^2	15.4 (4)	15.8 (4)	16,6 (4)	0.7	0.08
RV EDAI, cm^2/m^2	8.2 (2)	8.4 (2)	8.8 (2)	0.6	0.1
RV ESA, cm^2	9.8 (3)	10 (3)	10.3 (3)	0.3	0.06
RV ESAI, cm^2/m^2	5.2 (1.6)	5.3 (1.6)	5.5 (1.6)	0.3	0.08
RV EDV, ml	114 (27)	116 (24)	116.5 (18)	0.7	0.4
RV EDVI, ml/m^2	61 (14)	62 (13)	62 (10)	0.7	0.3
RV ESV, ml	61.6 (19)	63.6 (15)	62 (11)	0.8	0.4
RV ESVI, ml/m^2	32 (10)	34 (8)	33 (6)	0.8	0.3
RA, mm	34.6 (6)	32 (7)	35.7 (5)	<0.001	0.1
RAA, cm^2	14 (4)	13.5 (4)	15 (3.5)	0.09	0.09

Abbreviations: EDA, end-diastolic area; EDAI, end-diastolic area indexed to BSA; ESA, end-diastolic area; ESAI, end-systolic area indexed to BSA; RA, right atrium; RAA, right atrium area; RV, right ventricular; RVD1, basal RV linear dimension; RVD2 diast, mid-cavity RV linear dimension in diastole; RVD2 syst, mid-cavity RV linear dimension in systole; RVD3, long-axis RV linear dimension; RVOT, right ventricular outflow tract; RVOT 1-PLAX, RVOT measured in parasternal long-axis LV view; RVOT 2, proximal RVOT measured in parasternal short-axis view; RVOT 3, distal RVOT measured in parasternal short-axis view; TV, tricuspid valve

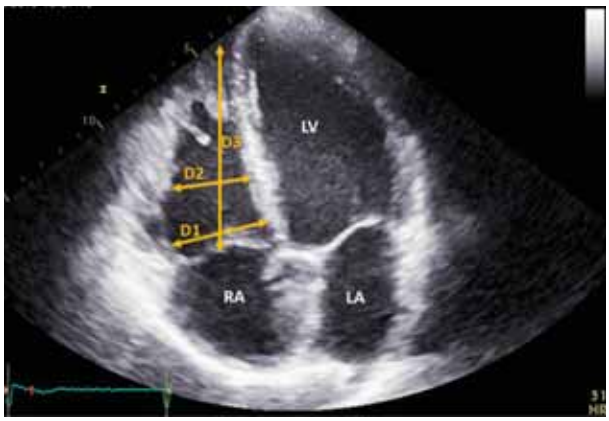

Figure 1. Apical 4-chamber view focused on the right ventricle. Example of measurement of basal (D1) and mid-cavity (D2) transverse dimensions, as well as a linear dimension (D3). The measurements of D2 in end-systole and end-diastole were used for the calculation of the right ventricular shortening fraction = (D2 diast – D2 syst)/ /D2 diast

Abbreviations: LA, left atrium; LV, left ventricle; RA, right atrium

[14, 15]. The echocardiographic quantitative assessment of the RV systolic function also included RV free wall longitudinal strain (RV FWSL) measurement based on the speckle tracking technique [16]. Additionally, we acquired 3D datasets enabling off-line calculation of RV volumes and ejection fraction (3D RV EF) using EchoPAC SW 202 (GE Healthcare, Boston, MA, US) [17]. Furthermore, the newly introduced parameter was assessed — RV shortening fraction (RV SF), calculated as the percentage shortening of the mid-cavity linear dimension of the right ventricle in the 4-chamber apical view.

Statistical analysis

All quantitative variables were initially subjected to an analysis of compliance with the normal distribution assessed in Kolmogorov-Smirnov's test. Normally distributed variables are expressed as mean (SD). Categorical variables are presented as percentages (%). A paired 2-tailed Student's t-test was used to test for difference in each of the echocardiographic variables between TTE1 and TTE2 and between TTE1 and TTE3. After a Bonferroni correction based on comparing the two primary echocardiographic endpoints, statistical significance was assumed when $P = 0.025$. All analyses were performed using MedCalc Software, Frank Schoonjans, Belgium.

RESULTS

Five patients died during the perioperative period (between the 3rd and the 14th day after cardiac surgery). Within one year of follow-up, no patient underwent myocardial infarction or developed new congestive heart failure. One patient died one month after hospital discharge.

TTE1 was performed on average (SD) 24 (15) hours before cardiac surgery (range 4–48 hours), whereas TTE2 and TTE 3 were performed on average (SD) 7.2 (3) days (range 3–17 days) and 346 (75) days after cardiac surgery.

Preoperative echocardiography was performed in all patients (n = 122), the postoperative examination was available in 117 patients, whereas follow-up examinations

Table 3. Values of parameters assessing the right ventricular function recorded during echocardiography performed preoperative, postoperative, and control (after one year)

Parameter	Echocardiography			*P* pre- vs. postoperative	*P* preoperative vs. follow-up
	Pre-operative mean (SD)	Post-operative mean (SD)	Follow-up mean (SD)		
RV FWSL, %	–23.4 (5)	–12.2 (4)	–19 (8)	<0.001	<0.001
TAPSE, mm	24 (4)	13.4 (2.5)	20.4 (4)	<0.001	0.001
RV S', cm/s	11.7 (2.3)	8 (2)	10.6 (2)	<0.001	<0.01
RV SF, mm	28 (7.6)	31.6 (10)	29.7 (8)	0.005	0.09
RV FAC, %	37 (10)	35.7 (11)	37.6 (6)	0.1	0.6
3D RV EF, %	46.4 (8)	45.3 (6)	46.2 (7)	0.2	0.2
RVSVI, ml/m^2	27.7 (7)	28 (6)	28.6 (6)	0.5	0.8

Abbreviations: RV, right ventricular; FAC, fractional area change; 3D EF, 3-dimensional ejection fraction; FWSL, free wall longitudinal strain; RV S', systolic velocity of the tricuspid annulus; SF, shortening fraction; SVI, stroke volume indexed to BSA; TAPSE, tricuspid annular longitudinal excursion

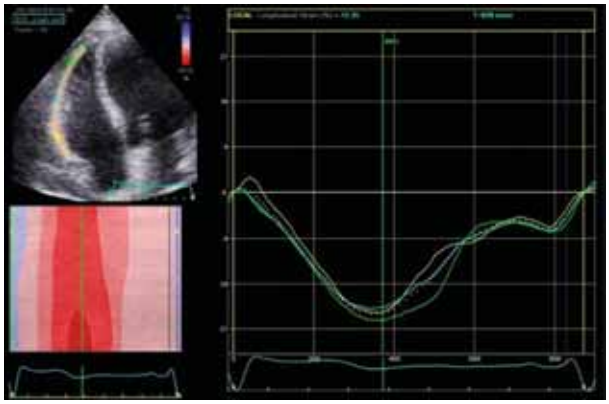

Figure 2. Quantitative evaluation of right ventricular function using speckle tracking echocardiography in apical 4-chamber view

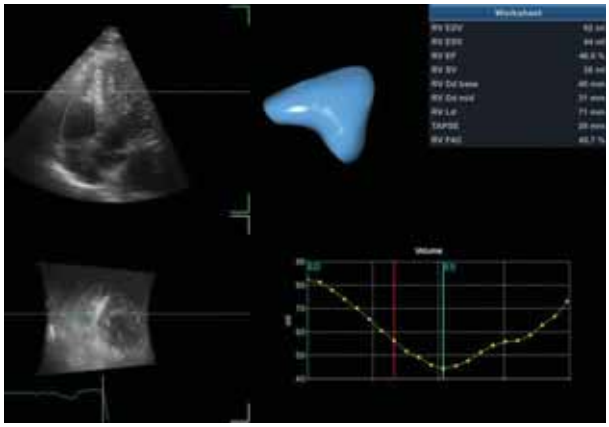

Figure 3. The RV model based on 3D echocardiography allowing measurement of RV volumes and ejection fraction

Abbreviations: RV, right ventricular

were performed in 116 patients. Due to the suboptimal image quality, 9.3% of segments were excluded from the RV FWSL analysis, and 11 (9%) patients were excluded from 3D assessment in the preoperative study. In the post-operative examination, 14% of the segments were excluded from the RV FWSL assessment and 25 (20.5%) patients from the 3D assessment. Eleven percent of segments and 12 (10%) patients were excluded from the study after one year.

Changes in RV morphology

Preoperative examination showed normal RV dimensions in all patients (Table 2). In the postoperative echocardiographic examination, a decrease in the diameter of the RV outflow tract and mid-cavity transverse dimension of the right ventricle (D2) was noted, while the mean longitudinal dimension (D3) increased (Figure 1). For the other parameters reflecting the RV size, including systolic and diastolic area, as well as 3D end-systolic volume and 3D en-diastolic volume, no significant difference was found between pre- and postoperative examination (Table 2).

The follow-up echocardiography showed a withdrawal of postoperative changes and return to baseline ranges.

Changes in RV function

In preoperative examination parameters of RV systolic function were within the normal range in all patients.

In the postoperative examination, a reduction in the mean values of TAPSE, RV S' and RV FWSL (Figure 4) was observed (Table 3, P <0.001). However, there were no significant changes in the mean FAC, 3D RV EF, and the 3D stroke volume index. In the postoperative study the RV SF value increased compared to preoperative examination (from 28% [7.6%] to 31.6% [10%]; P = 0.005).

The follow-up echocardiography showed improvement of RV longitudinal systolic function — TAPSE, RV S', RV FWSL, but their values were still slightly lower than at baseline, yet within the normal range. There were no significant changes in RV FAC, 3D RV EF, or 3D RV stroke volume indexed (Table 3). Figure 4 shows the TAPSE, RV FAC, and 3D RV EF plots assessed at three time points.

The mean (SD) left ventricular EF in the studied group of patients in the preoperative, postoperative, and control studies at one year was 49% (9%), 50.5% (8%), and 52.5% (7.4%), respectively.

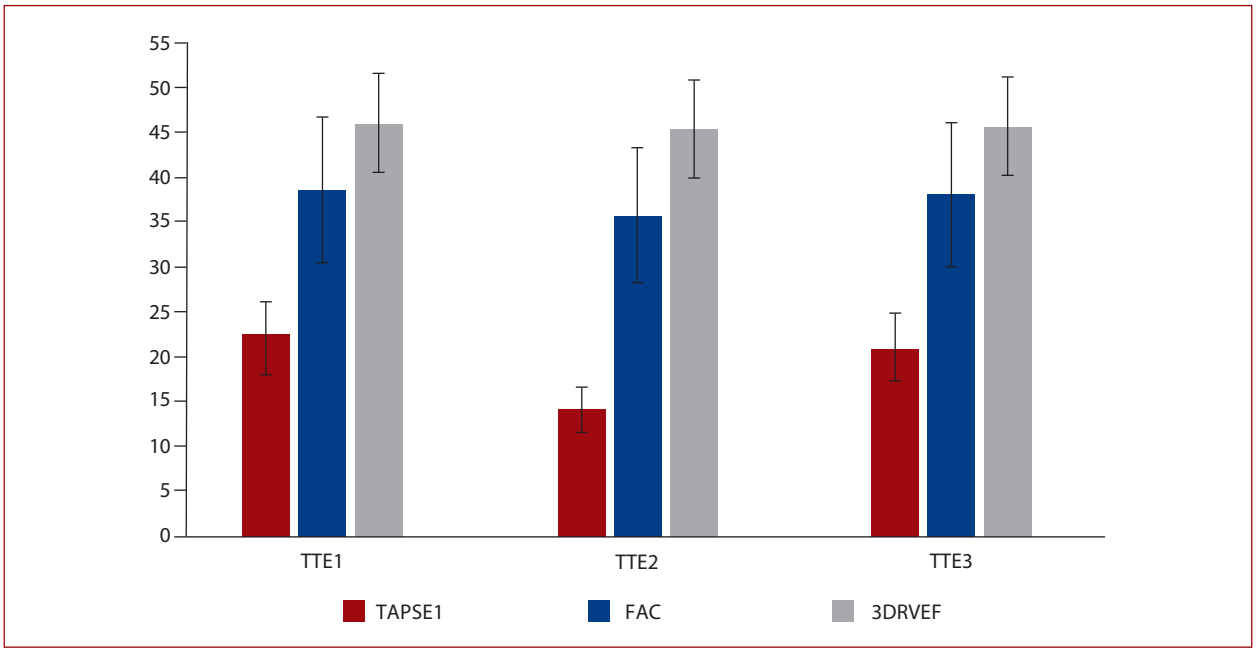

Figure 4. Plots demonstrating mean values and standard deviations of TAPSE, RV FAC, and 3D RV EF, assessed at 3 time points: before cardiac surgery (TTE1), during the postoperative period (TTE2), and after one-year follow-up (TTE3)

Abbreviations: RV FAC, right ventricular fractional area change; TAPSE, tricuspid annular longitudinal excursion; TTE, transthoracic echocardiography

DISCUSSION

We have demonstrated that RV shape and geometry, but not volume, undergo complex changes after uncomplicated cardiac surgery. We observed transient impairment of RV longitudinal function, which did not result in the impairment of global function assessed by both 2D and 3D echocardiography. This was due to a compensatory increase in circumferential and transverse function, as demonstrated by a new proposed parameter — the RV shortening fraction. These findings highlight the need for using more detailed parameters than TAPSE and RV S' in all patients undergoing cardiac surgery to properly diagnose perioperative RV global dysfunction.

The transient changes in the RV shape observed after cardiac surgery are expressed by a decrease in the diameter of the RV outflow tract and the mid-cavity RV transverse dimension with simultaneous RV elongation (an increase in the value of long-axis RV linear dimension — D3). It should be noted that the change in the values of the linear parameters was not accompanied by changes in the RV systolic and the diastolic surface area or its volume determined by the 3D method.

These observations add to currently existing scarce data on the RV size in patients undergoing cardiac surgery. In a group of 35 patients, Alam et al. [18] showed that the linear RV dimension decreased from 29 (4) mm to 28 (3) mm one month after the surgery and returned to baseline one year after the procedure. Tamborini et al. [19] compared RV volume before and after 3, 6, and 12 months following the cardiac surgery in a group of 40 patients. They did not observe a change in RV volume at any of the time points despite the post-operative reduction of RV performance along the long axis suggested by TAPSE and RVS'. The results of this study are consistent with our observations on a larger group — we did not notice a significant change in RV volume (or area) in the examination performed in the postoperative period.

The decrease in TAPSE and RV S' after cardiac surgery has been well documented [20, 21]. Yadav et al. [22] described selective RV impairment in 20 patients found on the basis of RV S' 3 months post CABG. Similarly, Diller et al. [23] evaluated the effect of CABG on ventricular function in a group of 32 patients. In the postoperative period (5 days after surgery), impairment of RV S' was observed without deterioration of left ventricular function. These observations were interpreted as isolated impairment of RV function, without changes in left ventricular function parameters or impairment of clinically assessed exercise capacity.

Similar to our findings, Bitcon and Tousignant [24] showed in a small group of 21 patients no effect of cardiac surgery on RV function measured with the use of FAC, whereas TAPSE, RV S', and RV free wall strain significantly deteriorated. Also, Khani et al. [25], who analyzed 30 patients undergoing coronary artery bypass grafting, observed postoperative deterioration of TAPSE, RV S' and longitudinal deformation of the RV free wall, while in the control examination, after three months, there was a slight improvement of these parameters.

Importantly, the analysis of 3D echocardiography in patients operated on in our center did not show any significant effect of cardiac surgery on the RV function.

The RV ejection fraction and indexed RV ejection volume remained unchanged in the study performed 7 days after cardiac surgery compared to the preoperative study. Similar results were described in a previous smaller study, where 40 patients were examined using transthoracic 2D and 3D echocardiography pre- and 3, 6, and 12 months after surgery. The 3D assessment of RV function showed unchanged 3D RV EF throughout the entire observation period despite a decrease in RV longitudinal fiber function parameters [17].

Rösner et al. [26] described similar observations on echocardiography and magnetic resonance imaging in a group of 57 patients undergoing cardiac imaging in the perioperative period and at 8–10 months after surgery. The authors postulated a slightly different etiology of changes observed in TAPSE — they observed the increase in RV sphericity in the post-CABG period and attributed this change to altered constraint and pressures caused by the opening of the pericardium during surgery. Rösner et al. [26] also found that despite the more spherical shape of the RV, there was no loss in systolic function based on various parameters including RVEF and SV by magnetic resonance imaging. The etiology of the decrease in TAPSE was interpreted as secondary to the morphologic changes present after differences in constraint of the RV by the pericardium in the early postoperative period.

All these data indicate the deterioration of the function of longitudinal fibers in patients undergoing cardiac surgery without impairment of global RV function. In an attempt to characterize this phenomenon, we introduced a new echocardiographic parameter — RV SF, which describes the shortening of the mid-cavity RV dimension in a 4-chamber apical view. It is a simple indicator enabling the assessment of the presence of a compensatory increase in non-longitudinal components of the RV systolic function. In the postoperative examination, the RV SF value increased significantly, thus compensating for impaired longitudinal function.

Limitations of the study

Compared to previous studies on this subject, we enrolled a large group of patients, but they were all operated in one center using standard access. Therefore, we believe that the described phenomena should be confirmed in a multicenter study. A larger group of patients and inclusion of cardiac surgeries complicated with RV infarction would allow us to determine the criteria for RV longitudinal function impairment indicative of global function impairment.

When using the speckle tracking technique, we measured only the longitudinal deformation of the RV free wall. Theoretically, it would be possible to assess transverse strain, but such measurements are not well validated.

CONCLUSIONS

In the postoperative period after uncomplicated cardiac surgery, we observe transient changes in the geometry of the right ventricle, as well as impairment of its longitudinal function with a simultaneous compensatory increase in other components of the RV function, which leads to the maintainance of global RV function at the unchanged level. In the follow-up examination (one year after surgery), an improvement of parameters reflecting the function of the RV longitudinal fibers can be observed.

Article information

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Incremental value of volumetric quantification for myocardial perfusion imaging by computed tomography

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ABSTRACT

Background: The extent of myocardial ischemia is the crucial prognostic factor for interventional treatment decision making for coronary artery disease. The ability of computed tomography perfusion (CTP) to provide the missing volumetric information and its clinical value remains unknown.

Aims: The study aimed to compare a novel ischemic volume quantification method based on dynamic computed tomography perfusion (VOL CTP) with other CT-based imaging modalities for revascularization prediction.

Methods: In this prospective study, 53 (25 females, 63.5 [8.5] years old) consecutive symptomatic patients with 50%–90% coronary artery stenosis (n ≥1) on coronary computed tomography angiography underwent computed-tomography-derived fractional flow reserve (CT-FFR) analysis and dynamic CTP. We calculated the percentage of myocardial ischemia on the CTP-derived images. A 10% cut-off was used to define functionally significant ischemia. The outcomes include coronary revascularization during the follow-up of 2.5 (interquartile range, 1.4–2.8) years. Physicians were blinded to the results of CTP and CT-FFR.

Results: Of the 53 patients in the study (68 arteries with 50%–90% stenosis), 16 underwent revascularization (12 elective, 4 event-driven). In the CTP quantitative analysis, 26 patients had ischemia. Overall, 18 patients had ischemia ≥10% on volumetric ischemia quantification based on dynamic computed tomography perfusion (VOL CTP), and 28 patients had CT-FFR <0.8. VOL CTP, standard CTP, CT-FFR, and computed tomography coronary angiography (CTA) ≥70% performed well for the prediction of total revascularization. Area under the curve was 0.973 vs. 0.865, vs. 0.793, vs. 0.668, respectively. The VOL CTP with ≥10% cut-off was superior to the CT-FFR, standard CTP, and CTA ≥70% (P <0.001; P = 0.002 and P <0.001 respectively).

Conclusions: VOL CTP quantification is feasible and adds important, actionable information to that provided by standard CTP or CT-FFR in patients with 50%–90% coronary artery stenosis.

Key words: computed tomography fractional flow reserve, computed tomography myocardial perfusion, dynamic computed tomography perfusion, myocardial ischemia

INTRODUCTION

Coronary computed tomography angiography (CTA) is recommended as the initial test for diagnosing coronary artery disease (CAD) in symptomatic patients in whom obstructive CAD cannot be excluded through clinical assessment alone [1]. Importantly, the anatomical assessment of the coronary arteries through anatomic methods is insufficient to predict functionally significant CAD in most (50%–90%) coronary artery stenosis cases [2]. To make appropriate decisions regarding further management, these patients usually require additional functional testing with regard to both the presence and the burden of ischemia. Recently, computed-tomography-derived fractional flow reserve (CT-FFR) and dynamic computed tomography perfu-

WHAT'S NEW?

Our study delved into the untapped potential of dynamic computed tomography perfusion (CTP) examination and provided new information on the feasibility, optimal method, and clinical value of the additional volumetric myocardial ischemia assessment. Its main finding is that volumetric CTP adds incremental value to the traditional CTP or computed-tomography-derived fractional flow reserve (CT-FFR) in identifying patients requiring coronary revascularization in a long-term follow-up. According to our data, the new method may better facilitate decisions on what invasive therapies to use to improve the patient's prognosis. Our results underline the importance of ischemic volume quantification for the appropriate planning of interventional therapies in chronic coronary syndromes and allow for the identification of outpatients with a smaller ischemic area who may not benefit from revascularization.

sion (CTP) have been increasingly tested for the assessment of the functional significance of coronary stenosis [3–5]. Despite the suggested equivalence of the diagnostic values of CT-FFR and dynamic CTP, however, both imaging modalities have unique advantages and disadvantages [3–5]. CT-FFR requires a high-quality CTA scan and preferably a lower calcium score, whereas dynamic CTP needs additional radiation but is more robust in patients with compromised quality coronary CTA or high calcium loads [4, 5].

One of the seminal considerations in the functional assessment of CAD is the myocardial ischemic burden. The invasive therapies are endorsed particularly for patients with a large ischemic area defined as >10% of the left ventricle (LV) because in such cases, coronary revascularization can improve the outcome [6]. CT-FFR does not offer such an assessment, but volumetric ischemia assessment may theoretically be done via CTP. Despite the potential added clinical value of volumetric perfusion deficits, the previous studies on CTP have not addressed this issue [7].

Therefore, our study aimed to develop a method for volumetric ischemia quantification based on dynamic CTP (VOL CTP) and evaluate its potential clinical impact in the context of CT-based anatomic and functional CAD diagnostic methods.

METHODS

Study population and follow-up

Patients who had undergone CTA due to suspected CAD and those with ≥1 50%–90% coronary artery stenosis were recruited for the ULYSSES study. The study exclusion criteria were symptoms of unstable coronary artery disease or acute coronary syndrome, the history of myocardial infarction, the history of percutaneous coronary intervention (PCI) or coronary artery bypass grafting, the glomerular filtration rate (GFR) <60 ml/min/1.72 m^2, body mass index (BMI) >35 kg/m^2, contraindications to computed tomography (including pregnancy, etc.); contraindications to the administration of an iodine contrast media or regadenoson; heart failure with reduced ejection fraction, a significant valvular heart disease, aortic aneurysm or aortic dissection; persistent atrial fibrillation or atrial flutter; hypertrophic cardiomyopathy. All patients had a 12-lead ECG before study examinations.

Clinical outcomes

Our study was part of the ULYSSES study (ClinicalTrials.gov NCT03917199). Caring physicians were blinded to the CTP and CT-FFR results. The patients were referred for invasive coronary angiography based on the clinical pathway recommended by the European Society of Cardiology (ESC) [1, 6]. The elective revascularizations were ischemia-guided (non-invasive imaging including CMR or invasive FFR). All the elective therapeutic procedures were completed 6 months after the initial examination. In all the patients who underwent non-elective revascularization, either invasive FFR or the evidence of acute ischemia according to the ESC Fourth Universal Definition of Myocardial Infarction was used as appropriate to guide revascularization [1, 6, 9].

Follow-up information was gathered through a review of the patients' hospital records and telephone interviews with the patients at a median of 2.5 (1.4–2.8) years from study enrolment. Elective and total (elective and event-driven) revascularizations were used as the study outcomes. No deaths were recorded.

The study protocol complied with the Declaration of Helsinki and received approval from the Ethics Committee at the National Institute of Cardiology. All the patients gave their written informed consent.

Computed-tomography angiography protocol and analysis

Coronary CTA was performed on a dual-source Somatom Force CT scanner (Siemens, Forchheim, Germany). Sublingual nitrates were administered before scanning in all the patients. If necessary, β-blockers were administered intravenously, targeting a heart rate of <70 bpm. The protocol for CTA image acquisition was recommended to comply with the guidelines [10]. Assessment of luminal stenosis was performed by an experienced reader (MK/CK >16 years' experience with CTA) using an 18-segment coronary model with CT coronary application through the Syngo.via software (Siemens Medical Systems). The calcium score was calculated according to the Agatston method. For all the

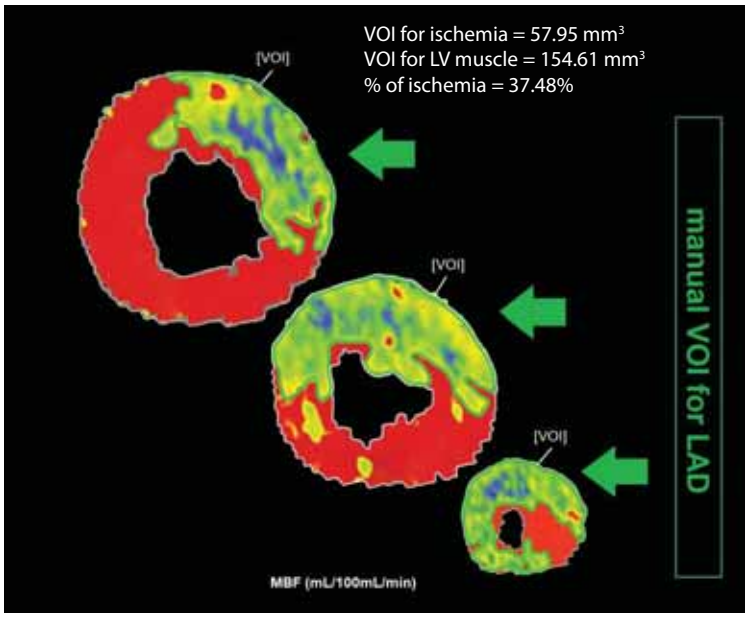


Figure 1. Methodology of volumetric perfusion analysis. Sample methodology of the volume of interest (volume of interest, green arrows) measurement at short-axis heart cross-sections (only selected ones are presented) and percentage of ischemia calculation

patients, the CAD reporting and data system (CAD-RADS) was evaluated.

Computed tomography-derived fractional flow reserve analysis

CT-FFR calculations were performed on the coronary CTA datasets onsite using the cFFR version 3.2.0 research software (Siemens, Germany) with previously validated diagnostic performance [11–14]. The software allows the computation of CT-FFR values in selected locations of the coronary tree and displays the CT-FFR values along the vessel in the form of color-coded coronary artery filling.

Data preparation required acceptance or correction of the luminal center lines and contours automatically generated by the software. The observer then marked any stenotic lesions before the software generated a patient-specific, three-dimensional mesh of the coronary artery tree (MD) validated by a second observer (MK). All discrepancies were resolved by consensus. The simulated CT-FFR value was established by one observer (MK), who was blinded to the CTA and CTP results. The CT-FFR value was measured 40 mm distal to the minimal luminal area [13]. CT-FFR <0.80 was considered significant.

Computed tomography perfusion protocol

The recruited patients underwent dynamic CTP using a dual-source CT scanner (Somatom Force, Siemens, Germany). A detailed description of the CTP protocol was published previously [8].

Computed tomography perfusion data analysis

The anonymized CTP data were analyzed by an experienced reader (AO, >10 years' experience with CTA and >5 years' experience with CTP) in a core lab at the National Institute of Cardiology in Warsaw, Poland. The interpretation differences were resolved through consensus with the second experienced reader (MK/CK >16 years' experience with CTA and >5 years' with CTP). The readers were blinded to the clinical history of the patients and the CTA results. Semi-automatic analyses of the dynamic CTP images were done using commercial software (CT Myocardial Perfusion, Siemens, Germany). Motion correction was applied if needed to correct the breathing-related artifacts or artifacts due to extrasystole. The endocardial and epicardial contours of the left ventricle (LV) were segmented automatically, with manual correction if needed. The images were analyzed with a constant window width/level for all the patients.

The CTP standard analysis included the assessment of ischemia presence in a 16-segment model by measuring the circular region of interest (ROI). The ROI had a minimal area of 50 mm^2. The indexed myocardial blood flow (index-MBF) with a <0.78 threshold was used to define myocardial ischemia [8]. The patient was diagnosed as having ischemia in CTP if the hypoperfusion involved at least one myocardial segment of an at-least-50% subendocardial layer.

Volumetric analysis of ischemia (volume of interest [VOI] of ischemia, mm^3) was done using manual VOI contours based on the index-MBF threshold on short-axis cross-sections for each slice. To normalize the inter-individual differences, the optimal patient-specific index-MBF was defined as the measured MBF/MBF (LV) 75% and was used at the 0.78 threshold for all the VOI measurements [8]. Therefore, the VOI contours included the area within the myocardial wall with index-MBF <0.78. In the next step, the measured VOI of ischemia was divided by the automatically measured total VOI for the LV muscle (VOI of LV muscle, mm^3). An example is presented in Figure 1. Like other non-invasive imaging methods of ischemia detection, 10% ischemia was used to define functionally significant ischemia in VOL CTP.

Table 1. Baseline patient characteristics

Parameter	Study group (n = 53)	Total revascularization (n = 16)	No revascularization (n = 37)	*P*-value
Age, years, mean (SD)	62.5 (8.5)	58.8 (9.0)	65.9 (7.5)	0.4
Male sex, n (%)	28 (53%)	12 (75%)	16 (43%)	0.04
BMI, kg/m^2, mean (SD)	27.7 (3.6)	27.9 (3.4)	27.6 (3.7)	0.8
Height, cm, mean (SD)	168.0 (9.0)	171.3 (7.5)	166.5 (9.3)	0.07
CAD risk factors				
Hypertension, n (%)	46 (87%)	14 (88%)	32 (86%)	1.0
Dyslipidemia, n (%)	52 (98%)	16 (100%)	36 (97%)	1.0
Diabetes, n (%)	13 (25%)	3 (19%)	10 (27%)	0.7
CAD family history, n (%)	31 (58%)	10 (63%)	21 (57%)	0.7
Active smoking, n (%)	5 (9%)	4 (25%)	1 (2.7%)	0.02
Past smoking[a], n (%)	26 (49%)	10 (63%)	16 (43%)	0.2

[a]Smoking cessation >1 year ago
Values are presented as mean (SD) or n (%)

Abbreviations: BMI, body mass index, CAD, coronary artery disease

Table 2. Baseline computed tomography coronary angiography results

Parameter	Study group (n = 53)	Total revascularization (n = 16)	No revascularization (n = 37)	*P*-value
CASC (Agatston)	366.7 (109.2–727.6)	216.6 (67.4–854.2)	417.5 (125.1–656.1)	0.7
One- or multi-vessel disease				
3–vessel CAD	0	0	0	
2–vessel CAD	15 (28%)	7 (44%)	8 (22%)	0.1
1–vessel CAD	38 (72%)	9 (56%)	29 (78%)	
CAD-RADS				
0-2	0	0	0	
3	41 (77%)	6 (37%)	35 (95%)	
4A	12 (23%)	10 (63%)	2 (5%)	<0.001
4B	0	0	0	
5	0	0	0	

Values are n (%) or median (interquartile range [IQR])

Abbreviations: CAD, coronary artery disease, CAD-RADS, Coronary Artery Disease – Reporting and Data System; CASC, coronary artery calcium score

The members of the recruiting team and the referring physicians were blinded to the CTP results. The patients' management was independent of the CTP results.

Statistical analysis

The continuous variables are presented herein as mean with standard deviation (SD) or median with interquartile range (IQR), as appropriate. The categorical variables are presented as frequencies and percentages. For the assignment of intra- and inter-observer variability, 20 anonymized CTP studies were re-analyzed by the same reader after 1 month, and by a second blinded reader (a standard approach using the MBF per segment and volumetrically as a percentage of ischemia per patient). The intra- and inter-observer variability were calculated using intraclass correlation coefficients (ICCs). Homogeneity analysis of variance for the variables with a normal distribution was done using Levene's test. The differences between the patients who underwent revascularization during the follow-up and those who did not were determined through Student's t-test (normal distribution) or the U Mann-Whitney test (non-normal distribution, independent variables). The differences between the qualitative variables were determined using the chi-square test or Fisher's exact test. In further analyses, a comparison of the receiver operating curves was used (elective or total revascularization as a classifier). The accuracy of the diagnostic methods was compared using McNemar's test. The net reclassification improvement (NRI) was calculated for VOL CTP in comparison to CTP standard analysis. $P < 0.05$ was considered statistically significant. The analyses were performed using MedCalc (18.11.3, Ostend, Belgium).

RESULTS

Baseline characteristics

The study population consisted of 53 patients (28 males and 25 females, 63.5 [8.5] years old, 27.7 [3.6] kg/m^2). There were no differences in age, BMI, the prevalence of diabetes, hypertension, dyslipidemia, smoking in the past, family history of CAD, and medication use between the patients who underwent revascularization and those who did not. There were more males and current smokers in the revascularization group ($P = 0.04$ and $P = 0.01$, respectively). The baseline characteristics of the study population are given in Table 1, Table 2, and Supplementary material, *Table S1*.

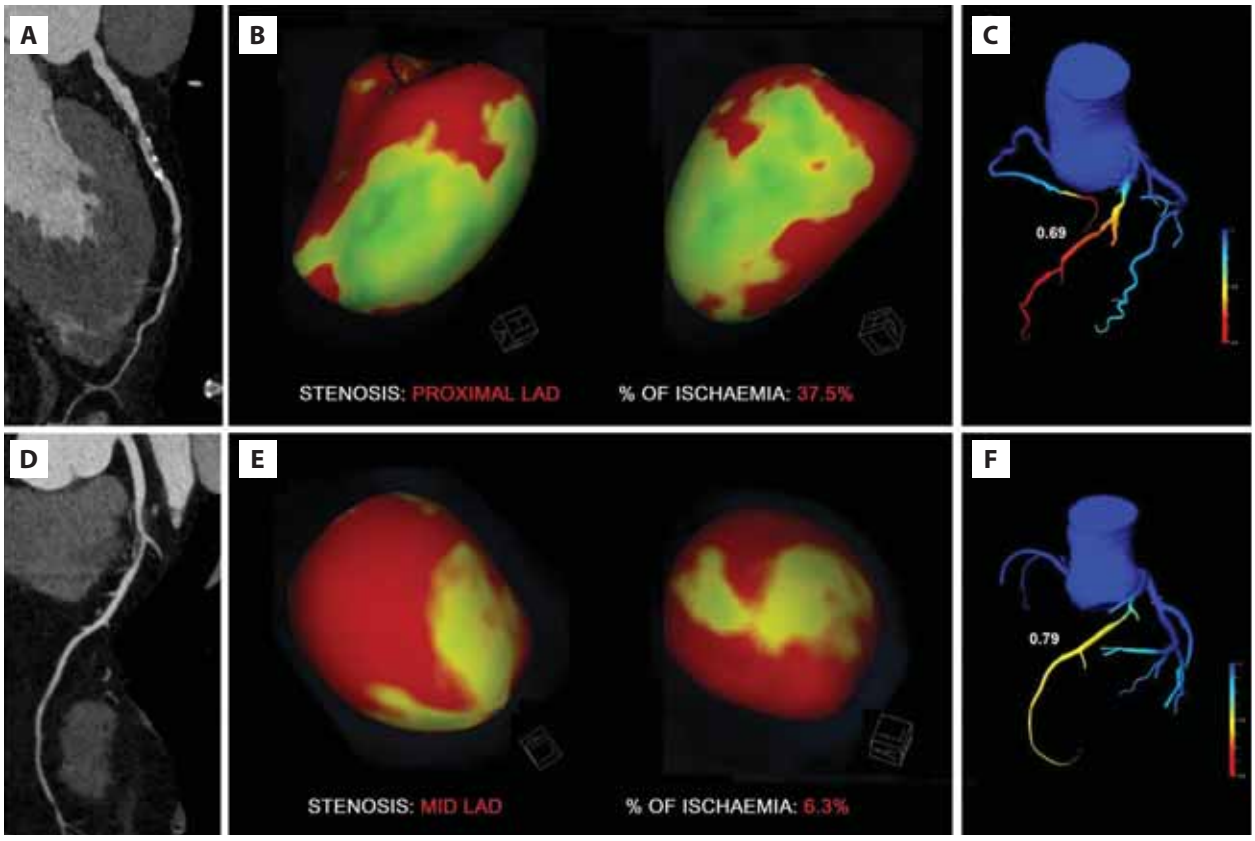


Figure 2. Results of coronary computed tomography angiography (CTA) (**A, D**), dynamic computed tomography perfusion (CTP) (**B, E**), and computed tomography-derived fractional flow reserve (CT-FFR) (**C, F**). 3D volume perfusion images of the left ventricle showing the ischemia extent and CT-FFR in different patients

Study outcomes

Twelve patients (22.6%) underwent elective revascularization following the study procedures within 6 months since CTA, and four patients (7.5%) underwent event-driven revascularization (1 non-fatal myocardial infarction, 3 unstable angina requiring hospitalization) during the 2.5-year (1.4–2.8) follow-up. Additionally, two patients had symptom progression during the follow-up and were referred by their physicians for invasive angiography (both had initially normal CTP). They underwent invasive angiography without revascularization (invasive FFR >0.8 in both cases).

Imaging results and revascularization prediction

In the 53 patients in the study, 159 coronary arteries were evaluated via CTA, and 68 (43%) were found to be 50%–90% stenosed. There were no differences in coronary artery calcium (CASC) score. The baseline CTA findings are provided in Table 2.

Through CT-FFR analysis, ischemia was detected in 28 patients. CT-FFR was not performed in three patients (one of whom had elective revascularization) due to heavy calcifications.

In CTP examinations, all images had optimal quality and were interpretable. Intra-observer and inter-observer ICC's for MBF as a representative measure from ROI were excellent: 0.987 (0.982–0.990) and 0.985 (0.979–0.989), respectively. Intra-observer and inter-observer ICC's for volumetric CTP (measured as percentage of ischemia per patient) were excellent: 0.999 (0.999–1.000) and 0.998 (0.994–0.999), respectively. The time needed to postprocess a CTP data set with volumetric ischemia evaluation was 10–15 minutes.

The median radiation dose for topogram and low-dose non-contrast scan was 38.6 (36.6–39.6) mGy × cm (0.54 [0.51–0.55] mSv) and, for dynamic CTP scan, was 352.0 (276.4–496.6) mGy × cm (4.93 [3.87–6.95] mSv).

Through the CTP standard quantitative analysis, an ischemic territory involving at least one myocardial segment was detected in 26 (49%) patients. According to the volumetric CTP analysis results, the mean ischemia percentage in the patients who underwent revascularization was 23.8 (8.5)% vs. 2.2 (4.7)% (P <0.001) in the non-revascularized patients. The sample results are presented in Figure 2. In total, the VOL CTP analysis revealed that 18 patients had over 10% ischemia, 16 of whom underwent revascularization (12 elective, 4 event-driven).

The clinical outcomes associated with different diagnostic strategies (CTA, CT-FFR, CTP, and VOL CTP-guided cohort) are summarized in Figure 3. The area under the curve (AUC) for the prediction of elective revascularizations by CTA ≥50% was 0.500 (95% confidence interval, 0.359–0.641), by CTA ≥70% was 0.692 (95% CI, 0.550–0.812),

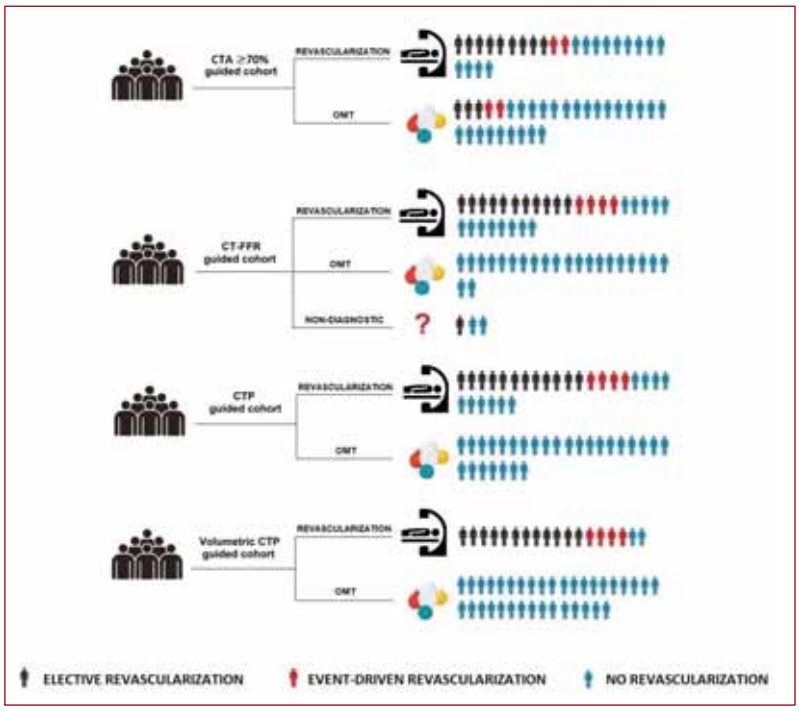


Figure 3. Summary of computed tomography-based diagnostic pathways with outcomes. Summary of the diagnostic pathways (CTA, CT-FFR, CTP, and volumetric CTP guided cohort) with outcomes (total revascularizations)

Abbreviations: OMT, optimal medical treatment; other — see Figure 2

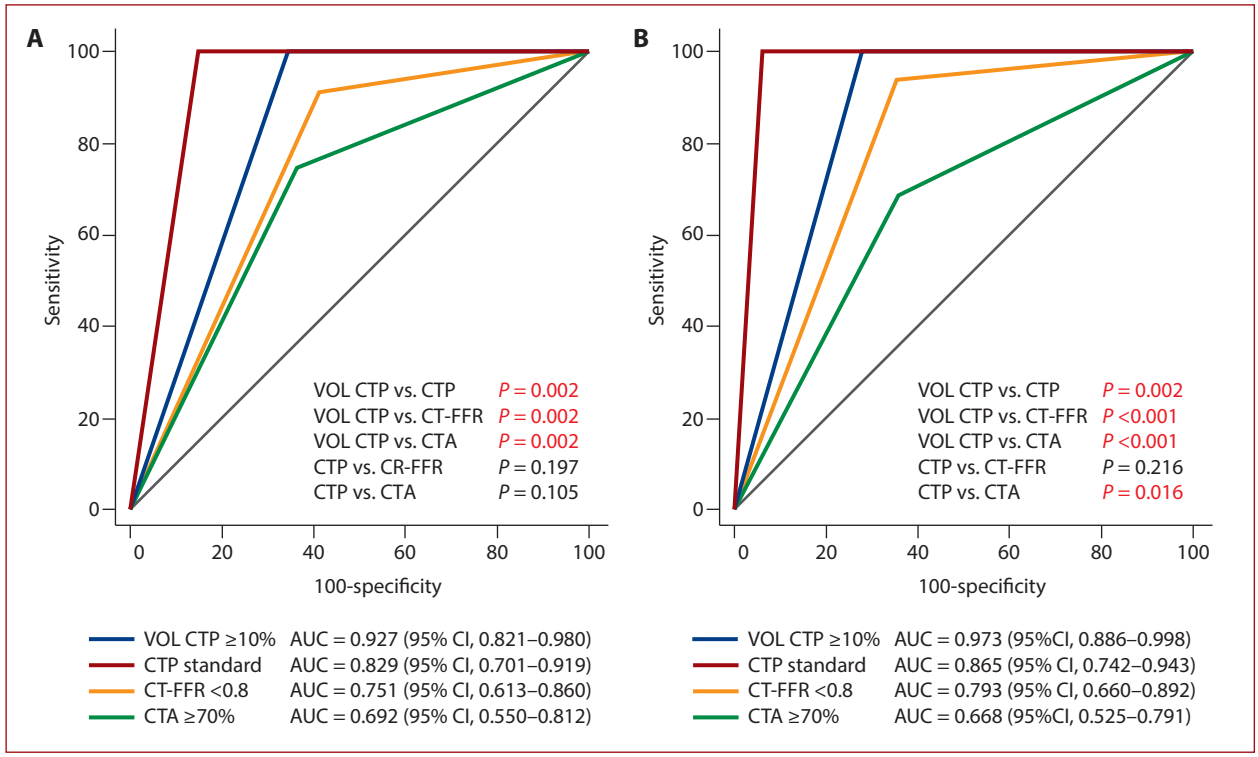
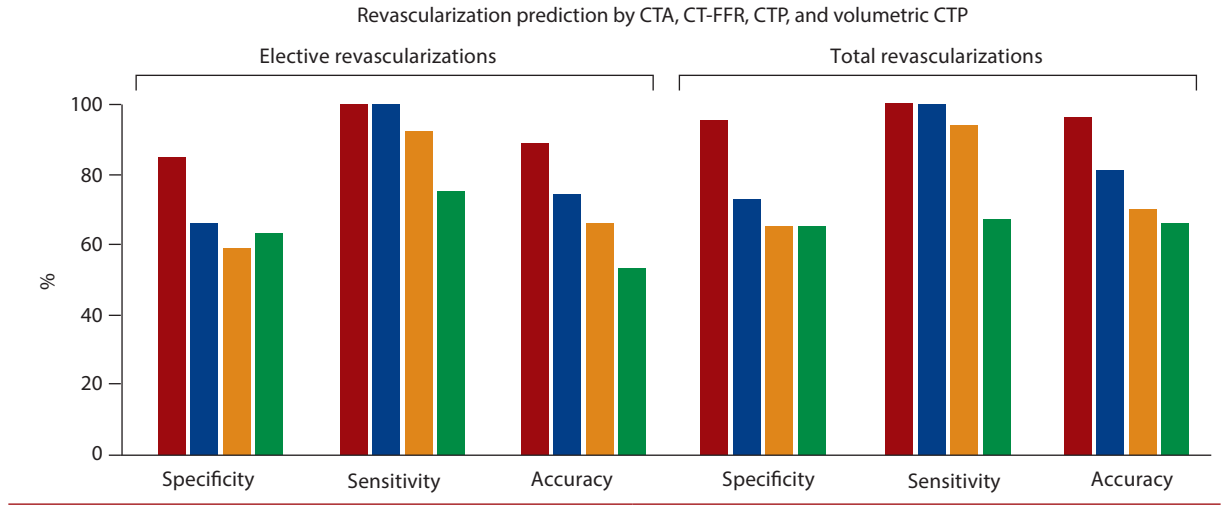


Figure 4. Comparison of ROC curves for revascularization prediction. Comparison of ROC curves for revascularization prediction (**A** — elective, **B** — total revascularizations) by CTA, CT-FFR, CTP using a standard approach and volumetric CTP (VOL CTP ≥10%)

Abbreviations: see Figure 2

by CT-FFR was 0.751 (95%CI, 0.613–0.860), by the CTP standard approach was 0.829 (95%CI, 0.701–0.919), and by VOL CTP (≥10%) was 0.927 (95% CI, 0.821–0.980). The ischemia detection via CTP using the standard approach was equal to that via CT-FFR for the prediction of elective revascularizations. The VOL CTP with a ≥10% cut-off, however, was better than the other methods in predicting elective revascularization (Figure 4A).

The AUC for the prediction of total revascularizations by CTA ≥50% was 0.500 (95% CI, 0.359–0.641), by CTA ≥70% was 0.668 (95% CI, 0.525–0.791), by CT-FFR was 0.793 (95% CI, 0.660–0.892), by the CTP standard approach



	Elective revascularizations			Total revascularizations		
	Specificity	Sensitivity	Accuracy	Specificity	Sensitivity	Accuracy
Volumetric CTP ≥10%	85	100	89	95	100	96
CTP standard approach	69	100	77	73	100	81
CT-FFR <0.8	59	92	66	65	94	70
CTA ≥70%	63	75	66	65	69	66

Figure 5. The diagnostic value of CT-based imaging for revascularization prediction.
Specificity, sensitivity, and accuracy of elective and total revascularization prediction during the follow-up by CTA, CT-FFR, CTP with a standard approach and volumetric CTP
Abbreviations: see Figure 2

was 0.865 (95% CI, 0.743–0.943), and by VOL CTP (≥10%) was 0.973 [95%CI: 0.886–0.998]. The ischemia detection via CTP using the standard approach was equal to that via CT-FFR for the prediction of total revascularizations, but the VOL CTP with a ≥10% cut-off was better than other methods in predicting total revascularization (Figure 4B).

The sensitivity, specificity, and accuracy of the analyzed imaging methods are presented in Figure 5 and Supplementary material, *Table S2*. The accuracy of VOL CTP (≥10%) was better than CTP ($P = 0.008$), CT-FFR ($P = 0.007$), and CTA ≥70% ($P < 0.001$) for total revascularization prediction.

The net reclassification index was 0.30 (30%) for VOL CTP as compared to CTP with a standard approach for both elective and total revascularizations.

DISCUSSION

Our study delved into the untapped potential of dynamic CTP examination and provided new information on the feasibility, optimal method, and clinical value of the additional volumetric myocardial ischemia assessment. According to our data, the new method is applicable and diagnostically robust compared to the more traditional alternatives for the prediction of coronary revascularization in the long-term follow-up and may facilitate decision-making on the invasive therapies to use, accounting for the prognostic dimension. The added ability of CT to evaluate the percentage of myocardial ischemia strengthens its potential to become the truly "one-stop shop" in CAD diagnostics.

We showed that VOL CTP is superior to the traditional CTP, coronary CTA, and CT-FFR in discriminating patients requiring coronary revascularization. Our results also underline the importance of MBF quantification for the appropriate planning of interventional therapies in chronic coronary syndromes. The newly developed VOL CTP uniquely combined the highest sensitivities and specificities in selecting patients for coronary revascularization, successfully sorting out the patients with a small ischemic area that can be successfully treated medically. This may save a significant proportion of patients from unnecessary invasive interrogation and therapies. The results of our study may upgrade the indications for CTP examination over the previously postulated ones in the case of suboptimal coronary CTA diagnostic results (e.g., diffuse calcifications, motion artifacts). VOL CTP should also be considered in the case of an uncertain CT-FFR, such as borderline CT-FFR, the case where the threshold value (≤0.80) is reached in the distal vessel, non-proximal stenosis, or stenosis in a relatively small vessel [12–14]. The more accurate designation of patients who may benefit from revascularization will likely be advantageous. VOL CTP-guided patient management allows for a more appropriate qualification for invasive therapies, which can prevent unnecessary revascularizations and enable earlier treatment of patients with probable future events. The prediction of not only elective but also total revascularizations through VOL CTP suggests that the method may be more

sensitive to ischemia already present during the baseline examination but overlooked while using other methods.

We advance the utility of CTP examination and propose an optimal clinical context concordant with the current guidelines [8, 15, 16]. Our study attempted to develop a method of volumetric myocardial ischemia evaluation in dynamic CTP using the myocardial blood flow threshold. Previously, Kwon et al. [17] calculated an ischemic percentage based on the visual analysis of the myocardial attenuation. Our findings were validated by clinical sequelae of revascularization. When performing VOL CTP analysis, we can also indicate the ischemia localization, like CTP standard analysis. Manual volumetric analysis based on the index-MBF allows precise assessment of the true rather than only the estimated percentage of myocardial ischemia (based on the number of affected segments). Moreover, index-MBF allows the normalization of the inter-individual differences in maximal MBF previously described in some studies [5, 18, 19].

There have been some studies that investigated the prognostic value of dynamic CTP, but none of them have analyzed volumetric ischemia assessment [20–25]. Tanabe et al. [7], in a small study (39 patients), investigated the expected MBF from Voronoi-diagram-based myocardial segmentation but did not evaluate the true percentage of myocardial ischemia. As shown in the meta-analysis conducted by Pontone et al., positive stress myocardial CTP added to coronary CTA has a very high diagnostic performance in identifying a functionally significant coronary lesion in a patient-based model [26]. The addition of dynamic CTP significantly improved the diagnostic performance of CTA in detecting functionally significant CAD, and it was shown to be comparable to the addition of CT-FFR [27]. The study by van Assen et al. [25] showed that dynamic CTP alone (using index-MBF defined as the ratio between the territory MBF and the global MBF) has a higher prognostic value for the prediction of major adverse cardiac events (including elective revascularization) than CTA and CT-FFR, independently of clinical risk factors. There have also been some recently published studies that compared CTP with CT-FFR [4, 5, 27, 28]. Baggiano et al. [28] recently reported that the addition of both CT-FFR and CTP to CTA in their study led to the reclassification of approximately one-third of the patients with an intermediate to high likelihood of CAD. Also, Pontone et al. [27] showed that the addition of dynamic CTP to CTA and CT-FFR in their study provided additional diagnostic accuracy with acceptable radiation exposure. The CTA+CTP strategy showed better performance than the CTA+CT-FFR strategy in ultimate therapeutic decision-making and choice of target vessels [28]. In contrast, Yang et al. [4] showed in their study that there was no significant difference between the area under the curve values of CT-FFR and CTP but that the diagnostic performance of CTA was improved by combining it with either CT-FFR or CTP. Also, Coenen et al. [5] showed that both CTP and CT-FFR can identify functionally significant CAD, with comparable accuracy. These are consistent with our results as we showed that the CTP standard approach has a similar diagnostic value (AUC) as CT-FFR for elective- and total-revascularization prediction.

Limitations

Our study was a single-center investigation with a limited sample size. Despite this, however, we were able to identify highly significant differences between the investigated methods and illustrate the incremental value of VOL CTP. However, multi-center studies assessing dynamic CTP with more definite endpoints, such as death or myocardial infarction during a long-term follow-up, would strengthen our findings. We did not perform additional ECG/echocardiography examinations during the follow-up. No deaths occurred in our study during the follow-up. Importantly, the low radiation dose reported during the examination should not be automatically assumed to be available for other CT systems capable of performing dynamic CTP.

Special attention is necessary for three-vessel CAD due to the possible lower global MBF in the case of the functional significance of all the three stenosed vessels. In our study, none of the patients had three-vessel CAD. This represents a possible bias as ischemia determination by CTP is less accurate in multivessel disease (e.g. partial overlap of perfusion defects or balanced ischemia). Therefore, the high accuracy values may not be representative of the true performance of VOL CTP in unselected real-world patients.

However, we did not detect a mismatch between ischemia localization and an obstructive vessel territory. The applicability of CT-FFR and dynamic CTP may differ based on their advantages and disadvantages. CT-FFR cannot be used to evaluate coronary stenosis in all CTA results [29]. In our study, CT-FFR was not performed in three patients who had heavy calcifications. Moreover, VOL CTP cut-off ≥10% should not be used as a basis for decision-making regarding invasive therapies until confirmed by larger trial data.

CONCLUSION

VOL CTP assessment is feasible and can provide incremental value to coronary artery stenosis assessment via CTA and ischemia evaluation via CT-FFR or the standard quantitative CTP for the prediction of coronary revascularization.

Supplementary material

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

Article information

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Impact of diabetes mellitus on outcomes in patients with myocardial infarction according to varying degrees of left ventricular systolic dysfunction

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ABSTRACT

Background: Diabetes mellitus (DM) is known to contribute to unfavorable short- and long-term outcomes in patients with myocardial infarction (MI). Particularly poor outcomes are associated with left ventricular systolic dysfunction after an MI. Our study aimed to compare the short- and long-term outcomes of MI in patients with DM and varying degrees of left ventricular systolic dysfunction with the corresponding outcomes in a non-diabetic control group.

Methods: This analysis focused on patients with MI registered in the Polish National Registry of Acute Coronary Syndrome between 2009 and 2011. For this analysis, diabetic patients were additionally stratified into three subgroups depending on the degree of left ventricular systolic dysfunction, as assessed during their hospitalization for MI. Subsequently, the 30-day, 12-month, and 36-month outcomes in the diabetic study subgroups were compared with those in the corresponding non-diabetic subgroups.

Results: This analysis encompassed a nationwide cohort of 58 123 patients. Twelve- and 36-months mortality was greater in diabetic patients than in non-diabetic patients. The highest 36-months mortality (46.64%) was in the group of patients with DM and reduced ejection fraction (EF) <40%. Multivariate analysis showed diabetes and low EF to be independent risk factors for 36-month mortality, increasing the risk of death by 35% for diabetes and by 30% for each 5-percentage point EF decrease. Higher mortality was observed in older patients, smokers, and patients with ischemic heart disease before the index hospitalization.

Conclusions: Both diabetes and reduced EF proved to be independent risk factors for increased mortality over a long-term follow-up after MI.

Key words: diabetes mellitus, ejection fraction, heart failure, myocardial infarction

INTRODUCTION

Non-cardiovascular comorbidities, depending on their severity, may render the prognosis for heart failure (HF) patients clinically challenging [1]. The correlation between diabetes mellitus (DM) and the risk of myocardial infarction (MI) has been thoroughly documented in the literature. DM increase the risk of hospitalisation for HF [2]. DM patients more commonly require extensive in-hospital treatment for MI compared to non-DM patients [3]. Diabetes worsens short- and long-term outcomes in patients with MI [4–6]. Left ventricular systolic dysfunction is an independent risk factor for mortality after MI [5]. Consequently, ejection fraction (EF) and HF symptoms included in the New York Heart Association (NYHA) functional classification are pivotal indicative criteria

WHAT'S NEW?

Worse prognosis has been observed in patients with myocardial infarction (MI) and previously diagnosed or new-onset diabetes mellitus compared with their non-diabetic counterparts. Moreover, diabetes was shown to be an independent risk factor for hospitalization for heart failure. However, up until now, there have been no large-population studies assessing the long-term effects of diabetes on the long-term prognosis for patients with various degrees of post-MI left ventricular systolic dysfunction. We evaluated a nationwide prospective cohort of over 58 000 MI patients in terms of long-term outcomes over three years.

for cardioverter-defibrillator implantation as primary prevention of sudden cardiac death [6–8]. Our study aimed to compare the short- and long-term outcomes of MI in patients with diabetes mellitus with varying degrees of left ventricular systolic dysfunction (quantified in terms of EF values) with the corresponding outcomes in a non-diabetic control group.

METHODS

Data of 58 123 consecutive patients who were hospitalized for MI (ST-segment elevation MI [STEMI] or non-ST-segment elevation MI [NSTEMI]) between January 2009 and December 2011 were obtained from the Polish National Registry of Acute Coronary Syndrome (PL-ACS). This Registry was initiated by the Silesian Centre for Heart Diseases in Zabrze and maintained in cooperation with the Ministry of Health and the National Health Fund as part of the National Program for the Prevention and Treatment of Cardiovascular Diseases. This vast nationwide Registry contains detailed data on over 640 000 patients hospitalized for the acute coronary syndrome (ACS) in Poland. It is not only the largest registry in Europe, but also it contains the most recent data relating to epidemiology, treatment, and outcomes in patients with ACS. Registry entry criteria were described elsewhere [9]. The investigation conformed to the principles outlined in the Declaration of Helsinki and was carried out in accordance with the local ethics department's policy. The Ethics Committee of the Medical University of Warsaw was informed about the study (AKBE/81/2019).

The study population consisted of patients with diabetes (type 1, type 2, and new-onset, i.e. diagnosed during hospitalization) and patients without diabetes who constituted the control group. In line with the classification adopted within the Registry, patients with DM were defined as patients who received diabetes treatment (insulin, oral medications, or diet) before hospitalization, patients with new-onset diabetes were defined as those whose fasting blood glucose levels exceeded 7 mmol/l (≥126 mg/dl) in two measurements or blood glucose levels exceeded ≥11.1 mmol/l (≥200 mg/dl) following an oral glucose tolerance test conducted after the acute phase of MI [10].

The study population was stratified by EF values and assessed in terms of short- and long-term MI treatment outcomes. For this analysis, patients were further stratified into three subgroups based on the degree of left ventricular systolic dysfunction measured during their index hospitalization for MI. Left ventricular systolic dysfunction, expressed using EF, was determined by echocardiography. Based on the last measurement of the degree of left ventricular systolic dysfunction assessed during hospitalization, diabetic and non-diabetic patients were stratified into the following subgroups:

- heart failure with reduced ejection fraction (HFrEF; <40%)
- heart failure with mid-range ejection fraction (HFmrEF; 40%–49%)
- heart failure with preserved ejection fraction (HfpEF; ≥50%).

Short-term (in-hospital and within 30 days post-discharge) and long-term (after 12 and 36 months) outcomes were assessed. Clinical endpoints are included in Supplementary material, *Table S1*.

Statistical methods

Continuous variables were presented as means and standard deviations (SD). Categorical variables were presented as percentages and absolute values. The chi-square test for frequency data and Student's t-test for continuous data were used to test the differences between the groups. The association between the groups and long-term mortality was analyzed using the Kaplan-Meier method for multiple group comparisons. Parameters from Table 1 and EF were included in the multivariable Cox proportional hazard model (the backward elimination method) to adjust the impact of diabetes on mortality at 36 months, and the results were expressed as hazard ratios (HRs) and 95% confidence interval (CI). Additional models were calculated to assess the impact of DM on 3-year mortality in different EF groups, and the impact of mildly reduced (40%–49%) and reduced (<40%) EF on 3-year mortality in dependence of diabetic status. Statistical significance was set at $P<0.05$. All reported P-values are two-sided. Analyses were performed with the use of Statistica version 13 (TIBCO Software Inc., Palo Alto, CA, USA) and NCSS 2020 Statistical Software, LLC (Kaysville, Utah, USA).

RESULTS

DM patients (n = 11 689) comprised 20% of the study cohort, whereas non-diabetic patients (n = 46 434) comprised 80%. Ninety-seven percent of patients with DM were diagnosed with DM type 2. A total of 41.75% of diabetic patients and 52.07% of controls were diagnosed with STEMI

Table 1. Baseline clinical characteristics

	Non-DM	DM	*P*-value
Number of patients	46 434	11689	
STEMI, n (%)	24 180 (52.07)	4880 (41.75)	<0.001
NSTEMI, n (%)	22 254 (47.93)	6809 (58.25)	
Age, years, mean (SD)	64.4 (12.1)	68.4 (10.4)	<0.001
Male gender, n (%)	15 233 (67.19)	5224 (55.31)	<0.001
BMI, kg/m^2, mean (SD)	27.2 (4.3)	29.7 (5.1)	<0.001
Hypertension (BP ≥140/90 mm Hg), n (%)	31 752 (68.38)	9915 (84.82)	<0.001
Hypercholesterolemia, n (%)	19 050 (41.03)	5605 (47.95)	<0.001
Chronic kidney disease, n (%)	2017 (4.34)	1310 (11.21)	<0.001
Former smoker, n (%)	12 739 (27.43)	3983 (34.07)	<0.001
Current smoker, n (%)	16 076 (34.62)	2047 (17.51)	<0.001
Family history of CVD, n (%)	5284 (11.38)	1500 (12.83)	<0.001
Past MI, n (%)	5835 (12.57)	2331 (19.94)	<0.001
Past PCI, n (%)	3476 (7.49)	1411 (12.07)	<0.001
Past CABG, n (%)	1001 (2.16)	492 (4.21)	<0.001
Coronary artery disease, n (%)	5027 (10.83)	2486 (21.27)	<0.001
Heart failure, n (%)	2854 (6.15)	1264 (10.81)	<0.001
Past stroke, n (%)	1474 (3.17)	701 (6.00)	<0.001
PAD, n (%)	1849 (3.98)	730 (6.25)	<0.001
Chronic lung disease, n (%)	1743 (3.75)	582 (4.98)	<0.001

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; CVD, cardiovascular disease; DM, patients with diabetes; MI, myocardial infarction; Non-DM, patients without diabetes; PAD, peripheral artery disease; PCI, percutaneous coronary intervention

Table 2. Invasive cardiac procedures and in-hospital mortality by diabetic status

	Non-diabetic (n = 46 434)	Diabetic (n = 11 689)	*P*-value
Cardiac catheterization, n (%)	43 781 (94.29)	11 689 (91.45)	<0.001
Percutaneous coronary intervention, n (%)	36 979 (79.64)	87 22 (74.62)	<0.001
Coronary artery bypass surgery, n (%)	1236 (2.66)	380 (3.25)	<0.001
Death, n (%)	1527 (3.29)	564 (4.83)	<0.001

(*P* <0.001). The EF ≥50%, EF 40%–49%, and EF <40% subgroups accounted for 53% (n = 30 780), 29% (n = 17 067), and 18% (n = 10 376) of the study cohort, respectively. The average EF values in the diabetic and control groups were 46% and 48%, respectively.

Table 1 presents the clinical characteristics of diabetic and non-diabetic patients. DM patients were usually older, were less likely to be male, and were more likely to suffer from chronic kidney disease in comparison with non-diabetic patients. In addition, DM patients were more likely to have a history of MI, stroke, HF, coronary artery disease, and peripheral vascular disease. Moreover, the diabetic group had a higher proportion of former smokers, whereas the non-diabetic group had a higher proportion of current smokers. Non-diabetic patients were more likely to have a history of hypertension and hypercholesterolemia.

In both groups, coronary angiography was performed in over 90% of cases involving MI. However, it was more frequently performed in the non-diabetic group than in the diabetic group (94.29% vs. 91.45%; *P* <0.001). Furthermore, non-diabetic patients underwent coronary angioplasty more often than patients with diabetes (79.64% vs. 74.62%; *P* <0.001). Likewise, patients with DM were more often qualified for coronary bypass surgery during hospitalization than non-diabetics (3.25% vs. 2.66%; *P* <0.001). Table 2 presents the number and percentage of diabetic and non-diabetic patients who underwent coronary angiography, coronary angioplasty, and coronary artery bypass surgery, as well as those who died in the hospital.

In multivariate analysis, diabetes (HR, 1.35; 95% CI, 1.30–1.42) and reduced EF (HR, 1.30; 95% CI, 1.29–1.31) proved to be independent risk factors for increased mortality within 36 months of the follow-up. Moreover, mortality was elevated in older patients (HR, 1.35; 95% CI, 1.33–1.36, for each 5-year age interval), smokers (former smokers: HR, 1.11; 95% CI, 1.07–1.17; current smokers: HR, 1.24; 95% CI 1.17–1.31), and patients with a history of ischemic heart disease (HR, 1.22; 95% CI, 1.16–1.28). Additionally, multivariate analysis showed hypercholesterolemia, hypertension, and higher body mass index (BMI) to be independent factors for lower mortality.

Diabetes increased the risk of death in all EF subgroups. The strongest effect was observed in the EF 40%––49% subgroup. On the other hand, low EF (<40%) doubled the risk of death in both diabetic and control groups in comparison with the risk of death in the preserved-EF

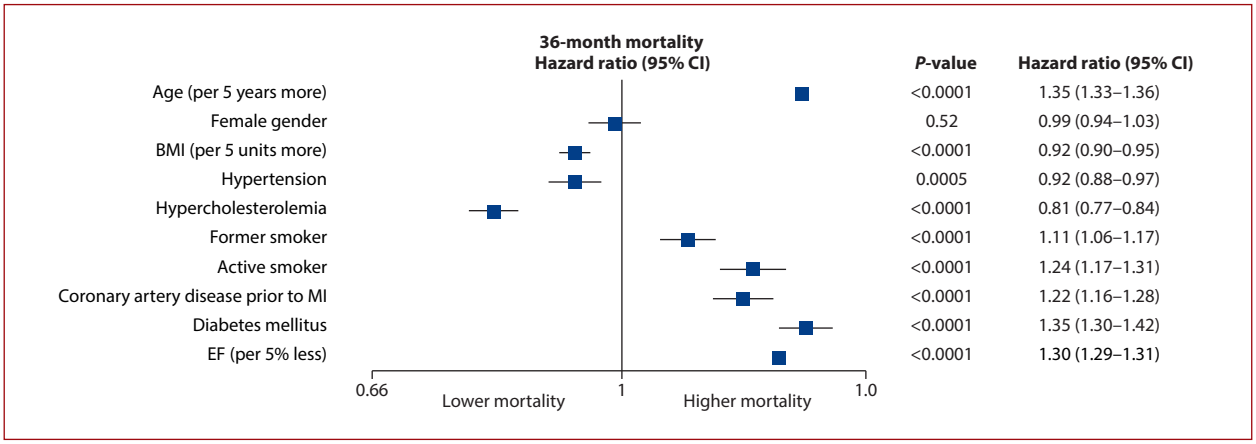

Figure 1. Multivariate analysis

Abbreviations: BMI, body mass index; CI, confidence interval; EF, ejection fraction; MI, myocardial infarction

Table 3. The adjusted hazard ratio for death at 36 months for patients with DM vs. non-DM stratified by EF. Parameters used for adjustment: age, sex, body mass index, hypertension, hypercholesterolemia, smoking, history of coronary artery disease before index myocardial infarction

EF	HR (95% CI)
≥50%	1.41 (1.30–1.54)
40%–49%	1.42 (1.31–1.54)
<40%	1.25 (1.17–1.34)

Abbreviations: HR, hazard ratio; CI, confidence interval; other — see Figure 1 and Table 1

Table 4. The adjusted hazard ratio for death at 36 months for patients with mildly reduced (40%–49%) and reduced (<40%) EF in control and diabetic groups. Parameters used for adjustment: age, sex, body mass index, hypertension, hypercholesterolemia, smoking, history of coronary artery disease before index myocardial infarction

	Control HR (95% CI)	Diabetes HR (95% CI)
EF 40%–49% (vs. ≥50%)	1.57 (1.48–1.67)	1.63 (1.48–1.79)
EF <40% (vs. 40%–49%)	1.93 (1.88–1.99)	1.86 (1.78–1.95)
EF <40% (vs. ≥50%)	2.37 (2.24–2.51)	2.11 (1.94–2.30)

Abbreviations: see Figure 1 and Table 3

Table 5. Total mortality (including in-hospital mortality) in DM and non-DM stratified by EF

Total mortality over the follow-up period	Control	DM	Control	DM	Control	DM
	EF ≥50% (n = 25 388)	EF ≥50% (n = 5 292)	EF 40%–49% (n = 13 393)	EF 40%–49% (n = 3 674)	EF <40% (n = 7 653)	EF <40% (n = 2 723)
30 days, n (%)	313 (1.23)	101 (1.91)	437 (3.26)	163 (4.44)	1045 (13.65)	411 (15.09)
	P <0.001		*P* <0.001		*P* = 0.06	
12 months, n (%)	1140 (4.49)	387 (7.31)	1151 (8.59)	499 (13.58)	2034 (26.58)	857 (31.47)
	P <0.001		*P* <0.001		*P* <0.001	
36 months, n (%)	2405 (9.47)	795 (15.02)	2169 (16.20)	927 (25.23)	2928 (38.26)	1270 (46.64)
	P <0.001		*P* <0.001		*P* <0.001	

Abbreviations: see Figure 1 and Table 1

subgroups (EF >50%). All multivariate analysis results are presented in Figure 1 and Tables 3 and 4.

All patients completed a 3-year follow-up. The total mortality rate over 36 months (including in-hospital mortality) is shown in Table 5. Kaplan-Meier curves show the total risk of death during the 36-month follow-up in all evaluated groups (Figure 2).

Analysis of cardiovascular events after hospital discharge

Long-term (12- and 36-month) follow-up after hospital discharge demonstrated a higher risk of re-infarction and stroke in all three EF subgroups of diabetic patients than in non-diabetic patients. Diabetic patients from all three EF subgroups were also more likely to be hospitalized for HF than non-diabetic patients. This observation was true for both the short-term (30-day) and long-term (12- and 36-month) follow-ups. Diabetes was also associated with higher rates of end-stage renal disease and the resultant need for dialysis in all EF subgroups. The diabetic subgroup with the lowest EF of <40% showed that the rates of coronary angiography, coronary angioplasty, or coronary artery bypass grafting (CABG), within the 12- and 36-month follow-up periods, were no higher than those in the control group. Cardiovascular events over the 30-day, 12-month, and 36-month post-discharge follow-up have been presented in Table 6.

After hospital discharge, there was no difference in the 30-day mortality in the EF <40% and EF 40%–49%

Table 6. Three-year post-discharge outcomes in non-diabetic and diabetic patients stratified by ejection fraction

	Follow-up	Non-DM, EF ≥50% (n = 25 075)	DM, EF ≥50% (n = 5191)	Non-DM, EF 40%–49% (n = 12 956)	DM, EF 40%–49% (n = 3511)	Non-DM, EF <40% (n = 6608)	DM, EF <40% (n = 2312)
Death, n (%)	30 days	107 (0.43)	34 (0.65)	113 (0.87)	42 (1.19)	185 (2.75)	80 (3.38)
		P = 0.03		*P* = 0.08		*P* = 0.12	
	12 months	910(3.62)	315 (6.04)	788 (6.05)	367 (10.36)	1110 (16.51)	501 (21.18)
		P <0.001		*P* <0.001		*P* <0.001	
	36 months	2175 (8.65)	723 (13.86)	1806 (13.86)	795 (22.44)	2002 (29.77)	914 (38.65)
		P <0.001		*P* <0.001		*P* <0.001	
Myocardial infarction, n (%)	30 days	215 (0.85)	58 (1.11)	152 (1.17)	58 (1.64)	116 (1.73)	42 (1.78)
		P = 0.07		*P* = 0.03		*P* = 0.87	
	12 months	984 (3.91)	341 (6.54)	644 (4.94)	298 (8.41)	495 (7.36)	226 (9.56)
		P <0.001		*P* <0.001		*P* <0.001	
	36 months	1720 (6.84)	575 (11.02)	1143 (8.77)	501 (14.14)	771 (11.47)	361 (15.26)
		P <0.001		*P* <0.001		*P* <0.001	
Stroke, n (%)	30 days	39 (0.16)	18 (0.34)	44 (0.34)	14 (0.40)	28 (0.42)	17 (0.72)
		P = 0.004		*P* = 0.61		*P* = 0.07	
	12 months	241 (0.96)	82 (1.57)	201(1.54)	76 (2.15)	130 (1.93)	74 (3.13)
		P <0.001		*P* = 0.01		*P* <0.001	
	36 months	656 (2.61)	216 (4.14)	453 (3.48)	172 (4.86)	320 (4.76)	151 (6.38)
		P <0.001		*P* <0.001		*P* = 0.002	
Hospitalization for heart failure, n (%)	30 days	183 (0.73)	63 (1.21)	189 (1.45)	104 (2.94)	330 (4.91)	169 (7.15)
		P <0.001		*P* <0.001		*P* <0.001	
	12 months	864 (3.43)	380 (7.28)	816 (6.26)	426 (12.03)	1390 (20.67)	614 (25.96)
		P <0.001		*P* <0.001		*P* <0.001	
	36 months	1541 (6.13)	661 (12.67)	1463 (11.23)	726 (20.50)	2018 (30.01)	867 (36.66)
		P <0.001		*P* <0.001		*P* <0.001	
Hospitalization for renal failure, n (%)	30 days	2904 (11.54)	728 (13.95)	1726 (13.25)	547 (15.44)	1119 (16.64)	479 (20.25)
		P <0.001		*P* <0.001		*P* <0.001	
	12 months	10 831 (43.06)	2630 (50.40)	6034 (46.32)	1861 (52.54)	3696 (54.97)	1417 (59.92)
		P <0.001		*P* <0.001		*P* <0.001	
	36 months	13 981 (55.58)	3400 (65.16)	7703 (59.13)	2366 (66.80)	4570 (67.97)	1696 (71.71)
		P <0.001		*P* <0.001		*P* <0.001	
Cardiac catheterization, n (%)	30 days	1608 (6.39)	364 (6.98)	906 (6.95)	245 (6.92)	376 (5.59)	135 (5.71)
		P = 0.12		*P* = 0.94		*P* = 0.83	
	12 months	6426 (25.55)	1449 (27.77)	3366 (25.84)	974 (27.50)	1549 (23.04)	570 (24.10)
		P <0.001		*P* = 0.046		*P* = 0.29	
	36 months	8132 (32.33)	1893 (36.28)	4241 (32.55)	1241 (35.04)	2065 (30.71)	758 (32.05)
		P <0.001		*P* = 0.005		*P* = 0.23	
PCI, n (%)	30 days	1411 (5.61)	325 (6.23)	784 (6.02)	207 (5.84)	300 (4.46)	109 (4.61)
		P = 0.080		*P* = 0.70		*P* = 0.77	
	12 months	5077 (20.18)	1166 (22.35)	2558 (19.63)	728 (20.55)	1094 (16.27)	403 (17.04)
		P <0.001		*P* = 0.22		*P* = 0.39	
	36 months	6144 (24.42)	1467 (28.11)	3095 (23.76)	921 (26.00)	1385 (20.60)	523 (22.11)
		P <0.001		*P* = 0.006		*P* = 0.12	
CABG, n (%)	30 days	256 (1.02)	84 (1.61)	146 (1.12)	52 (1.47)	76 (1.13)	34 (1.44)
		P <0.001		*P* = 0.09		*P* = 0.24	
	12 months	1460 (15.80)	420 (8.05)	822 (6.31)	272 (7.68)	402 (5.98)	131 (5.54)
		P <0.001		*P* = 0.004		*P* = 0.43	
	36 months	1624 (6.46)	476 (9.12)	932 (7.15)	302 (8.53)	458 (6.81)	158 (6.68)
		P <0.001		*P* = 0.006		*P* = 0.83	
ICD, n (%)	30 days	8 (0.03)	1 (0.02)	13 (0.10)	3 (0.08)	54 (0.80)	22 (0.93)
		P = 0.63		*P* = 0.80		*P* = 0.56	
	12 months	48 (0.19)	9 (0.17)	86 (0.66)	22 (0.62)	417 (6.20)	135 (5.71)
		P = 0.78		*P* = 0.80		*P* = 0.39	
	36 months	108 (0.43)	19 (0.36)	205 (1.57)	57 (1.61)	634 (9.43)	190 (8.03)
		P = 0.51		*P* = 0.88		*P* = 0.04	
CRT-D, n (%)	30 days	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	6 (0.09)	3 (0.13)
		-		-		*P* = 0.62	
	12 months	2 (0.01)	0 (0.00)	7 (0.05)	1 (0.03)	72 (1.07)	22 (0.93)
		P = 0.52		*P* = 0.56		*P* = 0.42	
	36 months	11 (0.04)	1 (0.02)	17 (0.13)	7 (0.20)	133 (1.98)	45 (1.90)
		P = 0.35		*P* = 0.82		*P* = 0.63	

Table 6 (cont.). Three-year post-discharge outcomes in non-diabetic and diabetic patients stratified by ejection fraction

	Follow-up	Non-DM, EF ≥50% (n = 25 075)	DM, EF ≥50% (n = 5191)	Non-DM, EF 40%–49% (n = 12 956)	DM, EF 40%–49% (n = 3511)	Non-DM, EF <40% (n = 6608)	DM, EF <40% (n = 2312)
ICD/CRT-D, n (%)	30 days	8 (0.03)	1 (0.02)	13 (0.10)	3 (0.08)	60 (0.89)	25 (1.06)
		$P = 0.63$		$P = 0.80$		$P = 0.47$	
	12 months	51 (0.20)	9 (0.17)	93 (0.71)	23 (0.65)	487 (7.24)	156 (6.60)
		$P = 0.65$		$P = 0.68$		$P = 0.29$	
	36 months	119 (0.47)	20 (0.38)	219 (1.68)	63 (1.78)	756 (11.24)	235 (9.94)
		$P = 0.38$		$P = 0.69$		$P = 0.08$	
Cardiac rehabilitation, n (%)	30 days	3452 (13.72)	610 (11.69)	1796 (13.79)	303 (8.55)	699 (10.40)	203 (8.58)
		$P < 0.001$		$P < 0.001$		$P = 0.01$	
	6 months	6134 (24.38)	1152 (22.08)	3440 (26.40)	655 (18.49)	1363 (20.27)	391 (16.53)
		$P < 0.001$		$P < 0.001$		$P < 0.001$	
	12 months	6454 (25.66)	1234 (23.65)	3590 (27.56)	708 (19.99)	1443 (21.46)	414 (17.51)
		$P = 0.002$		$P < 0.001$		$P < 0.001$	
Dialysis, n (%)	30 days	37 (0.15)	23 (0.44)	34 (0.26)	20 (0.56)	26 (0.39)	24 (1.01)
		$P < 0.001$		$P = 0.005$		$P < 0.001$	
	12 months	121 (0.48)	67 (1.28)	91 (0.70)	68 (1.92)	83 (1.23)	65 (2.75)
		$P < 0.001$		$P < 0.001$		$P < 0.001$	
	36 months	171 (0.68)	110 (2.11)	132 (1.01)	102 (2.88)	112 (1.67)	85 (3.59)
		$P < 0.001$		$P < 0.001$		$P < 0.001$	

Abbreviations: CABG, coronary artery bypass grafting; CRT-D, cardiac resynchronization therapy device; ICD, implantable cardioverter-defibrillator; PCI, percutaneous coronary intervention; other — see Figure 1 and Table 1

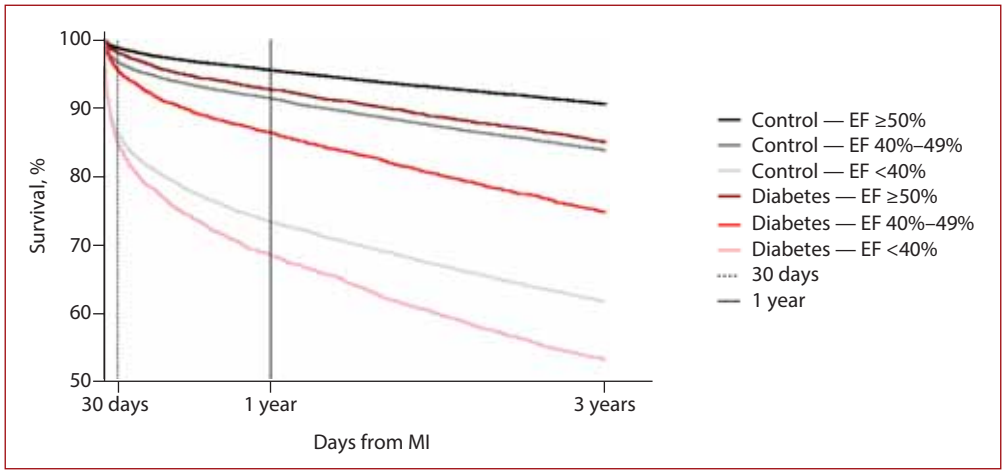

Figure 2. 36-month mortality in diabetic and control groups stratified by ejection fraction

Abbreviations: see Figure 1

subgroups, regardless of diabetes status. However, in the EF ≥50% subgroup, the 30-day mortality was significantly higher in patients with diabetes ($P = 0.03$).

Similarly, in terms of left ventricular systolic dysfunction, 12- and 36-month post-discharge mortality was significantly higher in all diabetic subgroups compared with that in the control subgroups ($P < 0.001$). For non-diabetic patients, the annual mortality rates after hospital discharge in the EF ≥50%, EF 49%–50%, and EF <40% subgroups were 3.62%, 6.05%, and 16.51%, respectively. The 12-month post-discharge mortality rates in the corresponding diabetic EF subgroups were considerably higher at 6.04%, 10.36%, and 21.18%, respectively. Ultimately, the highest 36-month mortality (38.65%) was found in patients with diabetes and an EF of <40%.

No significant differences were observed between patients with and without DM across all subgroups over the 30-day and 12-month follow-up periods in terms of the use of implantable cardiac defibrillators (ICD) or cardiac resynchronization therapy devices (CRT-D). This is in contrast with the 36-month follow-up data, in which non-diabetics from the EF <40% subgroup had higher rates of ICD implantation procedures compared with patients with DM from the EF <40% subgroup ($P < 0.05$). There was no difference in the rates of CRT-D implantation between diabetic and non-diabetic patients.

Unexpectedly, patients with diabetes participated less often in cardiac rehabilitation than patients in the control group over the 1-year follow-up. Despite proven benefits of cardiac rehabilitation, the proportions of diabetic

patients from EF ≥50%, 40%–49%, and <40% subgroups who underwent this type of treatment were lower, 23.65%, 19.99%, and 17.51%, respectively, than in the corresponding non-diabetic subgroups (25.66%, 27.56%, and 21.46%, respectively).

DISCUSSION

The present study attempted to assess the long-term prognosis for diabetic patients who were treated for MI. The outcomes in diabetic patients with reduced left ventricular EF were particularly unfavorable, compared with those in non-diabetic patients with similar EF values.

Long-term outcomes of diabetic patients after MI in the era of thrombolytic treatment have been assessed previously. The GUSTO-I study reported the annual mortality among diabetic patients with STEMI to be 14.5%, compared to 8.9% in non-diabetics [11]. Similar observations come from the OASIS and Valiant trials [12–13]. Also, the contemporary literature includes studies demonstrating a poor prognosis for diabetic patients undergoing treatment for MI [14]. Diabetic patients with MI are at a higher risk of adverse events than non-diabetic patients with MI (HR, 1.40; 95% CI, 1.20–1.64; *P* <0.001). Multivariate analysis results indicated that acute revascularization and medical therapy with aspirin and inhibitors of the renin-angiotensin system may improve patients' prognoses [14]. DM patients with reduced EF are more commonly found to receive insulin or no anti-diabetic treatment compared to DM with normal range EF. Conversely, a tendency towards oral anti-diabetic medication is observed in normal EF range DM patients [3]. New classes of antidiabetic drugs, such as sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1-RAs), are nowadays recommended in diabetes mellitus type 2 (DM2) patients with cardiovascular disease to improve outcomes [15]. Empagliflozin decreased the death rate from cardiovascular causes, non-fatal MI, and stroke and death from any cause in patients with DM2 at high risk for cardiovascular events, as compared with placebo [16]. In the LEADER Trial, Liraglutide reduced the risk of death from cardiovascular causes, MI and stroke in patients with DM [17].

We analyzed the prognosis for MI patients based on the degree of left ventricular systolic dysfunction (expressed in terms of EF). Stolfo et al. concluded that the EF assessed at hospital discharge proved to be a better predictor than the EF recorded earlier during hospitalization [18]. Our study results were based on the last measurement of EF made during hospitalization. Solomon et al. [19] revealed that most of the observed functional improvement occurred by day 14 after MI. The improvement in left ventricular EF after MI begins within three days of coronary revascularization [19]. Stolfo et al. [18] evaluated EF at three different time points after STEMI (<24 hours after coronary angioplasty, at hospital discharge, and three months after MI) and reported that the independent predictors of decreased EF (<35%) 3 months after revascularization are creatinine levels on hospital admission, peak troponin I levels, and EF during hospitalization. In our analysis, patients with DM from all evaluated EF ranges fared worse than their non-diabetic counterparts in the long-term follow-up, as evidenced by increased risks of mortality, stroke, re-infarction, hospitalization for HF, and end-stage renal failure requiring dialysis. The mortality rate in patients with HF, or reduced EF after MI, was twice as high as in patients with preserved or mid-range EF and no symptoms of HF [20, 21].

Yet another important observation from our study concerns the prognosis for patients with mid-range ejection fraction. Our study revealed that patients with EF of 40%–49% have a much worse prognosis than those with preserved EF regardless of their diabetic status. Multivariate analysis results showed that patients with EF of 40%–49% from both the diabetic and control groups had an over 50% higher risk of death compared with the groups with an EF of ≥50%. There have been no data in the current literature that are consistent with our findings.

Our study proves beyond any doubt that patients with diabetes are more prone to cardiovascular events and hospitalization prompted by HF. Re-infarction was more common among diabetic patients in all three EF subgroups. Similarly, the EPHESUS study assessed the impact of diabetes on the prognosis for patients with MI with reduced EF. Diabetes was also identified as an independent risk factor for the onset of another MI, but not necessarily resulting in death. However, no correlation was found between diabetes and the incidence of fatal MI during 2.5 years of follow-up [22]. In our study, diabetes correlated with the rate of hospitalizations for HF across all three EF subgroups. In an observational registry, ACS exacerbated by HF was shown to result in significantly worse outcomes than ACS without HF over a 6-month follow-up. HF was associated with reduced hospitalization and 6-month survival rates across all ACS subsets. ACS patients who were diagnosed with HF on admission had an approximately threefold decrease in their 6-month post-discharge survival rate (mortality rates of 8.5% in those with an admission diagnosis of HF vs. 2.8% in those without HF, respectively; *P* <0.001) and were also more likely to be re-hospitalized (23.6% vs. 15.7%, respectively, *P* <0.001) [23]. Similarly, Hung et al. [24] showed that the incidence of death in patients with MI complicated by HF was greater than in patients without HF after a 1-year follow-up. Development of HF within 90 days of the index MI hospitalization yielded an adjusted HR of 2.7 for 1-year mortality in 90-day survivors.

Every 5% reduction in EF increases the risk of cardiac arrest or sudden cardiac death by 21% in the first 30 days after MI [5]. Similarly, our patients with reduced EF had a much higher 30-day mortality rate (15.09% in DM and 13.65% in non-DM patients) compared with patients with mid-range EF (4.04% in DM and 3.36% in non-DM patients). We concluded that a reduction in EF increased 36-month mortality by 30% for each 5% decrease in EF.

Future investigations after the implementation of new recommendations will be interesting. SGLT-2 inhibitors in addition to standard care found a new place for both diabetic and non-diabetic patients with cardiovascular disease. Dapagliflozin or empagliflozin are recommended for patients with symptomatic HF and EF≤40% despite optimal medical therapy to reduce the risk of hospitalization and death. This first-class recommendation of the ECS guidelines results from recently conducted studies [25, 26].

We identified the following three parameters as independent factors for lower mortality: BMI, hypercholesterolemia, and hypertension. Higher BMI and lower mortality in chronic coronary artery disease and ACS patients are considered a "BMI paradox". Our observations are consistent with those resulting from analysis of other large registries [27, 28]. In the registry, which is a collection of data on 64 436 patients who underwent coronary angiography due to ACSs, the relation between BMI and mortality was U-shaped, the lower risk of mortality was noted in moderately overweight patients (BMI of 26.5–28 kg/m^2) [27]. In-hospital mortality was also assessed in over 50 000 patients hospitalized for STEMI in the United States [28]. Using patients with BMI between 30 kg/m^2 and 35 kg/m^2 as a reference, risk-adjusted in-hospital mortality rates were significantly higher only for patients with BMI of ≥40 kg/m^2 (HR, 1.64; CI, 95% 1.32–2.03).

Epidemiological data about the association between hypertension and prognosis in patients with ACS are inconclusive [29]. Some studies showed an unfavorable association between hypertension and in-hospital [30], 30-day [31], or long-term prognosis [32], whereas other studies demonstrated no association between hypertension and long-term mortality or even showed higher mortality in normotensive patients [33]. The possible explanation of lower mortality in patients with hypertension and hypercholesterolemia may be associated with the use of angiotensin-converting enzyme inhibitors, β-blockers, and statins in the period before hospitalization.

Our analysis of the 36-month data revealed that a greater proportion of non-diabetic patients in the EF <40% subgroup received an ICD compared with diabetic patients (P <0.05), despite the current guidelines. By way of explanation, diabetes may curtail the effectiveness of ICDs in patients with reduced EF [34]. In addition, in a recent meta-analysis [35] including a combined total of 3359 patients from MADIT I, MADIT II, DEFINITE, and SCD-HeFT studies, ICD implantation reduced overall mortality in non-diabetic patients but not in patients with DM. It is, therefore, imperative that prospective research studies be performed on whether to implant ICDs in patients with diabetes and reduced EF.

In-hospital and post-discharge care for AMI patients is related to a major adverse cardiovascular events rate reduction by 45% in 3 months [36]. Although cardiac rehabilitation after MI has been proven to reduce cardiovascular mortality by 20%, diabetic patients participated less frequently in cardiac rehabilitation within the first year after their MI (regardless of EF values) [37]. In addition, cardiac rehabilitation after MI improves exercise capacity, which is significantly lower in patients with diabetes compared to that in non-diabetics [38]. Consequently, greater emphasis should be placed on referring diabetic patients for cardiac rehabilitation.

Study strengths and limitations

The strength of this study derives from analyzing an extensive data set and the use of uniform diagnostic and treatment procedures. The percentage of missing values in the PL-ACS registry used in multivariate analyses was low (<0.5%) thus multivariate analyses were performed with the exclusion of patients with missing data. Since this was a non-randomized observational study, the possible interdependence of some variables, including the effects of the patients' medications, is unknown. We were unable to measure the EF after the index hospitalization. Possibly, the inter-observer variability could be an issue in this study, but the huge number of patients we analyzed from the different centers strongly reduces the possibility of its negative impact.

CONCLUSION

We presented data, representing 36-month post-MI follow-up, obtained from a large national ACS Registry. In addition, we conducted outcome analyses as a function of the degree of left ventricular systolic dysfunction after MI. The worst outcome with a 36-month mortality rate of 46.64% was in patients with diabetes and EF below 40%. In our multivariate analysis, diabetes and decreased EF after MI were independent risk factors of mortality during the 36-month follow-up.

Finally, we would like to emphasize that the present study is only an attempt to highlight the common clinical problems posed by MI treatment in patients with comorbid diabetes. Certainly, further research on the group of patients with mid-range EF would be interesting.

Our study is intended to spur a discussion on multivariate aspects of in-hospital and, which is equally important, outpatient treatment to improve the unfavorable prognosis in DM patients with MI.

Supplementary material

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

Article information

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Non-invasive right ventriculo-arterial coupling as a rehospitalization predictor in dilated cardiomyopathy: A comparison of five different methods

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ABSTRACT

Background: Right ventricular (RV) pulmonary artery coupling (RVPAC) is a predictor of outcome in left-sided heart failure (HF). Several echocardiographic estimates for RVPAC have been proposed.

Aims: This study aimed to compare multiple non-invasive methods to calculate RVPAC and to assess its prognostic role in patients with dilated cardiomyopathy (DCM).

Methods: We prospectively enrolled 60 stable patients with DCM. RVPAC was estimated using five methods: as the tricuspid annular plane excursion/pulmonary artery systolic pressure (PASP) ratio; as the RV global longitudinal strain/PASP ratio; as the RV free wall strain (RVFW-LS)/PASP ratio; as the three-dimensional (3D) RV ejection fraction (RVEF)/PASP ratio; and as the 3D RV stroke volume (SV)/end-systolic volume (ESV) ratio. Patients were followed for a mean period of 18 (9) months for the endpoint of HF rehospitalizations.

Results: Twenty-nine patients (48%) reached the endpoint. All RVPAC estimates were more impaired in those patients reaching the endpoint (P <0.001 for all) and all predicted rehospitalizations in unadjusted analysis. RVFW-LS/PASP and RVEF/PASP remained independent predictors of events, after adjustment for clinical and echocardiographic confounders. Using cut-offs obtained from receiver operating characteristic (ROC) analysis, we found that patients with RVFW-LS/PASP >–0.40 and patients with RVEF/PASP <1.30 had a higher risk of HF rehospitalization (log-rank P = 0.001 and P = 0.002, respectively).

Conclusion: RVFW-LS/PASP and RVEF/PASP as non-invasive estimates of RVPAC are independent predictors of HF rehospitalization in patients with DCM.

Key words: dilated cardiomyopathy, right ventricular-pulmonary artery coupling, RVEF/PASP ratio, RVFW-LS/PASP ratio

INTRODUCTION

The prognostic role of right ventricular (RV) dysfunction in various cardiovascular diseases is well established [1–3]. While impaired RV performance is a recognized outcome predictor in left-sided heart disease [4, 5], there is growing interest regarding the role of right ventriculo-vascular interplay in patients with heart failure (HF) [6, 7]. RV-pulmonary artery coupling (RVPAC) characterizes the interaction between ventricular contractility and its afterload, thus allowing the evaluation of the RV and pulmonary circulation as an anatomically and functionally interconnected system [8]. The gold standard for RVPAC measurement is the ratio between end-systolic RV elastance and pulmonary arterial elastance, derived from invasive pressure-volume loops [9]. However, RVPAC can be estimated non-invasively using echocardiography and several surrogate parameters [10–13].

We hypothesized that right ventriculo-vascular decoupling is related to the risk of rehospitalization for HF in patients with dilated

WHAT'S NEW?

In our study, we compared five different methods for the non-invasive estimation of right ventricular-pulmonary artery coupling (RVPAC) in patients with dilated cardiomyopathy. Patients with exacerbation of heart failure requiring hospitalization had significantly more impaired RVPAC. Among the different surrogates of RVPAC, the only two independent event predictors were the ratio of right ventricular free wall strain to pulmonary artery systolic pressure, and the ratio of three-dimensional right ventricular ejection fraction to pulmonary artery systolic pressure.

cardiomyopathy (DCM). We sought to assess the prognostic role of RVPAC in this setting while comparing different non-invasive methods for RVPAC estimation — using both conventional and advanced echocardiographic techniques such as three-dimensional (3D) and speckle-tracking echocardiography (STE).

METHODS

Study population

We prospectively enrolled consecutive outpatients with non-ischemic DCM who were referred to our echocardiography department between January 2019 and December 2019. DCM was defined [14] based on the following criteria: (1) dilated left ventricle (LV), according to cut-offs from the current guidelines of chamber quantification [15]; (2) Simpson biplane LV ejection fraction (LVEF) <40%; and (3) absence of significant coronary artery disease (defined as >70% stenosis of a major epicardial vessel). Since the right heart is highly dependent on loading conditions, we only included patients that were clinically and hemodynamically stable, with no change in diuretic dose in the two weeks before enrollment. We excluded patients with poor acoustic window, atrial fibrillation, or inability to hold the breath (which would have hampered 3D acquisitions), severe tricuspid regurgitation (TR), and cor pulmonale. Sixty patients formed the final study cohort. Investigators collected demographic and clinical data, including cardiovascular risk factors, a New York Heart Association (NYHA) class, and brain natriuretic peptide (BNP) levels, when available. The study protocol, complying with the Declaration of Helsinki, was approved by the local ethics committee of the Emergency Clinical Hospital of Bucharest, and all patients provided written informed consent at enrollment.

For our study, the endpoint was the first episode of HF exacerbation requiring hospitalization. Patients were prospectively followed by regular clinical visits and phone contact to ascertain the occurrence of the main endpoint, and the time of the first rehospitalization was used in our survival analysis. The follow-up was conducted for 18 (9) months.

Echocardiographic assessment

We performed comprehensive two-dimensional (2D) echocardiographic examinations for all patients with a Vivid GE Vingmed E9 ultrasound machine equipped with an M5S probe. Offline data analysis was done using dedicated software (EchoPAC BT 12, General Electric Healthcare, Milwaukee, WI, USA). For the LV, we assessed the dimensions, systolic and diastolic function according to current recommendations [16]. For the RV, we measured conventional parameters of systolic function such as tricuspid annular plane systolic excursion (TAPSE), peak systolic tissue Doppler velocity of the tricuspid annulus (S wave), and RV fractional area change (RV-FAC) from apical RV-focused view, as recommended [16, 17].

For RV strain, we used high frame-rate acquisitions and we manually traced the RV endocardial border at end-systole. Readjustments were made if needed, including in the region of interest, the whole RV wall, but excluding the pericardium. EchoPAC — Q Analysis software automatically divided the RV into six segments, three for the RV free wall (RVFW), and three for the interventricular septum (IVS). We then calculated the global longitudinal strain of the RV (GLS-RV) as the mean of the six segments, and the longitudinal strain of the RVFW (RVFW-LS) as the mean of the three RVFW segments, as recommended [18, 19]. Normal strain values are negative [18] because it is a measure of myocardial shortening; thus, values that are less negative reflect impaired myocardial shortening.

For estimation of pulmonary artery systolic pressure (PASP), we used the maximal velocity of the TR jet (TRV_{max}) obtained from the continuous wave Doppler spectrum and right atrial pressure (RAP): $PASP = 4 \times TRV_{max}^2 + RAP$. RAP was estimated based on the inferior vena cava diameter and respiratory collapsibility, as described in guidelines [16].

Using a 4V probe, we performed six-beat full-volume 3D acquisitions, with electrocardiographic gating during apnea. We used the apical RV-focused view for 3D data sets acquired for the assessment of the RV [20]. We performed offline image post-processing and reconstruction using 4D RV-Function software (TomTec Imaging Systems, Unterschleissheim, Germany). After tracing the endocardial surface of the RV at both end-systole and end-diastole, the software generated the RV stroke volume (SV), ejection fraction (RVEF), end-diastolic and end-systolic volume (ESV) (Figure 1). Inter- and intra-observer reproducibility for RV strain and RVEF in our laboratory has been recently published [5].

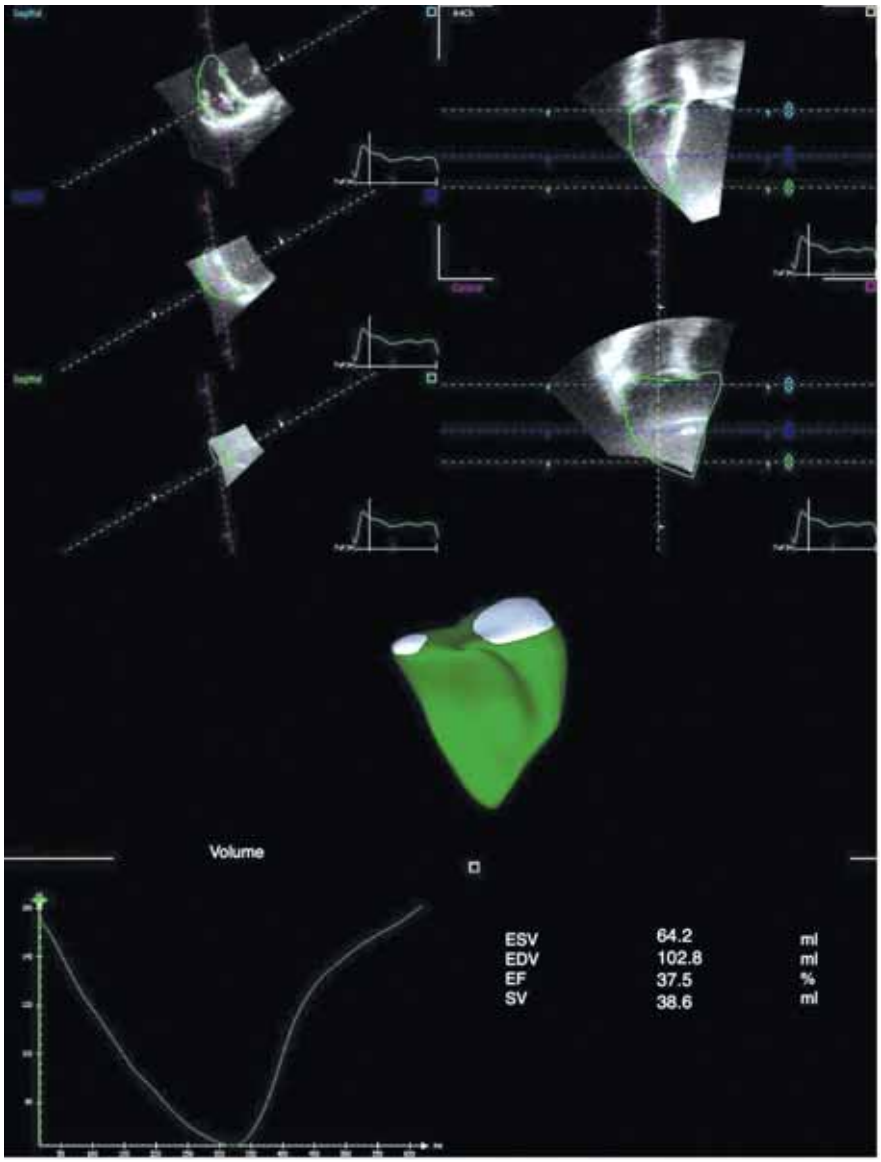

Figure 1. Three-dimensional volumetric assessment of the right ventricle using dedicated software

Abbreviations: ESV, end-systolic volume; EDV, end-diastolic volume; EF, ejection fraction; SV, stroke volume

Non-invasive estimation of RVPAC

We estimated the RVPAC using five different methods, all of which were previously proposed and studied:

- as the TAPSE/PASP ratio [10, 21];
- as the GLS-RV/PASP ratio [12, 22];
- as the RVFW-LS/PASP ratio [12, 23];
- as the 3D RVEF/PASP ratio [11]; and
- as the 3D SV/ESV ratio [24, 25].

Statistical analysis

All analysis was performed with SPSS version 20.0 statistical software package. The Kolmogorov-Smirnov test was used to check whether variables were normally distributed. Continuous data were expressed as mean (standard deviation [SD]) if normally distributed, or as median and interquartile range otherwise, and compared with Student's t-test or the Mann-Whitney U test (as dictated by distribution). Pearson's correlation coefficient was used to assess correlations between continuous variables. Categorical data were expressed as numbers and percentages, and they were compared using the test.

We used receiver operating characteristic (ROC) curves and the respective area under the curve (AUC) to identify optimal cut-off values for event prediction, based on the highest sum of sensitivity and specificity. Using these cut-offs, we performed Kaplan-Meier analysis for event-free survival, and we compared survival curves with the log-rank test. We performed Cox proportional hazards regression to determine the prognostic power of non-invasive RVPAC. Results were reported as hazard ratios (HR) with 95% confidence intervals (CI). We constructed the multivariable model choosing covariates that have clinical relevance and are well-established event predictors in DCM: age, an NYHA class, LVEF, and the mitral E/E' ratio. Statistical significance was defined as a two-tailed *P*-value <0.05.

Table 1. Basic characteristics

Variables	Overall (n = 60)	Hospitalized (n = 29)	Not hospitalized (n = 31)	*P*-value
Age, years	61 (14)	61 (14)	60 (14)	0.79
Men, n (%)	40 (67)	19 (66)	21 (68)	0.86
Systolic BP, mm Hg	124 (13)	122 (13)	125 (12)	0.32
Diastolic BP, mm Hg	75 (11)	72 (10)	77 (11)	0.04
Heart rate, bpm	78 (15)	80 (17)	77 (13)	0.44
NYHA class, n (%)				0.003
I	2 (3)	0 (0)	2 (6)	
II	27 (45)	7 (24)	20 (65)	
III	25 (42)	17 (59)	8 (26)	
IV	6 (10)	5 (17)	1 (3)	
Comorbidities, n (%)				
Hypertension	41 (68)	17 (59)	24 (77)	0.12
Diabetes mellitus	11 (18)	6 (21)	5 (16)	0.65
Smoking	19 (32)	8 (28)	11 (35)	0.51
CKD	37 (62)	19 (66)	18 (58)	0.55
Medication, n (%)				
ACE-I/ARBs/ARN-I	57 (95)	28 (97)	29 (94)	0.59
β-blocker	59 (98)	28 (97)	31 (100)	0.48
MRA	58 (97)	29 (100)	29 (94)	0.49
Loop diuretic	41 (68)	24 (83)	17 (55)	0.02
Digoxin	11 (18)	8 (28)	3 (10)	0.07
BNP levels, pg/ml	478 (286–910)	703 (404–1080)	388 (204–535)	0.005

Continuous data are expressed as mean (standard deviation [SD]) or median (interquartile range [IQR]), depending on the distribution. Categorical data are expressed as number (percentage)

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARN-I, angiotensin receptor neprilysin inhibitor; BP, blood pressure; BNP, brain natriuretic peptide; n, number of patients; NYHA, New York Heart Association; CKD, chronic kidney disease; MRA, mineralocorticoid receptor antagonist

RESULTS

Study population

The mean age in the study group was 61 (14) years and the majority (67%) were men. During the mean follow-up of 18 (9) months, 29 patients (48%) reached the main endpoint, being at least once hospitalized for an exacerbation of HF. Twelve patients (20%) were admitted more than once for decompensated HF during the follow-up. At the end of the follow-up period, there was a total number of 52 re-hospitalizations for HF, 4 deaths (all occurring in patients who had already reached the main endpoint), 5 non-fatal cardiac arrests, no heart transplantation, and no ventricular assist device implantation. There was no difference in terms of age and comorbidities between patients reaching the primary endpoint and those who did not (Table 1). Serum BNP was available in 52 (87%) patients. The prevalence of loop diuretic use, as well as BNP levels, were higher among patients who required rehospitalization (P = 0.02 and P = 0.005, respectively).

Echocardiographic data

All echocardiographic data are summarized in Table 2. While LVEF was similar between patients with and without adverse outcomes (P = 0.17), there were significant differences between the two groups in indices reflecting LV diastolic dysfunction. RV function, assessed by both conventional parameters and innovative parameters, was significantly more impaired in patients with adverse outcomes, while PASP was higher in patients with events, with marginal significance (P = 0.049). All five estimates of RVPAC were more impaired in patients with events (P <0.001 for all).

The prognostic role of non-invasive RVPAC

Table 3 shows the univariable and multivariable Cox regression for the primary endpoint of HF rehospitalizations. All RVPAC surrogates were endpoint predictors in unadjusted analysis. LVEF did not emerge as a predictor of hospitalizations in unadjusted analysis (P = 0.12). We also performed ROC analysis to assess the ability of RVPAC to predict rehospitalizations. As shown in Figure 2, all RVPAC surrogates outperformed LVEF, and they all had good AUCs (Table 4). However, after adjusting for the clinical and echocardiographic confounders in the multivariable model, the RVFW-LS/PASP ratio and the RVEF/PASP ratio were the only RVPAC estimates that remained independent predictors of rehospitalizations (Table 3). The best cut-off value for predicting outcome was –0.40 for RVFW-LS/PASP (sensitivity 69%, specificity 77%) and 1.30 for RVEF/PASP (sensitivity 83%, specificity 65%). Kaplan-Meier survival curves stratified by these cut-offs are shown in Figure 3. The risk of rehospitalization was higher in patients with RVFW-LS/PASP over –0.40 (HR, 3.653; 95% CI, 1.657–8.051; P = 0.001) and in patients with RVEF/PASP less than 1.30 (HR, 3.600; 95% CI, 1.464–8.854; P = 0.002) in univariable analysis.

Table 2. Echocardiographic data

Variables	Overall (n = 60)	Hospitalized (n = 29)	Not hospitalized (n = 31)	*P*-value
LV parameters				
LV end-diastolic diameter, mm	66 (9)	66 (8)	65 (10)	0.48
LVEDV, ml	225 (87)	233 (88)	217 (88)	0.48
LVESV, ml	170 (76)	179 (7)	161 (77)	0.38
LVEF, %	26 (7)	24 (7)	27 (7)	0.17
Mitral E/E' ratio	14.3 (6.6)	16.6 (8.1)	12.1 (4.8)	0.008
LA volume index, ml/m^2	45 (24)	56 (27)	34 (15)	<0.001
RV parameters				
RV basal diameter, mm	37 (33–42)	38 (35–47)	34 (31–37)	0.002
Tricuspid E/E' ratio	5.8 (2.9)	6.4 (3.3)	5.3 (2.4)	0.13
TAPSE, mm	18 (4)	16 (4)	20 (4)	<0.001
S wave velocity, cm/s	11.1 (2.8)	9.8 (2.7)	12.4 (2.2)	<0.001
RV-FAC, %	33 (12)	31 (12)	35 (11)	0.12
GLS-RV, %	–12.2 (5.3)	–9.8 (4.6)	–14.4 (5.0)	<0.001
RVFW-LS, %	–14.8 (9.3)	–11.1 (7.2)	–18.2 (10.1)	0.003
3D RVEDV, ml	139 (53)	140 (56)	139 (52)	0.94
3D RVESV, ml	80 (31)	88 (35)	72 (25)	0.051
3D RV SV, ml	60 (31)	52 (25)	67 (34)	0.06
3D RVEF, %	42 (10)	37 (9)	47 (9)	<0.001
PASP (mm Hg)	39 (17)	44 (16)	35 (17)	0.049
RVPAC estimates				
TAPSE/PASP	0.56 (0.28)	0.43 (0.21)	0.68 (0.29)	<0.001
GLS-RV/PASP	–0.37 (0.22)	–0.26 (0.17)	–0.47 (0.21)	<0.001
RVFW-LS/PASP	–0.45 (0.38)	–0.27 (0.36)	–0.61 (0.32)	<0.001
RVEF/PASP	1.28 (0.61)	0.97 (0.38)	1.57 (0.65)	<0.001
RV SV/ESV	0.80 (0.36)	0.62 (0.24)	0.96 (0.38)	<0.001

Data are expressed as mean (standard deviation [SD]) or median (interquartile range [IQR]), depending on the distribution
Abbreviations: see Figures 1 and 2

Table 3. Univariable and multivariable Cox regression analysis

Variables (per unit increase)	Unadjusted		Adjusted[a]	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
TAPSE/PASP	0.050 (0.008–0.302)	0.001	0.158 (0.019–1.280)	0.084
GLS-RV/PASP	31.193 (4.337–224.363)	0.001	8.215 (0.966–69.889)	0.054
RVFW-LS/PASP	5.010 (2.090–11.964)	<0.001	3.122 (1.135–8.584)	0.027
RVEF/PASP	0.245 (0.109–0.553)	0.001	0.381 (0.147–0.988)	0.047
RV SV/ESV	0.069 (0.014–0.347)	0.001	0.183 (0.032–1.033)	0.054

[a]Adjusted for age, NYHA class, LVEF, mitral E/E' ratio

Abbreviations: see Figures 1 and 2

Table 4. AUC for parameters to identify the risk of rehospitalization

Parameter	AUC (95% CI)	*P*-value	Cut-off
TAPSE/PASP	0.756 (0.635–0.877)	0.001	0.47
GLS-RV/PASP	0.784 (0.667–0.901)	<0.001	–0.37
RVFW-LS/PASP	0.766 (0.646–0.885)	<0.001	–0.40
RVEF/PASP	0.782 (0.667–0.897)	<0.001	1.30
RV SV/ESV	0.789 (0.673–0.904)	<0.001	0.65
LVEF	0.606 (0.461–0.752)	0.158	24.2

Abbreviations: see Figures 1 and 2

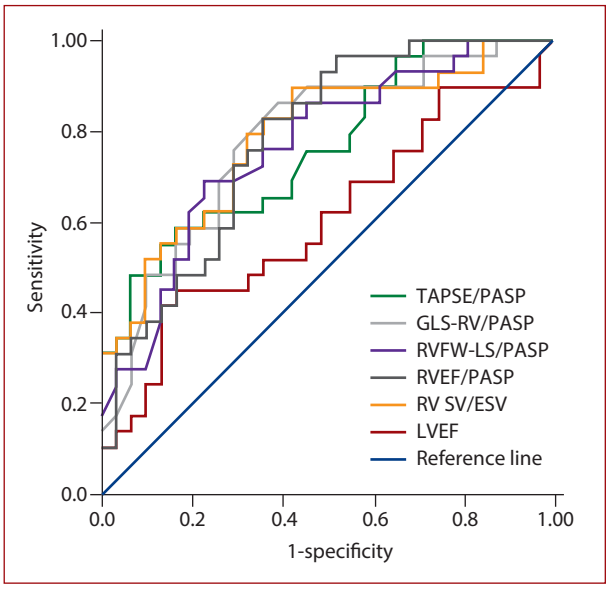

Figure 2. Receiver-operating characteristic analysis of RVPAC and LVEF for the prediction of rehospitalizations

Abbreviations: GLS-RV, global longitudinal strain of the right ventricle; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; ROC, receiver operating characteristic; RV, right ventricle; RVPAC, right ventricular-pulmonary artery coupling; RVFW-LS, longitudinal strain of the right ventricular free wall; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion; other — see Figure 1

We also tested the constituents of the RVFW-LS/PASP and RVEF/PASP ratios in the same multivariable model. RVEF independently predicted HF hospitalizations (HR, 0.951; 95% CI, 0.906–0.999; $P = 0.046$), while RVFW-LS and PASP did not (HR, 1.037; 95% CI, 0.996–1.080, $P = 0.08$ and HR, 1.011; 95% CI, 0.988–1.035; $P = 0.35$, respectively).

DISCUSSION

The findings of our study can be summarized as follows: (1) non-invasive RVPAC was significantly more impaired in patients with DCM who were rehospitalized for HF exacerbation, irrespective of the method used for RVPAC estimation; (2) the RVFW-LS/PASP and RVEF/PASP ratios were the only RVPAC estimates that remained independent predictors of hospitalization; (3) RVFW-LS/PASP >–0.40 and RVEF/PASP <1.30 were proposed as cut-offs for predicting a high risk of HF hospitalization.

In DCM, pulmonary hypertension develops as a direct consequence of increased left-sided filling pressures. Initially, the right ventricle will adapt by hypertrophy and remodeling, which will allow for an initial increase in contractility. As the disease progresses, RV maladaptation occurs, and the RV begins to dilate, leading to an impairment of its ejection force and ventriculo-vascular mismatch [26]. This loss of mechanical efficiency of RV contraction in relation to its afterload precedes overt right HF [27]. Hence, early identification of right ventriculo-vascular decoupling would potentially detect those patients at risk of developing RV failure [21]. Since RV functional assessment with echocardiography requires a multi-parametric approach [28], several non-invasive estimates for RVPAC have been proposed [10–13, 24]. However, this is the first study to compare the prognostic value of multiple RVPAC estimates in the same population, using parameters derived from both conventional and advanced echocardiography. To our knowledge, this study is also the first to assess RVPAC as an outcome predictor in DCM.

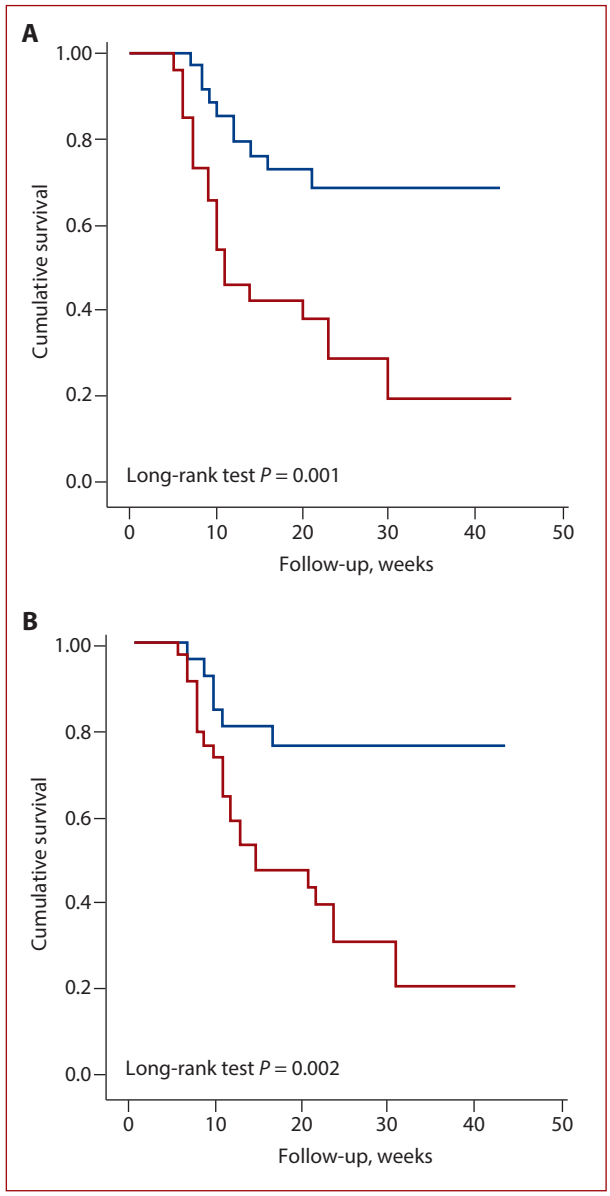

Figure 3. Kaplan-Meier analysis stratified by optimized cut-offs for RVFW-LS/PASP (**A**) and RVEF/PASP (**B**)

Abbreviations: RVEF, right ventricular ejection fraction; other — see Figures 1 and 2

All five RVPAC estimates were outcome predictors in unadjusted analysis in our study. Surprisingly, TAPSE/PASP — the most frequently used surrogate for RVPAC in existing literature [10, 13, 21] — as well as GLS-RV/PASP lost their predictive power in multivariable analysis. This

is contrary to the findings of some studies, which found that TAPSE/PASP [6, 10, 29] and GLS-RV/PASP [12] are independent predictors of events in chronic left-sided HF. The most probable explanation for this discrepancy is that none of these above-mentioned studies included in their multivariable model the mitral E/E' ratio or the left atrial volume. LV diastolic dysfunction is pathophysiologically linked to RV functional impairment [30], so indices of diastolic dysfunction may attenuate the predictive power of RV function in multivariable models. The SV/ESV ratio also lost its predictive role when adjusted for confounders, and it showed weaker correlations with all the other RVPAC surrogates (Table 3). While it was found to have a good correlation with invasive RVPAC in a recent study [24], the prognostic value of the SV/ESV ratio was only tested in a pediatric population with pulmonary hypertension [25], without available data on its role in left-sided HF.

RVFW-LS/PASP remained an independent predictor of HF hospitalizations in our cohort. Similar results were reported by Iacoviello et al. [12], who found that RVFW-LS/PASP was an independent predictor of death in chronic HF, in a clinical and echocardiographic multivariable model. However, our study is the first to report this RVPAC surrogate as an independent predictor of outcome after controlling simultaneously for both clinical and echocardiographic risk factors. Moreover, RVFW-LS/PASP outperformed RVFW-LS and PASP, which did not independently predict hospitalizations in our study. This suggests that indexing RV function to its afterload provides a better assessment of the interconnected system of the RV and pulmonary artery, and better identification of patients at risk, probably by identifying those patients who are in the phase of transition to overt RV failure [12]. In the current study, we also found RVEF/PASP to be an independent predictor of hospitalizations for DCM. This RVPAC estimate was previously tested by Nochioka et al. [11] in a community-based elderly cohort including both patients with clinically overt HF and at risk of developing HF, and it showed an independent predictive value for HF hospitalization or death.

The superiority of RVFW-LS/PASP and RVEF/PASP over other echocardiographic surrogates of RVPAC might be explained by the very superiority of RVFW-LS and 3D RVEF over other conventional parameters of RV function. Carluccio et al. showed in their previous study that RVFW-LS is a better outcome predictor in left-sided HF than TAPSE [4] and GLS-RV [31]. We reported in a recent article [5] that 3D RVEF is an independent predictor of adverse events in DCM, outperforming other RV functional indices in this clinical setting. Compared to other parameters assessing RV longitudinal function (such as TAPSE and S wave velocity), RVFW-LS detects subtle myocardial abnormalities and is relatively angle-independent [32]. Moreover, compared to GLS-RV, it is considered more specific for the RV [33] because GLS-RV also integrates the motion of the IVS (common to both ventricles), and LV dysfunction might restrict its value [31]. 3D RVEF is particularly useful for RV assessment because it is the only parameter that overcomes 2D geometric assumptions and integrates the longitudinal, radial, and anteroposterior components of RV contraction [33]. The fact that LVEF was not a predictor of rehospitalizations in our study might be partly explained by the fact that it was severely reduced throughout the entire cohort, with its values within a narrow range. Previous data suggested that the ability of LVEF to predict rehospitalizations is not related to its absolute value, but rather to its trajectory over time and its correlation with the patient's hemodynamic and neurohormonal status [34].

Implications

This echocardiographic study is the first to perform a point-by-point comparison of multiple methods to estimate RVPAC and of their prognostic role in DCM. Our results highlight the importance of evaluating the RV and pulmonary circulation as an integrative unit improving prognostic prediction accuracy when combining parameters of RV function with PASP. Among different non-invasive surrogates for RVPAC, RVFW-LS/PASP and RVEF/PASP — both derived from innovative echocardiographic techniques — are independent predictors for HF rehospitalizations in DCM and might improve risk stratification in clinical practice.

Limitations

The main limitation of this study is the lack of concomitant validation of echocardiographic RVPAC with gold-standard invasive measurements. However, the surrogates we chose in this study have been previously utilized and validated with catheterization-derived RVPAC [10, 24]. Another limitation comes from the small sample size and the single-center design. Last but not least, a good acoustic window and a regular heart rhythm are mandatory to accurately interpret 3D acquisitions and, by excluding patients with atrial fibrillation or poor window, our data became vulnerable to selection bias. This might be particularly important for atrial fibrillation patients because a recent study found that the prevalence of this arrhythmia among patients with DCM is as high as 30% [35]. Further research will be needed to establish if these results can be extrapolated to larger cohorts.

CONCLUSION

We found that RVFW-LS/PASP and RVEF/PASP are independent predictors for HF rehospitalization in patients with DCM. This study reinforces the idea that the RV and pulmonary circulation are intertwined components of a functional unit, that right ventriculo-vascular interaction has an independent prognostic role in left-sided HF and that RVPAC assessment, which can also be done non-invasively, might improve risk stratification, should it be validated in further research.

Article information

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Sleep-disordered breathing as a risk factor for unnecessary pacemaker implantation

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ABSTRACT

Background: Sleep-disordered breathing (SDB) is a risk factor for bradyarrhythmia, which is reversible with positive airway pressure therapy.

Aims: The study aims to evaluate the occurrence and number of severe sinus bradycardia and advanced atrioventricular block (AVB) in patients with cardiovascular diseases and SDB risk factors.

Methods: The analysis covered 207 patients with cardiovascular diseases aged 59.4 (standard deviation [SD], 10.49) years, including 177 men (85.51%), hospitalized in the Department of Electrocardiology and the Day Stay Cardiac Rehabilitation Ward Upper-Silesian Medical Centre in Katowice, Poland. The inclusion criterion was a high risk of SDB, in particular obstructive sleep apnea (OSA), in one of the following questionnaires: the Four-Variable Screening Tool, the STOP-Bang Questionnaire, and the Epworth Sleepiness Scale. Both level-3 portable sleep tests and electrocardiogram Holter recordings were made simultaneously.

Results: SDB was confirmed in 175 (84.5%) patients, including severe in 74 (35.7%), moderate in 42 (20.3%), and mild in 59 (28.5%) participants. The dominant type of SDB was OSA, which was found in 158 (76.3%) participants. The severe SDB was a predictor of third-degree AVB (odds ratio [OR], 11.61; 95% confidence interval [CI], 1.37–98.60), second-degree AVB type 2 (Mobitz) (OR, 4.51; 95% CI, 1.17–18.08), pauses above 3 seconds (OR, 10.26; 95% CI, 2.18–48.40), and sinus bradycardia below 40 bpm (OR, 3.00; 95% CI, 1.36–6.60) during sleep.

Conclusions: SDB, with particular emphasis on OSA, is a risk factor for sinus bradycardia and advanced AVB during sleep, which may lead to a hasty qualification for pacemaker implantation. The severity of SDB determines the frequency and number of bradyarrhythmic episodes.

Key words: conduction disorders, pacemaker implantation, sleep-disordered breathing

INTRODUCTION

Sleep-disordered breathing (SDB) in the forms of obstructive sleep apnea (OSA) and central sleep apnea (CSA) increases the risk of cardiovascular (CV) complications, such as difficult-to-control arterial hypertension, heart failure, coronary artery disease, cerebrovascular accidents, arrhythmias, and sudden cardiac death, as well as sinus bradycardia and atrioventricular block (AVB) [1–4]. Nocturnal episodes of upper airway obstruction due to pharyngeal wall collapse are a cause of OSA, with older age, male sex, obesity, and large neck circumference being major risk factors [5, 6]. CSA, on the other hand, is caused by unstable ventilatory control during sleep and occurs in a significant percentage of patients with congestive heart failure [6, 7]. Apnea-related bradycardia and AVB are associated with hypervagotonia [8] and are reversible

WHAT'S NEW?

Sleep-disordered breathing (SDB) is common in patients with cardiovascular diseases and is a risk factor for nocturnal bradyarrhythmias. Even severe bradycardia and advanced atrioventricular block in patients with sleep apnea syndrome can be vagally mediated. In this case, they do not require the implantation of a pacemaker. Published on August 29, 2021, the "2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy" recommend that patients with asymptomatic nocturnal sinus bradycardia or atrioventricular block be assessed for the presence of SDB (Class I C).

with the implementation of adequate treatment, including positive airway pressure (PAP) therapy [9, 10]. Nevertheless, a failure to diagnose and treat SDB may increase the risk of adverse CV outcomes [11–13] and lead to a hasty decision to implant a cardiac pacemaker (PM).

The purpose of this study was to evaluate the prevalence of bradycardia and advanced AVB in patients with CV diseases and SDB risk factors and to analyze the relationship of SDB severity with the occurrence and number of bradyarrhythmias.

METHODS

Questionnaires assessing the risk of SDB were conducted in a group of 443 consecutive patients with CV diseases hospitalized in the Department of Electrocardiology or the Day Stay Cardiac Rehabilitation Ward of the Upper-Silesian Medical Center in Katowice, Poland. In the further study, we included only those patients who were at high risk for SDB in terms of at least one of the following scales: the 4-Variable Screening Tool [14], the STOP-Bang Questionnaire [15], the Epworth Sleepiness Scale (ESS) [16], and who agreed to take the level-3 portable sleep test (L3PST) and electrocardiogram (ECG) Holter recording. The exclusion criteria were previously implanted PM and current SDB treatment with PAP therapy or intraoral appliances.

The Institutional Review Board of the Medical University of Silesia in Katowice, Poland, approved the study (no. KW/0022/KBI/77/18 and no. PCN/0022/KBI/77/I/18/20), and all patients signed informed consent.

Each eligible patient underwent L3PST using an Alice NightOne (Philips Respironics, Bothell, WA, USA) device [17]. The analysis was performed according to the recommendations of the American Academy of Sleep Medicine (AASM) [18], evaluating the following parameters: (1) the number of episodes of obstructive, central, and mixed sleep apnea, defined as the complete cessation of the airway flow for ≥10 seconds with or without preserved respiratory effort; (2) the number of hypopnea episodes, defined as the reduction in the airway flow by ≥90%, with a duration of ≥10 seconds, followed by a decrease in the hemoglobin oxygen saturation of ≥4%; (3) the number of apneas and hypopneas per hour of total recording time (respiratory event index [REI]) [events/hour]; (4) the mean duration of respiratory events (seconds); (5) the minimum and mean arterial oxygen saturation estimated by pulse oximetry (SpO_2) during sleep [%]; and (6) the total sleep time with oxygen saturation under 90% (TST90) [%].

ECG Holter recordings were performed between 10 p.m. and 6 a.m. The occurrence and number of the following events were analyzed: (1) episodes of third- or second-degree type 2 (Mobitz) AVB; (2) pauses longer than 3 seconds; and (3) sinus bradycardia episodes, defined as the heart rate slowing below 40 bpm. The study was conducted in accordance with the 2017 International Society for Holter and Non-Invasive Electrocardiology and the Heart Rhythm Society expert consensus statement on ambulatory ECG and external cardiac monitoring/telemetry [19].

Statistical analysis

The obtained results were analyzed using MedCalc 20.008 software (MedCalc Software Ltd, Ostend, Belgium). Quantitative parameters were characterized using the arithmetic mean and SD or median, interquartile range (IQR) and sample range, depending on the normality of the distribution assessed by the Kolmogorov-Smirnov test. The analysis of quantitative variables was conducted by assessing the significance of differences for two or more independent samples using: (1) the one-way analysis of variance with post hoc comparisons used the Tukey-Kramer test or (2) the Kruskal Wallis H-test with Conover *post hoc* analysis, according to the result of Levene's test for equality of variances. Qualitative data were expressed by incidence as percentages and compared using the Chi^2 test or Fisher's exact test if the number of expected frequencies in the subgroups was less than five. The logistic regression analysis was used to estimate the odds ratio (OR) of the incidence of bradycardia, AVB, or pauses in the SDB groups. The optimal cut-off value for REI, minimum SpO_2, and TST90 for predicting the combined incidence of bradycardia and advanced AVB during sleep were determined by receiver-operating characteristic (ROC) curve analysis. P <0.05 was used as the limit of the significance level in the tests conducted.

RESULTS

Based on the questionnaires, a high risk of SDB was found in 282 out of 443 respondents (63.7%). Diagnostic L3PST and ECG Holter recordings were performed in 207 participants at high risk for SDB, including 177 (85.5%) men and 30 (14.5%) women — these patients constituted the study group. The mean (SD) age of the participants

Table 1. Risk factors and the prevalence of cardiovascular diseases in patients with high vs. low to moderate risk of sleep-disordered breathing based on the Four-Variable Screening Tool, the STOP-Bang Questionnaire, and the Epworth Sleepiness Scale

Parameters of SDB integrated risk assessment by the use of scales	Number of patients and frequency		*P*-value[a]
	Group with a high risk of SDB	Group with a low to moderate risk of SDB	
Groups size, n (%)	282 (63.7)	161 (36.3)	
Male sex, n (%)	239 (72.6)	90 (27.4)	<0.001
Loud and frequent snoring, n (%)	188 (84.3)	35 (15.7)	<0.001
Observed stop breathing or choking/gasping during sleep, n (%)	124 (96.1)	5 (3.9)	<0.001
Excessive daytime sleepiness (>10 points in ESS), n (%)	54 (94.7)	3 (5.3)	<0.001
Diagnosed hypertension, n (%)	236 (66.3)	120 (33.7)	0.006
Age older than 50 years, n (%)	240 (64.0)	135 (36.0)	0.72
Neck circumference ≥43 cm (males), n (%)	156 (85.2)	27 (14.8)	<0.001
Neck circumference ≥41 cm (females), n (%)	27 (87.1)	4 (12.9)	<0.001
BMI >30 kg/m^2, n (%)	147 (79.0)	39 (21.0)	<0.001
BMI >35 kg/m^2, n (%)	67 (91.8)	6 (8.2)	<0.001
Cardiovascular diseases, n (%)			
Coronary artery disease, n (%)	225 (61.8)	139 (38.2)	<0.001
History of myocardial infarction, n (%)	196 (61.1)	125 (38.9)	<0.001
Difficult-to-control blood pressure, n (%)	102 (80.3)	25 (19.7)	<0.001
Atrial fibrillation, n (%)	38 (67.9)	18 (32.1)	0.65
History of ischemic stroke, n (%)	7 (58.3)	5 (41.7)	0.62
HFmrEF, n (%)	54 (64.3)	30 (35.7)	0.86
HFrEF, n (%)	20 (52.6)	18 (47.4)	0.35

[a]*P*-value for differences between groups

Abbreviations: BMI, body mass index, difficult-to-control blood pressure — systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg on antihypertensive treatment; ESS, Epworth Sleepiness Scale; HfmrEF, heart failure with mid-range ejection fraction; HfrEF, heart failure with reduced ejection fraction; OSA, obstructive sleep apnea; SDB, sleep-disordered breathing

Table 2. Distribution of sleep-disordered breathing and heart rate parameters in the study group

Test variable	SDB severity				*P*-value[a]
	None (A)	Mild (B)	Moderate (C)	Severe (D)	
Group size, n (%)	32 (15.5)	59 (28.5)	42 (20.3)	74 (35.7)	
REI	2.67 (1.64)	9.66 (2.75)	20.81 (4.86)	53.67 (16.79)	< 0.001
Mean SpO_2, %	92.78 (2.54) A≠D	92.59 (1.70) B≠D	92.24 (2.17) C≠D	90.01 (3.74)	< 0.001
Minimal SpO_2, %	84.26 (8.34) A≠D	83.56 (5.61) B≠D	81.81 (6.71) C≠D	74.31 (10.24)	< 0.001
TST90, %	14.14 (24.95) A≠D	10.19 (17.31) B≠D	14.98 (21.91) C≠D	29.43 (25.32)	< 0.001
Mean duration of respiratory events, sec	23.22 (8.31)	23.58 (6.30)	22.60 (5.17)	25.28 (8.26)	0.31
Mean HR	59.51 (9.03)	59.52 (7.41)	59.33 (9.10)	61.29 11.34)	0.63
Minimal HR	47.19 (8.61)	48.23 (6.14)	45.59 (9.31)	43.53 (8.32)	0.009

All data are given as mean (standard deviation [SD])

[a]*P*-value for differences between groups

Abbreviations: HR, heart rate estimated by pulse oximetry; REI, respiratory event index; SDB, sleep-disordered breathing; SpO_2, arterial oxygen saturation estimated by pulse oximetry; TST90, total sleep time with oxygen saturation under 90%

was 59.38 (10.37) years, the mean body mass index (BMI) 32.49 (7.25) kg/m^2, and the neck circumference 44.05 (3.81) cm. The parameters used to assess SDB risk, CV comorbidities, and their occurrence and number in the survey group are given in Table 1.

Based on L3PST, SDB was confirmed in 175 (84.5%) out of 207 subjects. The OSA found in 158 (76.3%) participants was the predominant type of SDB. Central apnea episodes predominated in 10 (4.8%) cases, whereas mixed apnea episodes predominated in seven (3.4%) cases. Mild SDB (REI, 5–14 events/hour) was found in 59 (28.5%), moderate SDB (REI, 15–30 events/hour) in 42 (20.3%), and severe SDB (REI, >30 events/hour) in 74 (35.7%) patients. SDB was not confirmed in 32 (15.5%) cases despite the high risk. The recorded L3PST parameters are shown in Table 2.

Sinus bradycardia and advanced AVB were recorded in 42 (20.1%) subjects, including 39 (18.4%) patients with SDB and only three patients without SDB (1.4%); $P = 0.07$. Sinus bradycardia <40 bpm was confirmed in 29 (18.6%), type 2 (Mobitz) second-degree AVB in nine (5.8%), third-degree AVB in seven (4.5%), and pauses >3 seconds in 12 (7.7%) patients. In 15 (8.6%) cases, two or three types of the foregoing disorders occurred jointly in the same patients. The incidence of bradyarrhythmias was not dependent on the type (obstructive vs. central vs. mixed) of respiratory events recorded. Pauses >3 sec-

Table 3. The ratio of patients with sinus bradycardia and nocturnal advanced atrioventricular block according to the severity of sleep-disordered breathing

Type of rhythm or conduction disturbances	SDB severity				*P*-value[a]
	None (A)	Mild (B)	Moderate (C)	Severe (D)	
Groups size, n (%)	32 (15.5)	59 (28.5)	42 (20.3)	74 (35.7)	
Sinus bradycardia <40 bpm, n (%)	2 (6.7)	3 (6.0) B≠D	8 (20.5)	18 (26.9)	0.009
2nd-degree AVB type 2 (Mobitz), n (%)	1 (3.3)	0 (0.0)	2 (5.1)	7 (10.4)	0.09
3rd-degree AVB, n (%)	0 (0.0)	0 (0.0)	1 (2.6)	6 (9.0)	0.04
Pauses >3 sec, n (%)	0 (0.0) A≠D	0 (0.0) B≠D	2 (5.1)	10 (14.9)	0.004
At least one of the above, n (%)	3 (10.0) A≠D	3 (6.0) B≠D	10 (25.6)	26 (38.8)	<0.001

[a]*P*-value for differences between groups ≠ –*P*< 0.05

Abbreviations: AVB, atrioventricular block; SDB, sleep-disordered breathing

Table 4. The number of episodes of sinus bradycardia and nocturnal advanced atrioventricular block according to the severity of sleep-disordered breathing

Type of rhythm or conduction disturbances	SDB severity				*P*-value[a]
	None (A)	Mild (B)	Moderate (C)	Severe (D)	
Groups size, n (%)	32 (15.5)	59 (28.5)	42 (20.3)	74 (35.7)	
Sinus bradycardia <40 bpm	0 (0.0–0.0) range 0–23 A≠D	0 (0.0–0.0) range 0–384 B≠D	0 (0.0–0.0) range 0–920	0 (0.0–0.0) range 0–1033	0.01
2nd-degree AVB type 2 (Mobitz)	0 (0.0–0.0) range 0–2	0 (0.0–0.0) range 0–2	0 (0.0–0.0) range 0–1135	0 (0.0–0.0) range 0–2133	0.15
3rd-degree AVB	0 (0.0–0.0) range 0–0 A≠D	0 (0.0–0.0) range 0–0 B≠D	0 (0.0–0.0) range 0–27	0 (0.0–0.0) range 0–14	0.04
Pauses >3 seconds	0 (0.0–0.0) range 0–0 A≠D	0 (0.0–0.0) range 0–0 B≠D	0 (0.0–0.0) range 0–400	0 (0.0–0.75) range 0–100	0.008

[a]*P*-value for differences between groups, ≠ -*P* <0.05, all data are given as median, interquartile range (in parenthesis), and sample range

Abbreviations: see Table 3

Table 5. The relative odds of the incidence of sinus bradycardia below 40 bpm, advanced atrioventricular block, and pauses above 3 seconds in patients with severe sleep-disordered breathing

Dependent variable	Independent variable: severe sleep-disordered breathing	
	Odds ratio (95% CI)	*P*-value[a]
Sinus bradycardia <40 bpm	3.00 (1.36–6.56)	0.007
Second-degree AVB type 2 (Mobitz)	4.51 (1.13–18.08)	0.03
Third-degree AVB	11.61 (1.37–98.60)	0.03
Pauses >3 seconds	10.26 (2.18–48.40)	0.003

[a]*P*-value for differences between groups

Abbreviations: CI, confidence interval; other — see Table 3

onds were found more often in the group of patients with episodes of atrial fibrillation (AF) during sleep compared to the rest of the studied population (n = 4, 33.3% vs. n = 8, 4.6%; *P* < 0.001). In patients with severe SDB, the occurrence and the number of bradyarrhythmias were significantly higher than in patients without SDB or with mild SDB (Tables 3 and 4).

The OR for the occurrence of the foregoing disorders in a patient with severe SDB was 3.00 (95% CI, 1.360–6.598) for sinus bradycardia <40 bpm, 11.61 (95% CI, 1.366–98.599) for third-degree AVB, 4.51 (95% CI, 1.126–18.075) for second-degree AVB type 2 (Mobitz), and 10.26 (95% CI, 2.176–48.397) for pauses >3 seconds, respectively (Table 5). The percentage of conduction disturbances in the group with moderate SDB was also high, so the cut-off point for REI in predicting sinus bradycardia <40 bpm or advanced AVB turned out to be >22 events/h (sensitivity, 78.57%; specificity, 65.97%) (Figure 1A). The relationship between minimal SpO_2 (cut-off point, ≤75%; sensitivity, 54.76%; specificity, 86.52%), TST90 (cut-off point, >5.42%; sensitivity, 80.95%; specificity, 52.82%), and the incidence of the foregoing disorders was also visible (Figure 1B–C).

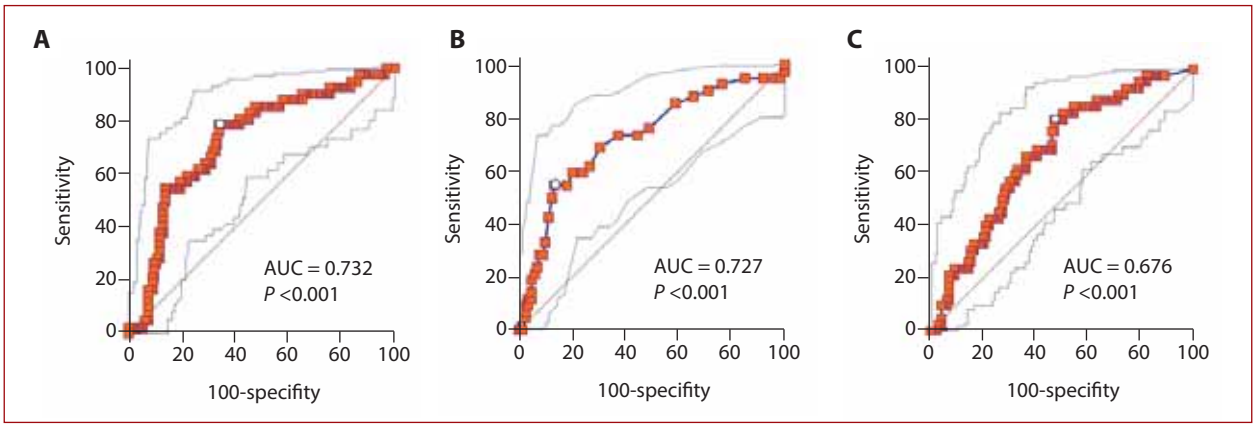

Figure 1. The cut-off point for **A.** respiratory event index; **B.** minimal arterial oxygen saturation; **C.** total sleep time with oxygen saturation under 90% in predicting sinus bradycardia <40 bpm or advanced atrioventricular block during sleep

Abbreviations: REI, respiratory event index; SpO_2, arterial oxygen saturation estimated by pulse oximetry; TST90, total sleep time with oxygen saturation under 90%, cut points are marked°

DISCUSSION

The presented study confirmed the high percentage of SDB, especially OSA, in the Polish population with CV diseases. The high prevalence of moderate to severe SDB has already been described in cardiac patients, estimating it at 30% to 80%, depending on the type of CV disease [7, 20–22]. This percentage is higher than in the general population in Poland, where it is reported to be 8.5% for women and 19.8% for men [23], and in the United States, 9% for women and 17% for men [6].

Common CV and SDB risk factors such as older age, male sex, obesity, and metabolic syndrome are responsible for such a high rate of SDB, predominately OSA, in patients with CV diseases [6, 10, 20, 24]. Similarly, in the surveyed group, most patients at high risk of SDB were men aged >50 years, with a BMI >30 kg/m^2 or higher. A high risk of SDB was significantly more likely to coexist with coronary artery disease, history of myocardial infarction, and difficult-to-control blood pressure, that warrants greater attention to this group of CV diseases.

Obesity and hypertension, a large neck circumference, and a history of loud/frequent snoring or pauses in breathing observed by household members are the basis of SDB risk assessment using prediction algorithms [14, 15]. The questionnaires used in our study, especially the STOP-Bang Questionnaire, allowed us to confirm SDB in 84.5% of those with a positive test, which is close to the positive predictive value for this test reported by Pivetta et al. [15]. At the same time, severe bradyarrhythmias were confirmed in as many as 20.1% of patients at high risk of SDB. However, a relatively small percentage (12.9%) of the surveyed CV patients reported increased daytime sleepiness. The diagnostic problem resulting from the low sensitivity of the ESS in patients with bradycardia and implanted PM was previously described by Garrigue et al. [25], who reported that a score >10 on the ESS scale was achieved by as little as 22.8% of those with the apnea-hypopnea index (AHI) >10 events/h. In addition, Velasco et al. [26] did not confirm the usefulness of the Berlin questionnaire in predicting nocturnal bradycardia. In this respect, the evaluation of other questionnaires may be useful in the bedside diagnosis of SDB-related bradyarrhythmias.

In the presented group, REI (>22 events/h) and desaturation (≤75%) were found to be predictors of nocturnal bradyarrhythmias. Patients with severe SDB appeared to be particularly at risk, which translated into a 3-fold-higher sinus bradycardia risk, an 11-fold-higher risk of third-degree AVB, a 5-fold-higher risk of second-degree AVB type 2 (Mobitz), and a 10-fold-higher risk of pauses >3 seconds in these patients. These findings are consistent with publications by other authors [2, 10, 27, 28]. Sinus bradycardia was found in approximately 1.5%–20.0% and advanced AVB in 8–20% of SDB patients [2, 9, 10, 28], compared to 1% in the healthy elderly population [29]. The incidence of bradycardia, pauses, and advanced AVB increases with higher AHI [10, 28, 30] and lower SpO_2 during apnea episodes [2, 27, 28, 30]. The incidence of bradyarrhythmias is also dependent on the sleep phase and found more frequently in the sleep phase with rapid eye movement as a result of longer duration of respiratory episodes and deeper desaturations [27, 28].

In the study group, as many as 67.9% of patients at high risk of SDB were diagnosed with AF, and pauses >3 seconds were found significantly more often in patients with episodes of AF recorded during sleep. The coexistence of sinus bradycardia during sleep and paroxysmal AF (tachycardia-bradycardia syndrome, T-B syndrome) occurred in nine patients (4.3%). It is worth noting that SDB is a significant and reversible risk factor of new-onset AF, T-B syndrome, and AF recurrence despite adequate pharmacological treatment or with the use of ablation techniques [2, 20, 31–33].

In the European Multicenter Polysomnographic Study by Garrigue et al. [25] conducted in patients with PM implantation, as many as 58% of patients with sinus node dysfunction and 68% with AVB had previously undiagnosed SDB. Among the study participants, 21.4% had severe SDB

with an AHI >30 events/h. In turn, Marti-Almor et al. [33], in a REgistry of Sleep APnea monItoring and Atrial Fibrillation in pacemakeR patients (RESPIRE study), found severe OSA, defined as a respiratory disturbance index of ≥20, in 31.1% of patients with PM capable of detecting SDB. The high sensitivity and specificity of PM with transthoracic impedance sensor in the diagnosis of severe SDB were confirmed by Defaye et al. [34] and may improve the initial diagnosis of OSA in the group of patients with permanent cardiac pacing.

The problem of an SDB-induced bradyarrhythmia incidence is strongly emphasized by the 2018 US [35] and the 2021 European [36] guidelines. Among patients with sinus bradycardia or AVB during sleep, it is recommended that the risk of SDB should be assessed and that polysomnography be performed if indicated (class I). According to the US guidelines, the diagnostics for SDB should also be considered in patients with a previously implanted PM who are at risk (class IIa).

At the same time, both guidelines [35, 36] pay attention to the high efficacy of PAP therapy, not only in reducing the incidence of respiratory events [37] but also in reducing CV risk [11–13]. The resolution of up to 80%–90% of bradyarrhythmias within three to six months after initiation of OSA treatment with continuous PAP therapy was confirmed by other authors [9, 10]. Additionally, an improvement in rhythm control with a 42% reduction in AF recurrence in patients treated with PAP has been documented [32], which reduces the need for multi-drug therapy and the risk of T-B syndrome. Thus, in patients with OSA-related bradycardia, it is recommended to implement PAP therapy with concomitant weight loss (class I in the United States) to avoid unnecessary PM implantation. In our presentation of 42 patients with bradyarrhythmias, seven (16.7%) had strong AASM recommendations to PAP therapy for OSA with REI ≥5 events/hour accompanied by increased daytime sleepiness, and an additional 25 (59.5%) had conditional recommendations to PAP therapy for OSA with REI ≥15 events/hour, regardless of symptoms [37]. However, when implementing such treatment for cardiac conduction diseases, it is worth remembering that adherence to PAP therapy is dependent on many factors and may be insufficient, especially among mildly symptomatic patients [38]. When SDB is treated unsystematically, bradycardia and drops in SpO_2 associated with respiratory events can form a dangerous duo and promote the incidence of ventricular arrhythmias [2, 3, 31].

Limitations of the study

Patient selection for the study was based on questionnaires assessing mainly OSA risk, and the study was conducted using the L3PST dedicated to the assessment of this SDB type. Thus, the group of patients with CSA was not adequately represented, and the results could not be extrapolated to patients with this type of SDB. Nevertheless, the percentage of patients with congestive heart failure for whom CSA was characteristic in the high-risk SDB group was only 7.1%. Unfortunately, because of the small female subgroup, caused by both the rarer incidence of SDB in females and the specificity of the surveys used, the data for males and females were analyzed together. Due to the relatively small number of cases of bradyarrhythmias in the groups, the confidence intervals for the OR of nocturnal bradyarrhythmias in patients with severe SDB were wide, despite sufficient test reliability. Another limitation of the study was the lack of follow-up with patients with diagnosed OSA-related bradyarrhythmias suitable for PAP therapy.

CONCLUSIONS

The SDB, specifically OSA, is common in the population with CV diseases. It constitutes a risk factor for vagally-mediated nocturnal sinus bradycardia, advanced AVB, and pauses longer than 3 seconds. The severity of SDB determines the prevalence and number of these disorders. Due to the reversible nature of SDB-related bradyarrhythmias, each patient should be evaluated for SDB risk before deciding to implant a PM and, if warranted, should undergo polysomnography or at least L3PST and PAP therapy.

Article information

Conflict of interest: None declared.

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Outcomes of cardiac surgical treatment for carcinoid heart disease

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INTRODUCTION

Neuroendocrine neoplasms of the small intestine (SI-NENs) originate in the midgut and are the third most common subtype of neuroendocrine neoplasms (NENs) in the gastroenteropancreatic system [1]. Carcinoid syndrome (CS) is the most prevalent paraneoplastic disease characterized by signs and symptoms related to the hormonal activity of SI-NENs. The classic type of CS is characterized by increased production of serotonin and/or other biologically active substances such as histamine, kallikrein, prostaglandins, and tachykinin [1, 2].

Carcinoid heart disease (CHD) is the most severe consequence of CS, characterized by fibrotic valve degeneration, particularly in the right heart chambers. Nguyen et al. described indications requiring valve surgery, including progressive right heart failure (HF) and echocardiographic findings of moderate to severe right-sided valve regurgitation [3]. Valve surgery has been found to decrease right HF, boost functional capacity, allow for more aggressive oncological therapy, and improve long-term prognosis in CHD patients. It is critical to plan surgery with preoperative dietary optimization and somatostatin analog therapy for carcinoid hormonal activity [4].

The Mayo Clinic's 30-year study involving 240 CHD-operated patients [3] represents the largest such study, with several shorter case series having also been published [5–7].

This retrospective study aimed to evaluate the medical data of operated patients with CHD, including tumor characteristics, indications for valve replacement, complications, and mortality.

METHODS

The protocol for this retrospective single-center cohort study was authorized by the institution's ethics committee (no. 18/2018) and had signed informed consent from all patients. The subject group was selected from a data set of 275 patients with SI-NEN confirmed in pathological examination, diagnosed and treated between 2004 and 2019. In all the cases, a pathologist specializing in NEN verified and reported the histology results, which provided details on the histological grade and the stage of the neuroendocrine neoplasm (TNM) according to the American Joint Committee on Cancer (AJCC)/ /Union for International Cancer Control (UICC) 2017 classification.

Transthoracic echocardiography (TTE) was used to screen patients with CS for CHD on a frequent basis if their 5-hydroxyindoleacetic acid or/and N-terminal pro-brain type natriuretic peptide levels were significantly elevated or if they presented with signs and symptoms of heart disease.

The analysis included a total of 28 (10%) patients with confirmed SI-NENs and diagnosed CHD based on signs and symptoms, typically CHD-related cardiac involvement,

detected using TTE and interpreted by a physician familiar with cardiac abnormalities caused by CHD. All subjects with thickened and retracted tricuspid valve leaflets failing to coapt and moderate or severe regurgitation confirmed by doppler echocardiography were included.

Of these 28 patients during the follow-up, 6 were referred for cardiac valve procedures and were further evaluated. The decision of whether to replace a valve was based on a multidisciplinary assessment of overall operability in relation to the oncological status and cardiac function. Patients with symptomatic right heart failure or ventricular dysfunction and with at least a 12-month survival prediction due to their oncologic status were operated on.

Early mortality was defined as mortality (of any cause) during hospitalization for valve surgery, or within 30 days of admission. Complications were identified through the application of institutional protocols and definitions.

Half of the study group comprised patients with well-differentiated (G1) SI-NEN and half with moderately differentiated (G2) SI-NEN. Clinical and pathological data were analyzed and summarized in Table 1.

Statistical analysis

Categorical variables were summarized using percentages and counts. Mean and standard deviations (SD) were used to report results. Median overall survival (OS) and the interquartile range (IQR) were determined using the Kaplan-Meier method in all patients and calculated from the time of the initial diagnosis of SI-NEN to either the date of death or the last follow-up visit. All statistical calculations were carried out using the Dell Inc. (2016), Dell Statistica (data analysis software system), version 13 (StatSoft Inc., Tulsa, OK, US)

RESULTS AND DISCUSSION

This study represents one of the largest series of patients with SI-NEN-related CHD in Poland as they were diagnosed and treated, with a long-term clinical follow-up.

Six patients at a mean (SD) age of 52 (11) years were included. The median overall survival (IQR) for all patients having undergone valve surgery (n = 6) was 40.22 (29.77–53.11) months. All patients had severe tricuspid valve regurgitation (TR) and typical CHD valve leaflet abnormalities seen in TTE (Table 1). Pulmonary valve regurgitation, either mild (50%) or severe (17%), was found in 67% of patients.

All patients were coordinated by an experienced multidisciplinary team during the peri-operative period, and to reduce the likelihood of a carcinoid crisis, were given a somatostatin analog infusion before and throughout the cardiac procedure until they were hemodynamically stable and off inotropes. Tricuspid valve replacements (TVR) were performed in all patients. A concomitant pulmonary valve replacement (PVR) was performed in one patient, and a mitral valve replacement (MVR) in one patient. There were no aortic valve replacements. Bioprosthetic valves were used in 5 (83%) patients. In one patient with metastasis to the right ovary, tricuspid valve repair with placement of an annular ring CE 28 mm and concomitant MVR with a mechanical prosthesis was used. A bioprosthetic valve was also used in one PVR. During the postoperative period, one patient suffered from cardiac tamponade treated with pericardiocentesis and needed implantation of a pacemaker due to a third-degree atrioventricular block. One patient suffered from a stroke with temporary right-sided hemiparesis. One patient died during open-heart surgery due to cardiac failure, and another died of progressive HF in the perioperative period. As a result, early mortality following surgery, which was observed in two patients, was estimated to be 33% in our study. This is consistent with Mayo Clinic findings ranging from 9 to 29% over the years [3].

In all remaining patients, we observed improvement in symptoms such as dyspnea and peripheral edema during the early follow-up, which supported previous findings that valve replacement surgery alleviates CHD symptoms [5]. These findings indicate that valve surgery may be considered in patients with symptomatic severe right heart valve disease to relieve their symptoms.

In our analysis, in which there was no loss of follow-up, 1-year survival was noted in 4 patients (67%), and 3-year survival in 2 subjects (33%). The cause of death in the follow-up period was commonly associated with the progressive tumor burden and recurrent pleural effusion found in one patient. An analysis by Bhattacharyya et al. reported one- and 2-year survival rates of 56% and 44%, respectively. In other short case series, survival rates closely matched our findings [6, 7].

The selection of the type of valve (biological or mechanical valve prosthesis) is a complex decision that should be made based on the patient's specific risk of bleeding, the specific tumor-related life expectancy, and potential future therapeutic interventions [8]. According to a prior study, surgery of the left-sided valves is not associated with poorer outcomes and should be done simultaneously with right-sided valve surgery, if necessary, as in our analyzed patient [4]. As reported in studies, earlier intervention enhances outcomes [3]. Currently, valve replacement surgery in CHD patients is indicated for symptomatic individuals. However, in the case of uncontrolled CS or a progressive carcinoid tumor, a significant number of symptomatic patients are not referred for valve surgery [5]. These findings suggest that all patients with SI-NENs require frequent cyclic analysis of their clinical status and TTE performance (every 3–6 months) to identify the initial development of CHD.

There is a continued development of surgical techniques for patients with TR. The use of a first-generation transcatheter tricuspid valve implantation device to treat severe symptomatic functional TR is linked to an improvement in the functional status with tolerable in-hospital mortality [9]. The transcatheter tricuspid edge-to-edge

Table 1. Patients undergoing valve surgery for carcinoid heart disease

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Sex	Male	Female	Female	Male	Female	Male
Age of initial diagnosis of SI-NEN, years	36	45	50	69	50	63
Histopathological grade	NET G2	NET G1	NET G1	NET G2	NET G2	NET G1
Size of the primary tumor (pathology), mm	20	69	40	10	45	20
Ki-67, %	10	1	2	5	3	2
pT (initial)	3	×	3	2	No data	×
N base on surgery/ follow-up/ /imaging	1	1	1	1	1	1
M base on surgery/follow-up/ /imaging	1	1	1	1	1	1
Primary tumor resection	No	No	Yes	Yes	Yes	No
Comorbidities	None	Atrial hypertension, chronic kidney disease stage 3	Multiple sclerosis, after uterine appendages resection	Atrial hypertension, thrombocytopenia, mild anemia	Atrial hypertension	Atrial hypertension
Carcinoid syndrome symptoms	Yes	Yes	No	Yes	Yes	Yes
LVEF, %	65	62	55	62	60	60
Mitral valve regurgitation	Mild	Mild	Severe	Mild	None	None
Tricuspid valve regurgitation	Severe	Severe	Severe	Severe	Severe	Severe
Aortic valve regurgitation	Mild	None	None	Mild	Mild	None
Pulmonary valve regurgitation	None	Mild	Mild	Mild	Severe	None
Preoperative NYHA class	II	III	III	II	III	IV
Type of valve surgery	TVR	TVR + PVR	TVR + MVR	TVR	TVR	TVR
Percutaneous/open heart surgery	Open heart surgery after failed percutaneous procedure	Open heart surgery	Open heart surgery	Open heart surgery after failed percutaneous procedure	Open heart surgery	Open heart surgery
Concomitant procedures: CABG or ASD/PFO repair	None	None	None	None	None	None
Early complications	Tamponade in perioperative period, pacemaker implantation due to third-degree atrio-ventricular block	No	No	Died due to progression of cardiac failure	Stroke with temporary right-sided hemiparesis	Died during cardiac surgery due to cardiac failure
Overall survival, months	30	70	43	49	27	34
Survival after valve surgery	~3 years	~1 year	~3 years	<1 month	~1 year	<1 month
Cause of death	—	Died due to recurrent pleural effusion and tumor progression	—	Died due to progression of heart failure	Progressive cachexia. Died due to tumor progression	Died during cardiac surgery due to cardiac failure

Abbreviations: ASD, atrial septal defect; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; MVR, mitral valve replacement; NET, neuroendocrine tumours; NYHA, New York Heart Association; PVR, pulmonary valve replacement; SI-NEN, neuroendocrine neoplasms of the small intestine; TVR, tricuspid valve replacement

repair may be a safe and possibly effective treatment for patients with HF and significant TR, leading to the reduction of TR's severity severity and clinical improvement [10].

In conclusion, carcinoid heart disease remains a tremendous challenge despite medical and surgical advances in this field. The mortality rates suggest that valve surgery for CHD is a high-risk procedure, but it might be valuable to patients with symptomatic severe right heart valve disease with at least a 12-month survival prediction due to symptomatic improvement. However, short-term mortality after valve replacement for CHD decreased in the present era, and overall survival is mostly limited by tumor progression. Patient selection, thorough preoperative planning, and perioperative management protocols, all under the supervision of a multidisciplinary team, are essential to succeed.

Article information

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SGLT2 inhibitors and the risk of urinary tract infections in patients with heart failure: A pooled analysis examining safety endpoints

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INTRODUCTION

Sodium-glucose cotransporter-2 inhibitors (SGLT2is) were originally envisioned as attractive hypoglycemic agents due to their promotion of glycosuria by inhibiting SGLT2 transporters in the proximal convoluted tubules of kidneys where approximately 90% of filtered glucose gets reabsorbed [1]. Due to their potent cardioprotective effects observed in trials focused on type 2 diabetes mellitus (T2DM) [2], it was hypothesized that SGLT2is might improve outcomes in heart failure (HF) patients. Indeed, it was demonstrated in landmark randomized controlled trials (RCTs) that, among patients with HF with reduced ejection fraction (HFrEF), the use of SGLT2is, compared to placebo, was associated with significant reductions in cardiovascular death and HF-related hospitalizations, both endpoints representing persistently unmet needs in HF [3]. Notably, in the DAPA-HF trial [4], patients with HF who received dapagliflozin had a 26% relative risk reduction in the composite of worsening HF or cardiovascular death, and results were concordant in the EMPEROR-Reduced trial [5] that evaluated the use of empagliflozin. Interestingly, robust reductions of mortality and morbidity among HFrEF patients were similar regardless of T2DM status at baseline. Similar trends were observed with dapagliflozin in the DECLARE-TIMI 58 sub-study [6] that was focused on a cohort of patients with T2DM and concomitant HF. On the other hand, the most recent SOLOIST-WHF [7] trial demonstrated a 33% relative risk reduction in the total number of deaths from cardiovascular causes and hospitalizations and HF-related urgent visits associated with the use of sotagliflozin *vs.* placebo in patients with decompensated HF. Finally, the most recent EMPEROR-Preserved trial was the first RCT that showed how a pharmacological intervention improved outcomes in patients with HF and preserved ejection fraction (HFpEF), as empagliflozin use was associated with a 21% relative risk reduction in a composite of cardiovascular death and hospitalizations [8].

However, post-market and surveillance studies indicated a possible association of SGLT2is and adverse events such as euglycemic diabetic ketoacidosis, genital and urinary tract infections (UTIs), Fournier gangrene, volume depletion, and limb amputations [9, 10]. Due to their implicated glycosuric effects, susceptibility for UTIs was examined providing mixed results in patients with T2DM [11]. In large population analysis, the risk for severe or non-severe UTIs was similar among SGLT2i users compared to users of other second-line hypoglycemic drugs [12].

However, the association of SGLT2i use and UTI events has not been previously examined in the HF population on a large scale. For this reason, we performed an up-to-date analysis of five landmark RCTs evaluating the use of

gliflozins vs. placebo in patients with HF. The main question we sought to investigate whether the risk of UTI events was increased with the use of SGLT2 is compared to placebo among patients with HF.

METHODS

Two investigators (JAB and JB) independently searched available literature in relevant databases such as PubMed and SCOPUS to include large RCTs (enrolling >1000 patients) examining the use of any SGLT2 inhibitor vs. placebo and that reported safety endpoints, such as UTI events, in the population of patients with HF. According to the PICOS (Population, Intervention, Comparator, Outcome, Study design) principle, a population of HF patients with a whole spectrum of ejection fractions (both HFrEF and HFpEF) was included. We included studies that examined the oral use of any SGLT2 inhibitor (dapagliflozin, empagliflozin, sotagliflozin) as an intervention while the comparator group received a placebo. The principal outcome of interest was the occurrence of UTI events (as reported and adjudicated by the respective study investigator committees). Due to the low number of UTI events registered in the DAPA-HF trial, we also counted events such as urosepsis, pyelonephritis, acute pyelonephritis, and staphylococcal UTI to the composite endpoint. Finally, we only considered studies that were designed and conducted as RCTs.

In short, five landmark RCTs in this setting were included, and all provided safety outcome data concerning the occurrence of UTIs. Two trials examined the use of 10 mg dapagliflozin once-daily (DAPA-HF and DECLARE-TIMI 58), two examined the use of 10 mg empagliflozin once-daily in HFrEF (EMPEROR-Reduced) and HFpEF (EMPEROR-Preserved), while one trial examined the use of sotagliflozin 200 mg once daily with an eventual dose increase to 400 mg once daily (SOLOIST-WHF). A total of 32 823 patients from five RCTs were included.

Statistical analysis

The Q Cochran test and Higgins I^2 statistic were calculated to estimate heterogeneity across included studies. We reported risk ratios (RR) with 95% confidence intervals (CIs) derived by using the Mantel-Haenszel random-effects statistical model. The analysis was carried out by using RevMan 5.3 (Cochrane Collaboration, London, UK). A sensitivity analysis was performed for leaving out a trial with the largest contribution to results (DECLARE-TIMI 58) to inspect if this would significantly impact the main result. The risk of bias (RoB) assessment for each trial was carried out by two investigators independently (JAB and JB), and eventual discrepancies were resolved by the third investigator (MK). The distribution of numerical variables was presented as mean (standard deviation [SD]) or median (interquartile range [IQR]). The Cochrane Collaboration's tool for assessing the risk of bias in randomized trials was used [13]. *P*-values <0.05 were considered statistically significant.

RESULTS AND DISCUSSION

Among 16 414 patients that received SGLT2i, 585 UTI events were recorded, while 529 UTI events were recorded in 16 409 patients that received a placebo. The weighted mean rate of UTI events across five landmark trials (adjusted for sample size) was 6.9 (4.1) % in the SGLT2i group (from 0.8% to 9.9%; range, 9.1) and 5.5 (3.2) % in the placebo group (from 1.1% to 8.1%; range, 7.0). Trials predominantly enrolled patients with HFrEF. The median duration of follow-up was 9.2 months in SOLOIST-WHF, 16 months in EMPEROR-Reduced, 18.2 (0–27.8) months in DAPA-HF, 26.2 (18.1–33.1) months in EMPEROR-Preserved, and finally, 50 months in DECLARE-TIMI 58. Two trials enrolled HF patients with left ventricular ejection fraction (LVEF) <40% (DAPA-HF and EMPEROR-Reduced) while patients enrolled in SOLOIST-WHF had a median LVEF of 35 (28–46) %. Furthermore, the EMPEROR-Preserved trial enrolled patients with HF and LVEF >40% with a mean LVEF of 54.3 (8.8) %. In two HFrEF cohorts, the average LVEF was 31.1 (6.8) % in DAPA-HF and 27.5 (6.1) % in the EMPEROR-Reduced trial. Patients with HFrEF in DECLARE-TIMI 58 (defined as those with LVEF <45%) had a median LVEF of 38 (30–40) % while those with documented HF without known reduced LVEF had a median LVEF of 55 (50–61) %.

As shown in Figure 1, the use of SGLT2i was similar to placebo with regard to the risk of UTI events in patients with HF (RR, 1.09; 95% CI, 0.94–1.26; $P = 0.24$), and this observation was based on the evidence characterized by the low degree of heterogeneity ($I^2 = 25\%$; $P = 0.25$). Leave-one-out sensitivity analysis validated the main result (RR, 1.15; 95% CI, 0.99–1.33; $P = 0.07$). All trials were adjudicated as low risk of bias across all seven domains in the RoB tool.

This analysis has some limitations worth mentioning. In most of the trials, UTI events were not defined in sufficient detail, and they were not designated as events of special safety interest. Therefore, such events might be underreported, which might introduce bias with respect to the reported number of events. For example, the DAPA-HF trial reported a significantly lower number of UTI events compared to other trials since these events were not routinely collected in a pre-specified safety monitoring manner. However, in the revised analysis, we added events such as urosepsis, pyelonephritis, acute pyelonephritis, and staphylococcal UTI from this trial to the composite endpoint of UTI events. Finally, no protocol has been prospectively registered for this analysis.

Taken together, our results based on high-quality randomized trial data, show that the risk of UTI events is similar among HF patients assigned to SGLT2 inhibitor compared to those assigned to placebo, although this might be biased due to inadequate definitions and the lack of systematic registration of these events in most of the examined trials. These findings provide important safety reassurance for patients with HF, as well as for practicing cardiologists and other prescribers of this class of drugs.

Study or subgroup	SGLT2is Events	SGLT2is Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random (95% CI)	Year
DECLARE-TIMI 58	127	8582	133	8578	24.5%	0.95 (0.75–1.21)	2019
DAPA-HF	18	2368	26	2368	5.4%	0.69 (0.38–1.26)	2019
EMPEROR-Reduced	91	1863	83	1863	18.7%	1.10 (0.82–1.47)	2020
SOLOIST-WHF	52	605	44	611	11.8%	1.19 (0.81–1.75)	2021
EMPEROR-Preserved	297	2996	243	2989	39.6%	1.22 (1.04–1.43)	2021
Total (95% CI)		**16414**		**16409**	**100%**	**1.09 (0.94–1.26)**	
Total events	585		529				

Heterogeneity: Tau² = 0.01; Chi² = 5.34, df = 4 (*P* = 0.25); I² = 25%
Test for overall effect: Z = 1.16 (*P* = 0.24)

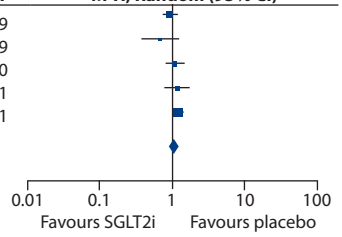

Figure 1. Results of a meta-analysis showing the relative risk of urinary tract infection events associated with SGLT2 inhibitor vs. placebo use among patients with heart failure

Abbreviations: CI, confidence interval; SGLT2is, sodium-glucose cotransporter-2 inhibitors; M-H, Mantel-Haenszel

Article information

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Right ventricular wall thickness indexed to body surface area as an echocardiographic predictor of acute pulmonary embolism in high-risk patients

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INTRODUCTION

The abnormalities in acute pulmonary embolism (PE) observed in a transthoracic echocardiographic examination (TTE) are ascribed to the right ventricular (RV) pressure overload and dysfunction evoked by PE, but those findings can also be present in the absence of acute PE and may occur due to concomitant cardiac or respiratory diseases [1, 2]. The recommendations for TTE use in PE diagnostics present a general approach without standard individualization to the patients' body size [1].

This study aimed to assess the usefulness of classic echocardiographic parameters indexed to the height and the body surface area (BSA) for prediction of acute PE in patients with a high clinical probability of PE referred for computed tomography pulmonary angiography (CTPA).

METHODS

Study group

This was a cross-sectional observational single-center study including consecutive patients referred for CTPA at an Internal Medicine Department with a high clinical probability of PE, from August 1, 2018 to June 11, 2019. The diagnostic algorithm and treatment regimens were adopted from the guidelines of the European Society of Cardiology [1, 3]. Exclusion criteria and echocardiographic assessment methodology are described in the Supplementary material. The study protocol complied with the Declaration of Helsinki and was approved by the Bioethics Committee of the Regional Medical Chamber in Tarnow, Poland (no. 3/0177/2019).

Statistical analysis

Statistical analysis was performed with the R Project for Statistical Computing version 3.6.3 (R Foundation for Statistical Computing, Free Software Foundation Inc., Vienna, Austria). Categorical variables were presented as absolute frequencies or relative percentages, while continuous variables as median with interquartile range (IQR) or as mean with standard deviation (SD). Categorical variables were compared using the $\chi 2$ test or the Fisher test.

The normality of distribution was investigated with the Shapiro-Wilk test. For quantitative variables and normal distribution, the t-test was applied. For the non-normal distribution, the Mann-Whitney test was used. Two-sided *P*-values <0.05 were considered statistically significant. Calculated *P*-values were not adjusted for multiple testing. Detailed statistical analysis is described in the Supplementary material.

RESULTS AND DISCUSSION

The study comprised 108 consecutive patients, 5 of whom had contraindications to CTPA and were transferred to another unit for further diagnostics. Another 9 patients had echocardiograms of poor quality that were excluded. Three patients had nondiagnostic CTPA. Finally, 91 individuals were eligible to

be enrolled in the survey. Baseline characteristics of these patients are presented in the Supplementary material, *Table S1*. As many as 49 patients had PE confirmed in CTPA; 22 subjects had central PE (44.9%), whereas 27 individuals (55.1%) had peripheral PE: segmental —18 (36.7%) or subsegmental — 9 (18.4%). Forty-two patients had no radiological signs of PE.

Clinical and biochemical variables

Considering clinical data, there were no differences in sex, age, body size, clinical prediction rules for PE, or in most comorbidities. The individuals with PE had less often coronary artery disease (CAD) and chronic heart failure (CHF, Supplementary material, *Table S1*). In the analysis of laboratory tests results, they had only a higher concentration of D-dimer (Supplementary material, *Table S2*). The calculated cut-off value for D-dimer as a single predictor of PE, with a sensitivity of 57% and specificity of 80% in the study group, was 4.891 ng/ml.

Classic TTE parameters

The only parameter that was different in the groups of patients with and without PE was the right ventricular wall thickness (RVWT, average values of 4.97 [0.77] vs. 5.58 [1.75] mm; $P = 0.046$) (Supplementary material, *Table S3*). There were no significant differences regarding the severity of valvular defects between the groups.

Indexation of echocardiographic parameters to height

The left atrial end-diastolic area (LA EDA) indexed to height and RVWT indexed to height were significantly lower in the group with PE (Supplementary material, *Table S1*).

Indexation of echocardiographic parameters to BSA

Indexation to BSA revealed the differences between patients with and without PE in the left ventricle (LV) and the left atrium (LA) sizes. The indexed derivatives of left ventricular end-diastolic diameter (LVEDd), the left ventricular transverse diameter (LVTD), the left atrium diameter parasternal window — long-axis views (LAd PLAX), LA EDA — were decreased in the group with PE. RVWT indexed to BSA was also lower in patients with PE (Supplementary material, *Table S3*).

Specific echocardiographic signs of PE

The only specific TTE sign for PE, i.e. a mobile thrombus in the right atrium or right ventricle, was more frequently observed in the PE group (Supplementary material, *Table S4*).

Clinical and echocardiographic predictors for PE

In the univariate logistic regression the variables significantly associated with the PE diagnosis comprised (1) CAD, CHF (occurrence of both lowered the chances for PE); (2) serum D-dimer concentration (positively correlated with PE); (3) RVWT; (4) LAd PLAX indexed to BSA; (5) LVEDd indexed to BSA; (6) pulmonary artery (PA) indexed to BSA; (7) LA EDA indexed to BSA; (8) RVWT indexed to BSA (all negatively correlated with PE). In the multivariable analysis, the factors independently positively associated with PE included the absence of CAD, higher D-dimer concentration, and lower RVWT indexed to BSA (Supplementary material, *Table S5*).

Clinical significance

To evaluate a possible clinical utility of RVWT indexed to BSA, we performed receiver-operating characteristic (ROC) analysis and calculated the optimal cut-off value. The obtained area under the curve (AUC) was 0.68 (95% confidence interval [CI], 0.56–0.80; $P = 0.002$), the upper cut-off value of 3.19 mm/m^2 with accuracy of 60% predicted acute PE. Its sensitivity was 0.14 (95% CI, 0.06–0.27) and specificity was 0.69 (95% CI, 0.53–0.82; Supplementary material, *Figure S1*). To enhance the predictive potential of RVWT indexed to BSA, we combined it with D-dimer levels in the multiple regression model. ROC and model statistics are shown in the Supplementary material, *Figure S2*. In this model AUC equaled 0.776 (95% CI, 0.669–0.883; $P < 0.001$), with sensitivity of 0.76 (95% CI, 0.60–0.89) and specificity of 0.68 (95% CI, 0.50–0.82).

Echocardiography is an underutilized tool in PE diagnostics and outcome prognosis. RV dysfunction on TTE is associated with an increased risk of short-term mortality even in an initially hemodynamically stable patient with PE [4–6]. TTE may also help to identify possible candidates for early thrombolytic treatment, thus TTE should be widely used in clinical practice in all patients with PE [7, 8]. In the presented study, nearly 50% of subjects had a negative result for PE in CTPA. It stresses the urgent need for the search for additional predictive factors. Our results of RVWT indexed to BSA confirm the usefulness of TTE and its potential in this area.

Indexing of heart cavities size to BSA is becoming a standard in echocardiography [9]. Nevertheless, indexation of ventricular wall thickness (WT) to BSA has an emerging role. Left ventricular wall thickness (LVWT) showed significant relation with BSA. Indexed LVWT was similar in men and women, but it differed among races and was associated with decreased hypertrophic cardiomyopathy diagnoses [10–12].

The only biochemical and clinical variables independently associated with PE diagnosis were D-dimer concentration and CAD. The current algorithms use D-dimer testing in patients with low/moderate clinical probability of PE to rule out PE [1]. Our findings should stimulate future research on D-dimer in PE diagnostics.

Due to low accuracy and sensitivity, RVWT indexed to BSA is not useful as a single indicator of PE. An open question remains about possible associations between RVWT and other RV indices and their diagnostic utility for PE diagnosis, which is beyond the scope of this article but requires future research. Standard indexation of TTE param-

eters reveals differences between the groups of patients of high clinical probability of PE with and without acute PE. The factors independently associated with PE include the absence of CAD, higher D-dimer concentration, and lower RVWT indexed to BSA.

Supplementary material

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

Article information

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HIV-infected patients on combined antiretroviral treatment had a similar level of arterial stiffness to the patients with ST-segment elevation myocardial infarction

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INTRODUCTION

Human immunodeficiency virus (HIV) is an independent risk factor for cardiovascular disease, and HIV-infected patients have a higher risk of myocardial infarction than HIV-negative patients. Consequently, age-related comorbidities, such as cardiovascular disease, have become more common in this population [1, 2]. We can use invasive and non-invasive methods to assess endothelial function and arterial stiffness. One of the non-invasive techniques is reactive hyperemia peripheral arterial tonometry (RH-PAT) that allows for the evaluation of peripheral microcirculation vessels [3]. The study by Kikuya et al. [4] presented another non-invasive method for evaluation of arterial stiffness. The authors confirmed the significance of periodic changes in blood pressure and their influence on arterial stiffness. Nadel et al. [5] compared HIV-infected patients to the non-HIV-infected over a median period of 38 months and showed an increased risk of acute coronary syndrome without ST-segment elevation (NSTEMI) in HIV-infected patients. Moreover, they showed that HIV-infected patients had more severe coronary atherosclerosis on computed tomography (CT) angiography and higher rates of NSTEMI compared to uninfected patients [5]. The attention was focused on the influence of combined antiretroviral therapy (cART) on lipid metabolism and increased cardiovascular risk, especially in patients treated with protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and nucleoside reverse transcriptase inhibitors (NRTIs) [6].

Evaluating cardiovascular risk among HIV-infected people is not an easy assignment. The Framingham score used in HIV-infected patients is underestimated. Moreover, the importance of cART treatment, drugs interaction, and side effects are underlined [7, 8].

In terms of the goal of the study, because the cardiovascular risk in HIV-infected patients is higher than in the HIV-negative and the pathomechanism of these changes is still unknown, we decided to compare the arterial stiffness and the endothelial dysfunction in adult HIV-infected patients with non-HIV-infected persons at week 4 after ST-elevation myocardial infarction (STEMI).

METHODS

From January to December 2016, we recruited 63 patients, including 34 HIV-infected (18 on cART) and 29 HIV-negative patients at week 4 after STEMI. On the visit day, each HIV-infected patient underwent a basic medical examination. The body mass index (BMI) and laboratory results were collected. Despite the fact that the Centers for Disease Control and Prevention (CDC) defines tobacco smokers as people who smoked at least 100 cigarettes in their lifetime and who currently smoke cigarettes [9], we defined current tobacco smokers as individuals who smoked at least 20 cigarettes/day for more than 5 years (5 pack-years). The arterial stiffness was calcu-

Table 1. Baseline patient characteristics

	HIV group (n = 34)	STEMI group (n = 29)	*P*-value
Age, years, mean (SD)	38.9 (11.7)	55.3 (8.6)	<0.01
Male gender, n (%)	30 (88.2)	26 (89.7)	1.00
BMI, kg/m^2, mean (SD)	23.8 (4.1)	28.4 (3.4)	<0.01
Active smoking, n (%)	19 (55.9)	21 (72.4)	0.20
Hypertension, n (%)	2 (5.9)	17 (58.6)	<0.01
Diabetes mellitus, n (%)	0 (0.0)	4 (13.8)	0.04
ACEI, n (%)	1 (2.9)	28 (96.6)	<0.01
Statins, n (%)	2 (5.9)	29 (100.0)	<0.01
Systolic blood pressure, mm Hg, mean (SD)	125 (18)	129 (19)	0.41
Diastolic blood pressure, mm Hg, mean (SD)	78 (12)	82 (12)	0.19
Heart rate, bpm, mean (SD)	77 (12)	70 (9)	0.01
Hemoglobin, g/dl, mean (SD)	13.8 (2.1)	14.4 (1.7)	0.15
White blood cells, 1000/mcL, mean (SD)	6.2 (2.3)	9.2 (2.8)	<0.01
AI, %, mean (SD)	1.5 (18.2)	11.4 (18.7)	0.04
AI@75, %, mean (SD)	3.3 (14.0)	8.2 (16.8)	0.21
lnRHI, mean (SD)	0.7 (0.3)	0.5 (0.2)	<0.05

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitors; BMI, Body Mass Index; AI, augmentation index; AI@75, AI corrected for a heart rate of 75 beats per minute; lnRHI, natural logarithm of reactive hyperemia index

lated by the EndoPAT 2000 (ITAMAR®, Caesarea, Israel) and the endothelial function with Peripheral Arterial Tonometry (PAT®; ITAMAR). The endothelial dysfunction was defined for the natural logarithm of the reactive hyperemia index (lnRHI) ≤0.51. Arterial stiffness was assessed as the augmentation index (AI) and AI adjusted for a heart rate of 75 beats per minute (AI@75). Among HIV-negative patients after STEMI, similar procedures were carried out at week 4 since admission to the hospital, except for laboratory tests performed at the time of acute coronary syndrome (ACS). The exclusion criterion in the HIV-infected group was having experienced myocardial infarction. It was a retrospective analysis in parallel groups.

To assess distributions of continuous variables the Shapiro-Wilk test was used. For all analyzed continuous variables, normal distributions were found. Continuous variables were presented as mean values and standard deviations (SD). Differences between subgroups were calculated with Fisher's exact test and Student's t-test, respectively, for categorical and continuous variables. In the case of 3 subgroups, analysis of variances (ANOVA) and paired Student's t-tests were performed. Tests were considered significant for *P*-values $P < 0.05$ and $P < 0.017$ for multiple comparisons, according to Bonferroni correction.

To reduce the age as a confounding variable, propensity score matching was used, with the 1:1 ratio for numbers of patients in each subgroup. Statistical analysis was performed using SAS® software, version 9.4 (SAS Institute, Cary, NC, US).

The study was approved by the Bioethics Committee of the Medical University of Warsaw. All participants signed written informed consent.

RESULTS AND DISCUSSION

The mean (SD) of cART duration was 172.3 (90.6) weeks and contained: NRTIs–13, NNRTIs–4, PIs–14, and integrase strand transfer inhibitors (INSTIs) — 4 patients. Among 18 patients on cART 5 (27.7%) had endothelial dysfunction, and 10 (55.5%) smoked cigarettes. In the group of 16 patients without cART, 7 (43.7%) had endothelial dysfunction, and 9 (62.5%) smoked cigarettes (Table 1).

In the STEMI group, a high percentage of patients with diabetes and hypertension (13.8% and 58.6%, respectively) was observed in comparison to the HIV group (0% and 5.9%, respectively). Comparisons of AI, AI@75, and lnRHI values in analyzed groups: HIV on cART, HIV without cART, and STEMI are presented in Supplementary material, *Table S1*.

There are several studies concerning the effect of HIV and cART on arterial stiffness augmentation. In the study by Alvi et al. [10], ritonavir-boosted protease inhibitors (PIs/r) had a significant impact on serum lipids and enhanced atherosclerotic lesions [11]. Our results may confirm the negative influence of cART (especially PIs) on arterial stiffness.

We got lnRHI results significantly lower in the STEMI group than HIV-infected patients, which may suggest more intense endothelial dysfunction in the STEMI group. This trend was also observed after analysis of groups matched by age and number. The significant difference in the degree of endothelial dysfunction was for the STEMI group and the cART-treated HIV-infected group, which may suggest the protective effect of cART on endothelial function. However, we did not find any differences for lnRHI in HIV-infected patients on and without cART.

Subsequently, we compared the HIV and STEMI groups, each consisting of 20 patients matched in terms of age and parity (1:1). Data are presented as mean (SD) for the HIV and STEMI groups respectively. Subsequently, we compared age, AI, AI@75 bpm and lnRHI of the HIV and STEMI groups, each consisting of 20 patients matched in terms of age and parity (1:1). Age results as mean (SD) for the HIV and

STEMI groups were respectively — 45.8 (10.3) years and 50.8 (5.8) years with $P = 0.07$. Results of AI as mean (SD) for the HIV and STEMI groups were respectively — 6.9 (19.3) % and 12.0 (21.1) % with $P = 0.43$. Results of AI@75 bpm as mean (SD) for the HIV and STEMI groups were respectively — 8.3 (13.6) and 9.1 (18.8) % with $P = 0.88$. Results of lnRHI as mean (SD) for the HIV and STEMI groups were respectively — 0.71 (0.34) % and 0.52 (0.24) % with $P = 0.06$.

After the 1:1 matching, we confirmed that the arterial stiffness in the HIV-infected group is similar to the STEMI patients, which may be an indirect proof of the severity of cardiovascular changes in this group of patients.

Cigarette smoking is one of the main factors that increase endothelial abnormalities and is also an independent cardiovascular risk factor [12]. We observed a high percentage of patients who smoked cigarettes in both groups. We did not show a statistically significant difference in the rate of smoking between studied groups, but the risk of coronary vascular injury caused by smoking was similar in all patients.

CONCLUSIONS

We report that HIV-infected patients on cART may have similarly high values of arterial stiffness as non-HIV-infected persons at week 4 after STEMI. Assessing cardiovascular risk is very important especially in infected patients on cART therapy. Modification of risk factors should be the basic element of care for HIV-infected patients. More studies are required to validate our observation concerning arterial stiffness and elevated risk of cardiovascular disease in this group of patients, independently of age, smoking status, and concomitant chronic diseases.

Supplementary material

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

Article information

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Treatment outcomes of COVID-19 patients in bi-disciplinary cardiology and cardiac surgery ward

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INTRODUCTION

SARS-CoV-2, a coronavirus causing severe acute respiratory syndrome, emerged at the end of 2019 and triggered a pandemic forcing rapid changes in the organization of public healthcare both at the national and in-hospital level [1]. Patients infected with COVID-19 underwent treatment in designated hospitals and other existing facilities with infectious diseases departments.

Patients with either exacerbation of chronic heart disease or patients recently affected by acute cardiac disorders are at high risk of death if infected with SARS-CoV-2 [2]. Unfortunately, in Poland, some COVID-19 designated hospitals do not have medical facilities to conduct highly specialized cardiological therapies. A transfer to COVID-19 dedicated cardiology or cardiac surgery units reduces an opportunity to achieve optimal medical outcomes [3]. Depending on available healthcare resources, urgent cardiac procedures with documented efficacy should be continued during consecutive waves of the COVID-19 pandemic [4]. To provide prompt treatment and diminish the risk of the virus spread, our hospital, which is a multi-specialist non-COVID-19 dedicated hospital, established a combined unit for COVID-19 patients. The ward functioned for 6 months (from October 23, 2020 to October 23, 2021) during the 2 waves of the highest intensity of the pandemic in Poland.

The study aims to present the clinical characteristics, the course of hospitalization, outcomes, and risk factors of death among our patients.

METHODS

The cases comprised 227 patients hospitalized in the newly created ward for exacerbation of chronic cardiovascular diseases or acute illnesses and requiring urgent cardiac surgery or cardiac invasive procedure. Patients were diagnosed with COVID-19 in accordance with the recommendations of the Polish Association of Epidemiologists and Infectiologists with the use of the real-time polymerase chain reaction method [5]. Others who tested negative on admission were hospitalized separately and tested regularly twice a week or in case of any infection symptoms.

Patients were hospitalized for acute heart failure (New York Heart Association [NYHA] class III or IV), acute coronary syndrome, pulmonary embolism, infective endocarditis, arrhythmia, hypertension crisis, myocarditis, pericarditis, a need for urgent cardiac surgery, post-sternotomy complication treated with vacuum-assisted closure (VAC) therapy, or pneumonia in patients with multiple cardiovascular comorbidities. There were no exclusion criteria.

Both risk factors and cardiovascular diseases were identified based on a medical history of prior diagnosis or treatment and defined according to the current European Society of Cardiology guidelines [6].

Blood samples were drawn on admission using a minimal stasis and atraumatic venipuncture from an antecubital vein.

Left ventricular ejection fraction was assessed using transthoracic echocardiography and the biplane Simpson method with Philips

Table 1. Demographic and clinical characteristics of the studied groups

Variable	All patients (n = 227)	Survivors (n = 179)	Non-survivors (n = 48)	*P*-value
Age, years	69.6 (13.4)	68.5 (13.7)	73.4 (11.8)	0.028
Male sex, n (%)	150 (66)	115 (64)	35 (73)	0.26
Body mass index, kg/m^2	30.3 (6.2)	31.0 (6.5)	28.1 (4.4)	0.069
Length of hospital stay, days	14 (9–22)	14 (11–22)	13 (6–21)	0.12
Left ventricular ejection fraction, %	50 (35–56)	50 (40–60)	40 (20–48)	0.003
Main cause of hospitalization, n (%)				
Acute coronary syndrome[a]	64 (28)	46 (26)	18 (38)	0.11
Heart failure	58 (26)	45 (25)	13 (27)	0.78
Pulmonary embolism	13 (6)	10 (6)	3 (6)	0.74
Infective endocarditis	11 (5)	7 (4)	4 (8)	0.25
Arrhythmia[b]	26 (11)	23 (13)	3 (6)	0.2
Hypertension	6 (3)	6 (3)	0 (0)	0.35
Urgent cardiac surgery[c]	17 (7)	17 (9)	0 (0)	0.027
Pneumonia	30 (13)	23 (13)	7 (15)	0.75
Peri/Myocarditis	2 (1)	2 (1)	0 (0)	1.00
Risk factors and comorbidities, n (%)				
Diabetes mellitus	76 (33)	55 (30)	21 (44)	0.09
Arterial hypertension	158 (70)	127 (71)	31 (65)	0.39
Heart failure	109 (48)	84 (47)	25 (52)	0.53
Coronary artery disease	49 (22)	34 (19)	15 (31)	0.07
Atrial fibrillation	95 (42)	69 (39)	26 (54)	0.051
Cardiac pacing	16 (7)	13 (7)	3 (6)	1.00
Rheumatic disorder	12 (5)	10 (6)	2 (4)	1.00
Obesity	60(26)	48 (27)	12 (25)	0.80
Pulmonary disease	9 (4)	7 (4)	2 (4)	1.00
Laboratory parameters on admission				
Hemoglobin, g/dl	12.76 (2.25)	12.82 (2.22)	12.56 (2.39)	0.49
Platelets, 10^9/l	198 (142–261)	204 (153–264)	169 (117–239)	0.015
White blood cells, 10^9/l	7.1 (5–9.8)	6.8 (4.7–9.1)	8.8 (6–13.8)	0.002
Creatinine, µmol/l	86.2 (67.4–120.3)	82.2 (65.0–109.6)	109.6 (81.8–150.8)	<0.001
hsCRP, mg/l	39 (13–87)	29 (9–66)	86 (44–154)	<0.001
Maximum hsCRP, mg/l	67 (24–131)	49 (17–108)	128 (84–187)	<0.001
Procalcitonin, ng/ml	0.14 (0.07–0.42)	0.1 (0.06–0.24)	0.35 (0.15–1.38)	<0.001
NT-pro-BNP, pg/ml	4018 (985–13273)	2720 (701–6586)	12974 (4510–35000)	<0.001
hsTnI, ng/l	73 (19–754)	43 (14–463)	585 (116–7316)	<0.001
D-dimer, ng/ml	1165 (652–5303)	1008 (570–3652)	3381 (1160–19943)	<0.001
TSH, mIU/l	1.08 (0.48–1.88)	1.1 (0.54–1.9)	0.92 (0.28–1.51)	0.089
Therapy, n (%)				
Noninvasive oxygen therapy	125 (55)	101 (56)	24 (50)	0.51
Mechanical ventilation >24 hours	21 (9)	1 (1)	20 (42)	<0.001
Antiplatelet therapy	92 (41)	71 (40)	21 (44)	0.61
Anticoagulants	191 (84)	147 (82)	44 (92)	0.11
β-blockers	179 (79)	149 (83)	30 (63)	0.002
ACEIs/ARBs	125 (55)	109 (61)	16 (33)	<0.001
Statin	120 (53)	97 (54)	23 (47)	0.44
Antibiotics	140 (62)	97 (54)	43 (90)	<0.001
Steroids	122 (54)	92 (51)	30 (63)	0.17
Convalescent plasma	17 (7)	11 (6)	6 (12)	0.21
Remdesivir	64 (28)	50 (28)	14 (29)	0.87
Procedure during hospitalization, n (%)				
Coronary angiography	83 (37)	64 (36)	19 (40)	0.62
PCI	54 (24)	41 (23)	13 (27)	0.54
CIEDs implantation	11 (5)	11 (6)	0 (0)	0.13
Temporary cardiac pacing	3 (1)	1 (1)	2 (4)	0.11
CIEDs removal	3 (1)	2 (1)	1 (2)	0.51
Cardiac ablation	4 (2)	4 (2)	0 (0)	0.58
Cardiac surgery[c]	20 (9)	20 (11)	0 (0)	0.009

Values are given as mean (standard deviation [SD]), number (percentage), or median (interquartile range [IQR])
[a]Acute myocardial infarction or unstable angina according to the fourth universal definition of myocardial infarction; [b]Atrioventricular block at least the second degree, ventricular arrhythmias including electrical storm, symptomatic bradycardia, atrial fibrillation, atrial flutter or reentrant supraventricular tachycardias; [c]Coronary artery bypass graft, valve repair or replacement, ascending aortic replacement, thoracic endovascular aortic repair, transcatheter valve implantation or VAC therapy

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors, ARBs, angiotensin receptor blockers; CIEDs, cardiac implantable electronic devices; hsCRP, high-sensitivity C-reactive protein; hsTnI, high-sensitivity troponin I; NT-pro-BNP, N-terminal prohormone of brain natriuretic peptide; PCI, percutaneous coronary intervention; TSH, thyroid-stimulating hormone

Affiniti CVx (Philips Healthcare, Amsterdam, The Netherlands).

The analyzed endpoint in our study was in-hospital mortality from any cause. We have also analyzed the need for oxygen supplementation i.e. non-invasive oxygen therapy (including Optiflow® High Flow Nasal system), mechanical ventilation, duration of hospital stay, use of cardiovascular drugs grouped into drug classes (β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers [ACEIs/ARBs], statins, anticoagulation treatment, and antiplatelet therapy), and other recommended therapy (steroids, antibiotics, convalescent plasma, and remdesivir) [7]. The last part of Table 1 summarizes invasive procedures performed throughout the hospitalization.

Statistical analysis

Statistical analysis was performed using PQStat v.1.8.2. Software (Poznań, Poland). Continuous variables are presented as a mean and standard deviation if parametric (assessed using the Shapiro-Wilk test) or as a median and interquartile range (IQR) for continuous variables. Categorical variables are presented as numbers and percentages. The χ^2 test, Fisher's exact test, Student's t-test, and the Mann-Whitney U-test were used, as appropriate, for group comparison. The univariate logistic regression was applied to assess predictors of in-hospital death or mechanical ventilation. The results were presented as odds ratio (OR) with 95% confidence intervals (CI). A two-sided *P*-value of <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Demographic and clinical characteristics of survivors and non-survivors are presented in Table 1. From October 23 to April 23 227 patients were admitted to the bi-disciplinary cardiology and cardiac surgery ward and completed their hospital course (i.e. discharge or death). Most of the cases were tested positive on the first day of hospitalization (median [IQR], 1 [1–4] day), hence they were defined as community-acquired infections. The median hospitalization duration was 14 (9–22) days. Overall, in-hospital mortality was 21% (48 of 227 patients). Seventy-nine percent of non-survivors were older than 65 years (38 of 48 patients). There was no difference between the survivor and non-survivor groups with respect to sex (17% in female vs 23% in male; *P* >0.05), the body mass index, and the duration of hospital stay (Table 1). Reduced left ventricular ejection fraction was observed in the non-survivor group.

There were no intergroup differences regarding the main cause of hospitalization. The most frequent reasons for hospitalization were acute coronary syndromes (28%), acute heart failure (26%), and pneumonia (13%) in patients with multiple cardiovascular comorbidities. The most prevalent cardiovascular risk factor or disease was arterial hypertension (70%), followed by heart failure (48%), atrial fibrillation (42%), diabetes mellitus (33%), obesity (26%), and coronary artery disease (22%). Seven percent of patients had a cardiac pacemaker or implantable cardioverter defibrillator previously implanted.

Our data confirm that elderly patients with numerous comorbidities are at the highest risk of hospitalization [8].

Non-survivors had a higher level of troponin I, N-terminal prohormone of brain natriuretic peptide, white blood cells count, creatinine, D-dimer, C-reactive protein, and procalcitonin on admission than survivors. β-blockers and ACEIs/ARBs were used more frequently by survivors than by non-survivors. By contrast, antibiotics were used less frequently by survivors than by non-survivors. No difference amongst the groups was observed regarding using steroids, convalescent plasma, or remdesivir.

Oxygen supplementation was necessary for 64% of patients (n = 146). Mechanical ventilation (>24 hours to exclude resuscitation and perioperative period) was applied in 21 cases (9%). Nasal high-flow oxygen therapy (including prone position) was applied in the preceding stage of invasive ventilation and also in 26 patients (11%). The mortality rate was high in patients requiring mechanical ventilation (95%).

Age over 65 years (OR, 2.33; 95% CI, 1.09–4.97; *P* = 0.029) and ejection fraction <50% (OR, 3.94; 95% CI, 1.9–8.18; *P* <0.001) were independent predictors of in-hospital death, whereas treatment with ACEIs/ARBs (OR, 0.32; 95% CI, 0.16–0.62; *P* <0.001) or β-blockers (OR, 0.34; 95% CI, 0.17–0.68; *P* = 0.002) were associated with a lower risk of in-hospital death and mechanical ventilation (OR, 0.16; 95% CI, 0.05–0.5; *P* = 0.002 and OR, 0.31; 95% CI, 0.12–0.79; *P* = 0.014, respectively).

The most frequently performed procedures were coronary angiography in 83 patients (37%), percutaneous coronary intervention in 54 patients (24%), and cardiac surgery in 20 patients (9%), most of whom underwent coronary artery bypass grafting or valve replacement/repair procedure (75%). It is worth noting that there were no deaths among patients in the cardiac surgery group.

Our study presents data of the unique group of patients both with SARS-CoV-2 infection and acute cardiac disorders or exacerbation of chronic heart diseases treated in a bi-disciplinary unit of the multi-profile tertiary referral hospital that was not solely dedicated to COVID-19 patients. Establishing such a department made it possible to effectively separate infected patients from healthy ones and to maintain access to highly specialized procedures.

Article information

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COVID-19 mortality in patients after orthotopic heart transplantation: A single-center one-year observational study

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INTRODUCTION

Reports on transplant patients affected by SARS-CoV-2 suggest that not only the immunosuppressive regimen but also comorbidities and advanced age influence the clinical course of the infection [1]. Based on the available case series, reports, and meta-analyses, the COVID-19 mortality rate in solid organ transplant patients is higher than in the general population. We aimed to assess COVID-19 mortality and morbidity in heart transplant (HTx) recipients who were under the surveillance of one Polish center.

METHODS

This was a one-year prospective clinical observational study from a single transplant center regarding susceptibility to SARS-CoV-2. Patients were analyzed from March 2020 to March 2021. The data were collected during hospitalization, home medical visits, phone calls, and from the open database of the National Health Fund. All patients signed written informed consent to participate in the study.

The patients were considered infected if they had positive results of reverse transcription-polymerase chain reaction tests of nasopharyngeal swab samples or a history of typical signs and symptoms of COVID-19 with the presence of anti-SARS-CoV-2 antibodies.

The whole group of patients comprised 540 patients after HTx (112 patients ≤1 year and 428 patients >1 year after HTx), and among them there were 50 SARS-CoV-2 infected patients, including 10 patients ≤1 year after HTx.

Forty patients (80%) received tacrolimus, including 12 patients (24%) on monotherapy, 27 patients (54%) in combination with mycophenolate mofetil, and one patient (5%) in combination with everolimus. Eight patients (16%) received cyclosporine A, including 6 subjects (12%) who received cyclosporine A in combination with mycophenolate mofetil and 2 subjects (10%) took it in monotherapy. One patient received everolimus with mycophenolate mofetil, and another patient was given sirolimus in combination with mycophenolate mofetil.

Patients up to one year after transplantation were administered prednisone as the basic regimen in tapered doses. All patients were given statins and acetylsalicylic acid (75 mg/day).

As antiviral and antibacterial prophylaxis, all patients were administered valganciclovir up to day 110 and sulfamethoxazole-trimethoprim up to 6 months after transplantation.

Table 1 shows clinical and laboratory parameters.

The Bioethics Committee of the Medical University of Silesia approved the study (decision no. PCN/CMN/0022/KB1/30/21).

Statistical analysis

Categorical variables were presented as counts and percentages. Continuous variables were presented as the mean and standard deviation for normally distributed data or median with lower and upper quartiles. The Shapiro-Wilk test was used to verify the normal distribution of data. The Chi^2 test

Table 1. Clinical patient characteristics

	Whole group (n = 50)	Survivors (n = 44)	Deceased (n = 6)	*P*-value
Age, years, mean (SD)	57.1 (12.2)	56.5 (12)	61.32 (13.5)	0.405
Female sex, n (%)	10 (20)	9 (20.5)	1 (16.7)	0.91
Time from HTx to infection, years, median (IQR)	7.01 (0.38–12.5)	7.43 (2.12–26.4)	3.93 (0.38–12.25)	0.51
Infection-to-death time, days, median (IQR)	38.0 (28–47)	NA	38.0 (28–47)	NA
Patients hospitalized for COVID-19, n (%)	14 (28)	8 (18.2)	6 (100)	<0.001
Hospitalization for COVID-19, days, mean (SD)	21.3 (10.94)	20.75 (10.63)	25.33 (15.19)	0.517
Hypertension, n (%)	40 (80)	36 (81.8)	4 (66.7)	0.3
Bodyweight, kg, mean (SD)	81.45 (14.3)	81.18 (13.9)	83.47 (15.71)	0.71
Height, cm, mean (SD)	173.18 (7.57)	173.9 (7.81)	172.33 (5.47)	0.71
BMI, kg/m^2, mean (SD)	26.94 (4.07)	26.77 (3.81)	28.15 (5.61)	0.44
Active cancer, n (%)	0 (0)	0 (0)	0 (0)	NA
Previous cancer, n (%)	3 (6)	3 (6.8)	0 (0)	0.499
Previous TIA, n (%)	2 (4)	2 (4.5)	0 (0)	0.585
Previous stroke, n (%)	6 (12)	6 (13.6)	0 (0)	0.322
Impaired glucose metabolism				0.454
None, n (%)	17 (34)	14 (31.8)	3 (50)	
Glucose intolerance, n (%)	8 (16)	8 (18.2)	0 (0)	
Diabetes, n (%)	24 (48)	21 (47.7)	3 (50)	
COPD, n (%)	3 (6)	2 (4.5)	1 (16.7)	0.26
Graft vasculopathy, n (%)	9 (18)	8 (18.2)	1 (16.7)	0.9
Previous PTCA, n (%)	6 (12)	5 (11.4)	1 (16.7)	0.74
Chronic renal failure, n (%)	36 (72)	30 (68.2)	6 (100)	0.116
Chronic dialysis, n (%)	6 (12)	3 (6.8)	3 (50)	0.02
Dialyses in the course of COVID-19, n (%)	7 (14)	3 (6.8)	4 (66.7)	<0.001
NYHA I, n (%)	44	41 (93.2)	3 (50)	0.008
NYHA II, n (%)	4	3 (6.8)	1 (16.7)	
NYHA III, n (%)	1	0 (0)	1 (16.7)	
NYHA IV, n (%)	1	0 (0)	1 (16.7)	
LVEF, % (median, IQR)	55.9 (45–60)	56 (55–60)	55 (45–58)	0.31
Leukocyte count before the SARS-CoV-2 infection, ×10^9/l, median (IQR)	6.74 (5.6–10.12)	6.57 (5.6–7.84)	7.96 (5.95–10.12)	0.261
Leukocyte count after the SARS-CoV-2 infection, ×10^9/l, mean (SD)	6.29 (1.92)	6.33 (1.8)	5.99 (2.64)	0.737
Lymphocyte count before the SARS-CoV-2 infection, ×10^3/ /μl, median (IQR)	1.37 (0.27–1.93)	1.49 (1.12–1.93)	0.46 (0.27–0.65)	0.063
Creatinine level before the SARS-CoV-2 infection, μmol/l, median (IQR)	129.7 (95.47–354)	120.5 (95.47–156)	197.5 (164–354)	0.014
Creatinine after the SARS-CoV-2 infection, μmol/l, median (IQR)	121.6 (87.0–244.5)	114.0 (87.0–144)	177.5 (109–244.5)	0.256
Acute cellular rejection treatment one year before the SARS--CoV-2 infection, n (%)	6 (12)	6 (13.6)	0 (0)	0.31
Peripheral vascular disease, n (%)	6 (12)	4 (9.1)	2 (33.3)	0.099
Therapy with the lymphocyte depleting agent 6 months before the SARS-CoV-2 infection	None	None	None	NA
Bacterial or viral infection requiring hospitalization or during hospitalization for other reasons one year before the SARS-CoV-2 infection, n (%)	6 (12)	4 (9.1)	2 (33.3)	0.099
Past CMV infection, n (%)	7 (14)	6 (13.6)	1 (16.7)	0.86
Active CMV infection, n (%)	0 (0)	0 (0)	0 (0)	NA
Past HBV infection, n (%)	3 (6)	3 (6.8)	0 (0)	0.504
Past HCV infection, n (%)	2 (4)	2 (4.5)	0 (0)	0.58

Abbreviations: BMI, body mass index; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; HBV, hepatitis B; HCV, hepatitis C; IQR, interquartile range; LVEF, left ventricular ejection fraction; NA, not applicable; NYHA, New York Heart Association; OHT, orthotopic heart transplantation; PTCA, percutaneous coronary angioplasty; SD, standard deviation; TIA, transient ischemic attack

was utilized to compare categorical variables, whereas the t-test or the Mann-Whitney U test was applied to compare continuous variables where appropriate. A *P*-value <0.05 was considered statistically significant. SAS software, version 9.4 (SAS Institute Inc., Gary, NC, US) was used for all calculations.

RESULTS AND DISCUSSION

The whole population of patients with COVID-19 included 50 patients (9.23% of all patients). Clinical patient characteristics are given in Table 1.

Patients within the first year after HTx (n = 10) comprised 20% of COVID-19 subjects. The percentage of

SARS-CoV-2 positive patients within the first year after HTx was 8.9% (10/112), and 9.3% (40/428) after the first year following HTx. The death rate was 30% (3/10) within the first year after HTx, and 7.5% (3/40) after the first year following HTx. Four patients, who were intubated due to respiratory failure, died. In one patient, renal replacement therapy *de novo* was introduced. In 3 patients (6%), the left ventricular ejection fraction was already decreased before COVID-19. In none of the patients, left ventricular ejection fraction changed by more than 5% when compared to the baseline examination. In one patient after COVID-19, a significant acute cellular rejection was diagnosed based on elective endomyocardial biopsy. Two patients within the first year after HTx and 5 patients after the first year following Htx were asymptomatic.

Immunosuppressive modifications were performed only in symptomatic patients and included dose reduction of mycophenolate mofetil or cessation and/or additional steroid administration. Dose reduction of mycophenolate mofetil was used in 2 patients (5%), and temporary cessation in 11 patients (37% of the whole group on mycophenolate mofetil). Among the deceased patients, mycophenolate mofetil was used in four subjects. However, it was suspended due to the disease (n = 2). The doses of tacrolimus were not modified and the median whole blood concentration of tacrolimus in survivors was 8.81 ng/ml (interquartile range [IQR]: 6.21–10.52 ng/ml), and 7.2 ng/ml in deceased patients (IQR, 6.17–8.49 ng/ml; $P = 0.493$). The doses of prednisone were not modified due to the disease.

Additional doses of dexamethasone were introduced in two patients (>1 year after HTx). In four patients, convalescent plasma was used, whereas azithromycin was given to four patients. Other antibiotics were administered to three patients. Remdesivir was used in one patient who recovered.

In our study, total mortality of confirmed SARS-CoV-2 infection cases reached only 12%, but it was still unacceptably high when compared to the general population (2.6%) [2].

Notably, the mortality rate in patients within the first year after HTx was four times higher than in the group >1 year after HTx. This could be explained by more potent immunosuppressive treatment and a weakened general condition due to HTx and previous long-standing end-stage heart failure. In particular, we also observed that comorbidities, such as heart or renal failure, resulted in an unfavorable outcome. We found significant differences in the baseline creatinine level in favor of survivors. Also, lower exercise capacity before infection, assessed by the New York Heart Association (NYHA) classification, adversely influenced the outcome. The association between heart failure and adverse outcomes in COVID-19 patients was reported for the general population previously [3, 4].

All the clinical symptoms were typical of the general population. In our group of patients, despite a low number of COVID-19 cases, it was noticeable that the deceased patients had a lower lymphocyte count compared to the survivors.

Article information

Conflict of interest: None declared.

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Lumbar spinal canal stenosis: An early sign of amyloid transthyretin related amyloidosis

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Amyloid transthyretin-related amyloidosis (ATTR) onsets due to the extracellular multiorgan deposition of misfolded transthyretin, a serum protein that synthesizes mainly in the liver. Two different forms of the disorder have been identified to date, namely wild type ATTR (wtATTR), previously referred to as "senile" since it was mainly diagnosed in the elderly; and an inherited ATTR (hAATR), caused by mutant transthyretin.

ATTR amyloidosis is often overlooked or misdiagnosed owing to its non-specific presentation.

Amyloid deposits can determine musculoskeletal manifestations, such as carpal tunnel syndrome (CTS), lumbar spinal canal stenosis (LSCS), or distal biceps tendon rupture (DBTR) several years before any cardiac manifestations, particularly in patients with wtATTR.

Cardiac manifestations of wtATTR (wtATTR-CA) include aortic stenosis, hypertrophic cardiomyopathy, heart failure with preserved ejection fraction, and hypertensive cardiomyopathy, although the cardiac signs and symptoms resemble those of other cardiovascular conditions of different etiology during the course of the disease [1].

We present radiological images of an 80-year-old man who had wtATTR-CA and LSCS. At the age of 65, he had had bilateral CTS. Ten years later, he began to report pain and loss of strength in the lower limbs mainly localized in the buttocks and quadriceps. Computed tomography (CT) of the spine showed a LSCS due to ligamentum flavum hypertrophy (LFH) considered to result from fibrous degeneration (Figure 1A). ATTR-CA was diagnosed (Figure 1C) four years later. Genetic investigations yielded a negative result for hATTR. Upon further investigation, spinal magnetic resonance imaging (Figures 1D, E) and a second CT scan of the spine (Figure 1B) showed significant LFH with narrowing of the spinal canal.

The LF covers the rear surface of the spinal dural sac and has a protective effect on the spinal cord, controlling the extension of the intervertebral movement.

In the elderly, LFH is one of the most frequent causes of LSCS, and its onset has been related to a degenerative fibrotic condition. Patients usually complain of intermittent claudication, low back pain and leg numbness, and pain [2]. Several authors recently reported amyloid deposits in elderly patients with LFH and LSCS. In a recent study, where 250 patients underwent surgery for LSCS due to LFH, Eldhagen et al. identified an amyloid presence in 88.4% of the histological samples, and ATTR was found in 37% of the cases [3]. In a large group of 324 patients who underwent surgery for LSCS, Godara et al. found wtATTR in 13% of the cases. wtATTR-CA was diagnosed in two of those cases. LF amyloid deposits could thus be considered an early manifestation of systemic ATTR disease [4]. Compared with CTS, LFH is a less known musculoskeletal wtATTR manifestation and is generally attributed to changes in fibrotic ligaments. Unfortunately, ^{99m}Tc-diphosphanate scintigraphy, which is a useful diagnostic tool to detect wtATTR-CA, is not able to demonstrate LF amyloid deposits [5].

A correct interpretation of these manifestations, together with the cardiological

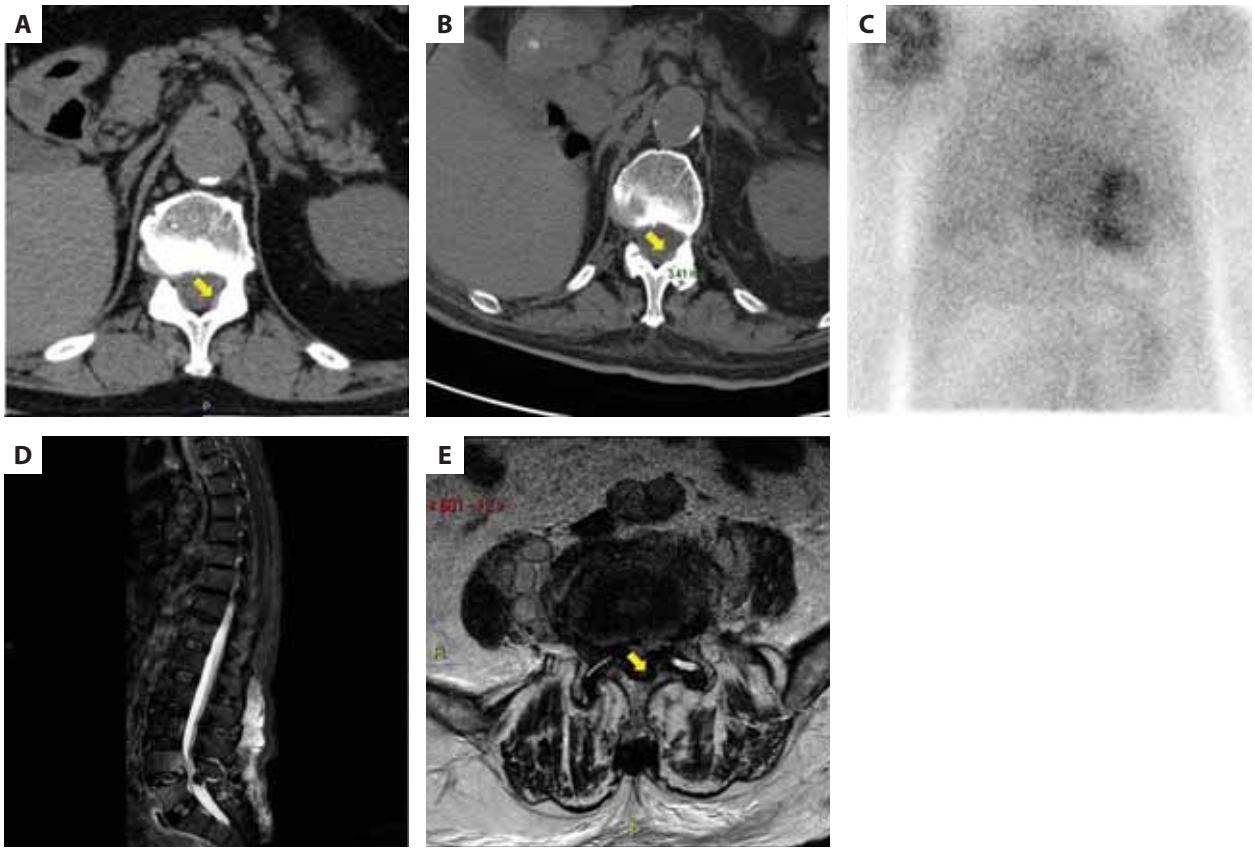

Figure 1. A. Computed tomography (CT) of the spine showed a LSCS due to ligamentum flavum hypertrophy (yellow arrows). **B.** A second spinal CT after five years since the former revealed an increased thickness of the ligamentum flavum. **C.** ^{99}mTc-3,3-diphosphono-1,2-propanodicarboxylic allows for a diagnosis of wtATTR. **D, E.** The magnetic resonance confirmed the ligamentum flavum hypertrophy

signs of the disease, allows for early diagnosis and faster access to therapy. For this reason, improved inter-specialty communication is required for managing patients with ATTR amyloidosis.

Article information

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A unique case of unicuspid aortic valve with severe regurgitation combined with coronary-pulmonary fistula

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Congenital heart diseases may be considered in isolation, as well as in connection with other anomalies. Prevalence of the unicuspid aortic valve is only 0.02 % in the adult population, which makes this congenital malformation very rare [1]. Moreover, it has male predominance [2]. It usually presents in the third to fifth decade of life with severe aortic stenosis, less frequently with aortic regurgitation. Diagnosis can be made with echocardiography, computed tomography (CT), or cardiac magnetic resonance. The preferred treatment of patients with severe aortic valve stenosis or regurgitation is surgical repair or replacement of the affected valve.

The coronary artery fistulas (CAFs) are rare abnormalities, and their prevalence is estimated to be 0.9% in the adult population. CAFs are usually asymptomatic due to their small size, although they may cause pulmonary hypertension or high cardiac output heart failure. CAFs may be diagnosed with selective coronary angiography, although electrocardiogram-gated CT has higher sensitivity in the detection of small fistulas [3]. Symptomatic CAFs can be treated with surgical ligation or percutaneous transcatheter closure. To our best knowledge, the combination unicuspid aortic valve with CAF has not been described so far.

We present a case of a 36-year-old woman with progressive exertional dyspnoea the New York Heart Association (NYHA) class III, with severe aortic regurgitation (vena contracta 7 mm, prominent holodiastolic reversal in descending aorta), and only mild stenosis (mean pressure gradient 25 mm Hg, aortic valve area 1.62 cm^2) due to the unicuspid aortic valve combined with coronary-pulmonary fistula. The patient first underwent transthoracic echocardiography detecting the presence of the dilated left ventricle (left ventricular end-diastolic diameter 65 mm; left ventricular ejection fraction 62%) due to severe aortic regurgitation (leaflet prolapse; calcifications and fibrotic changes of the valve) and the suspicion of unicommissural unicuspid valve was raised (Supplementary material, *Video S1*). These findings were subsequently confirmed with 2D and 3D transesophageal echocardiography (Figure 1A, B and Supplementary material, *Video S2*). Electrocardiogram-gated CT coronary angiography was performed showing the calcified unicuspid aortic valve (Agatston calcium score of the aortic valve of 1249) (Figure 1D). Moreover, the CT depicted a coronary anomaly, a coronary artery originating in the ascending aorta close to the ostium of the right coronary artery and terminating in the pulmonary artery (Figure 1C). No other pathology of coronary arteries was present.

The patient was treated surgically by a bioprosthetic aortic valve replacement. The coronaro-pulmonary fistula was evaluated as hemodynamically insignificant and was not treated.

In the early postoperative period, a permanent complete atrioventricular block occurred, and a pacemaker had to be implanted. The patient's recovery was subsequently uneventful, and one month after the cardiac surgery the patient was asymptomatic. Nor-

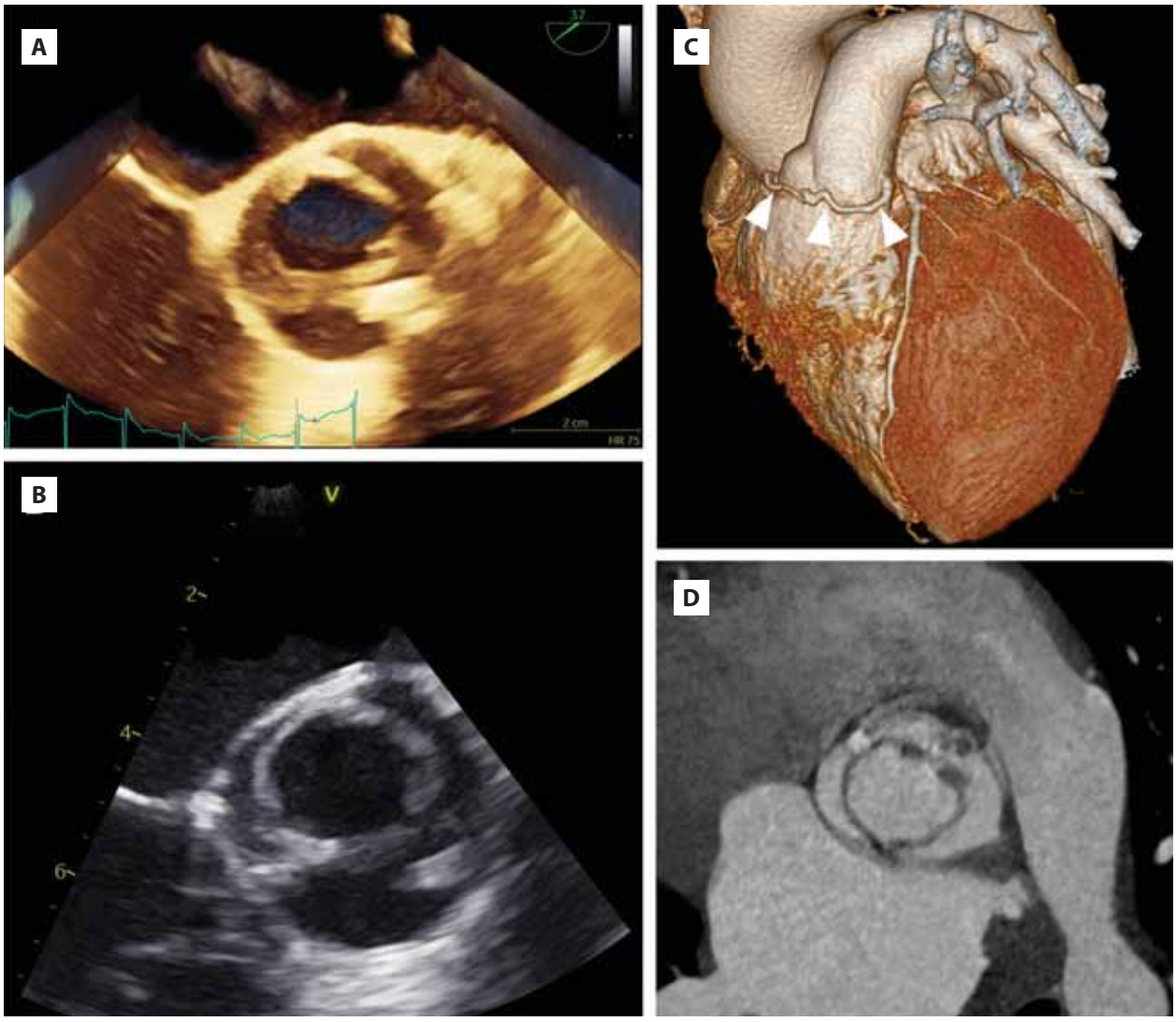

Figure 1. A. Transesophageal 3D echocardiography, aortic valve view depicting unicommissural unicuspid aortic valve. **B.** Transesophageal 2D echocardiography, upper esophageal aortic short-axis view showing unicuspid aortic valve. **C.** Cardiac computed tomography, 3D volume rendering technique showing the coronary-pulmonary fistula (arrows). **D.** Cardiac computed tomography, oblique axial minimum intensity projection showing unicuspid aortic valve with leaflet thickening and presence of calcification

mal functions of aortic bioprosthesis and left ventricule in systole were found by transthoracic echocardiography.

Supplementary material

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

Article information

Conflict of interest: None declared.

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Diagnostic challenges to determine the cause of pulmonary hypertension in a patient with heart failure with preserved ejection fraction and borderline pulmonary artery wedge pressure

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Pulmonary hypertension (PH) related to left heart disease (LHD) accounts for 65%–80% of PH cases [1]. LHD may lead to isolated post-capillary PH, or combined post- and pre-capillary PH ("reactive" PH) [2]. In the case of mixed PH, a primary cause of the pre-capillary component (arterial PH or chronic thromboembolic PH [CTEPH]) must be considered due to potential targeted treatment [3]. We highlight here diagnostic challenges in this clinical scenario.

A 75-year-old man with exertional dyspnea (New York Heart Association [NYHA] class III), a history of myocardial infarction treated with stent implantation in the circumflex artery, moderate-severe mitral regurgitation, and four hospitalizations for right ventricular (RV) heart failure (HF) in the preceding year was admitted for diagnostic work-up. Echocardiography showed enlargement of both atria (left atrial volume index, 53 ml/m^2; right atrial area, 23 cm^2); normal left ventricular (LV) ejection fraction (EF) (62%); increased LV filling pressures (E wave velocity, 1.1 m/s, E/e' ratio 13) with restrictive mitral inflow pattern (E/A ratio, 3.7) despite normal lateral mitral annulus velocity (e') (12 cm/s), and close-to-normal septal e' (6 cm/s). RV systolic function was normal. He had moderate mitral regurgitation (MR), mild tricuspid regurgitation (TR; TR peak velocity [TRV], 3.5 m/s), and a dilated pulmonary artery with shortened acceleration time (67 ms) with midsystolic notching (Figure 1A). N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration was 583 pg/ml. The electrocardiogram showed atrial fibrillation and LV hypertrophy. The HFA-PEFF criteria were met (6 points in the HFA-PEFF score).

Exercise echocardiography was performed revealing a rapid increase in TRV (to 4.3 m/s at 50 Watt), increase in TR severity (to moderate) and an RV basal diameter (from 3.8 to 4.4 cm). There were no LV systolic abnormalities and no increase in MR severity. Regarding LV diastolic function, lateral e' increased to 14 cm/s, while septal e' decreased to 5 cm/s, with an average E/e' of 15 (Figure 1A). Coronary angiography revealed no significant lesions (Figure 1B). Computed tomography angiography excluded acute pulmonary embolism and CTEPH (Figure 1C).

The patient was diagnosed with heart failure with preserved EF. However, a significant increase in TRV during exercise, disproportionate to a relatively small increase in the E/e' ratio, suggested the concomitant presence of pre-capillary PH. Right heart catheterization (RHC) demonstrated mean pulmonary arterial pressure (mPAP) of 30 mm Hg (confirming PH), with pulmonary artery wedge pressure (PAWP) of 13 mm Hg and pulmonary vascular resistance (PVR) of 5 Wood units (indicative of pre-capillary PH) [3]. However, repeated RHC in the reference center showed mPAP of

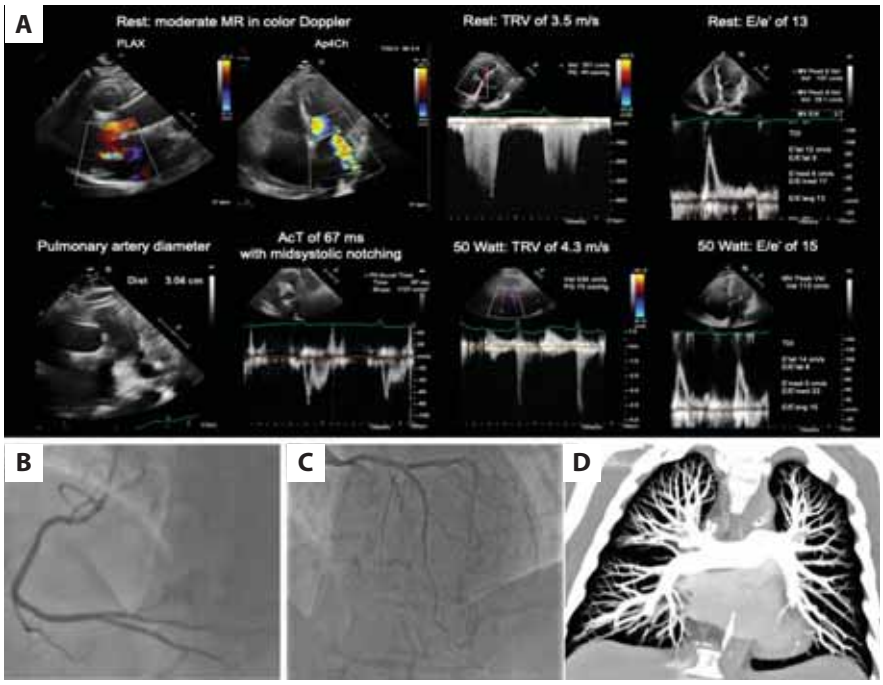

Figure 1. A. Bicycle exercise echocardiography showing a moderate mitral regurgitation at rest with TRV 3.5 m/s and the transmitral early peak velocity (E) by pulsed wave Doppler over mitral annulus velocity (e') (E/e') 13 and a rapid increase in TRV (up to 4.3 m/s at 50 Watt), TR severity (from mild to moderate) and RV basal diameter (from 3.8 to 4.4 cm) at exertion (50 Watt). **B, C.** Coronary angiography demonstrating no significant coronary lesions in the right coronary artery (**B**) and a patent stent in the proximal left anterior descending artery (**C**). **D**. Computed tomography angiography with no pathological findings

Abbreviations: RV, right ventricle; TR, tricuspid regurgitation; TRV, tricuspid regurgitation peak velocity

37 mm Hg, PAWP of 17 mm Hg, and PVR of 6.5 Wood units, indicating combined post- and pre-capillary PH due to LHD. HF therapy was optimized, and the patient was discharged for ambulatory care.

While a PAWP >15 mm Hg confirms LHD-PH, values between 13–15 mm Hg are considered borderline. The PAWP of 13 mm Hg in the first RHC in our patient might have been due to diuretic treatment and a lower pulmonary blood flow secondary to pre-capillary "reactive" vascular disease resulting in lower LA pressure. The respiratory cycle also may have contributed to the differences in PAWP measurements. PAWP and LVEDP should ideally be measured at the end-diastole, averaged for the respiratory cycle, and by using QRS gating, which brings them as close as possible to intrathoracic pressure correction. Intrathoracic pressure is approximately 3 mm Hg at functional residual capacity in healthy resting individuals [4]. This pre-capillary component of PH in our patient might have led to predominating RV HF symptoms, as well as a significant increase in TRV with a disproportionately small increase in the E/e' ratio during exercise echocardiography. Caution is required before initiating targeted therapies not recommended in patients with PH-LHD [5].

Article information

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Patent ductus arteriosus obscured by a giant aortic aneurysm in a young man with acute heart failure

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A 32-year-old man without previous history of cardiovascular diseases was admitted to the intensive care unit due to acute heart failure. The patient complained of severe dyspnea which had lasted for two days. He denied chest pain, palpitations, and syncope. Blood pressure was 134/52 mm Hg. An electrocardiogram showed sinus tachycardia with a heart rate of 140 bpm and an incomplete left bundle branch block. The concentrations of troponin T (365 ng/l, normal <14 ng/l) and N-terminal pro-brain natriuretic peptide (>30 000 pg/ml, normal <125 pg/ml) were significantly increased. Markers of kidney and liver injury were also elevated (creatinine 1.76 mg/dl; total bilirubin 3 mg/dl; alanine aminotransferase 151 U/l; international normalized ratio 1.8). Due to the development of pulmonary edema, the patient required mechanical ventilation and infusion of dobutamine and nitroglycerin. Transthoracic echocardiogram (TTE) revealed an enlarged, hypokinetic left ventricle (end-diastolic dimension 92 mm, ejection fraction [EF], 33%), giant ascending aortic aneurysm, and severe regurgitation of the aortic valve that seemed to be bicuspid (Figure 1A; Supplementary material, *Videos S1* and *S2*). The maximum diameter of the aorta measured on computed tomography (CT) was 105 mm (Figure 1B). Neither dissection nor additional anomalies were detected (Figure 1C). The patient underwent Bentall procedure including implantation of St. Jude Medical 31 mm prosthesis. The surgeon described the valve as unicommissural with one true commissure between the left and non-coronary cusps. Pre-discharge TTE showed unexpectedly continuous flow between the aorta and the pulmonary artery at the site typical for patent ductus arteriosus (PDA) (Figure 1D; Supplementary material, *Video S3*). Subsequent CT confirmed the diagnosis of PDA, which had a length of 13 mm and a diameter of 5 mm at the junction to the left pulmonary artery (Figure 1E, F). Reanalysis of the initial CT study ensured us that no communication between the aorta and pulmonary artery had been overlooked at that time. Due to the accumulation of fluid in the pericardial cavity with features of imminent cardiac tamponade, the patient needed pericardiocentesis and after rehabilitation, he was discharged home. Three months later the patient was feeling well, a modest improvement of left ventricular function was evident (EF about 38%). Cardiac catheterization revealed normal pulmonary artery pressure (mean 18 mm Hg). Although the left ventricular dilation had resulted most probably from the aortic regurgitation, PDA could not have been excluded as an additional factor preventing complete recovery of the left ventricular function. Therefore, the Heart Team decided to recommend the percutaneous closure of PDA for this patient. The procedure was performed with Amplatzer Duct Occluder 8/6 mm.

In the adult population, PDA is very rarely encountered. The key diagnostic method

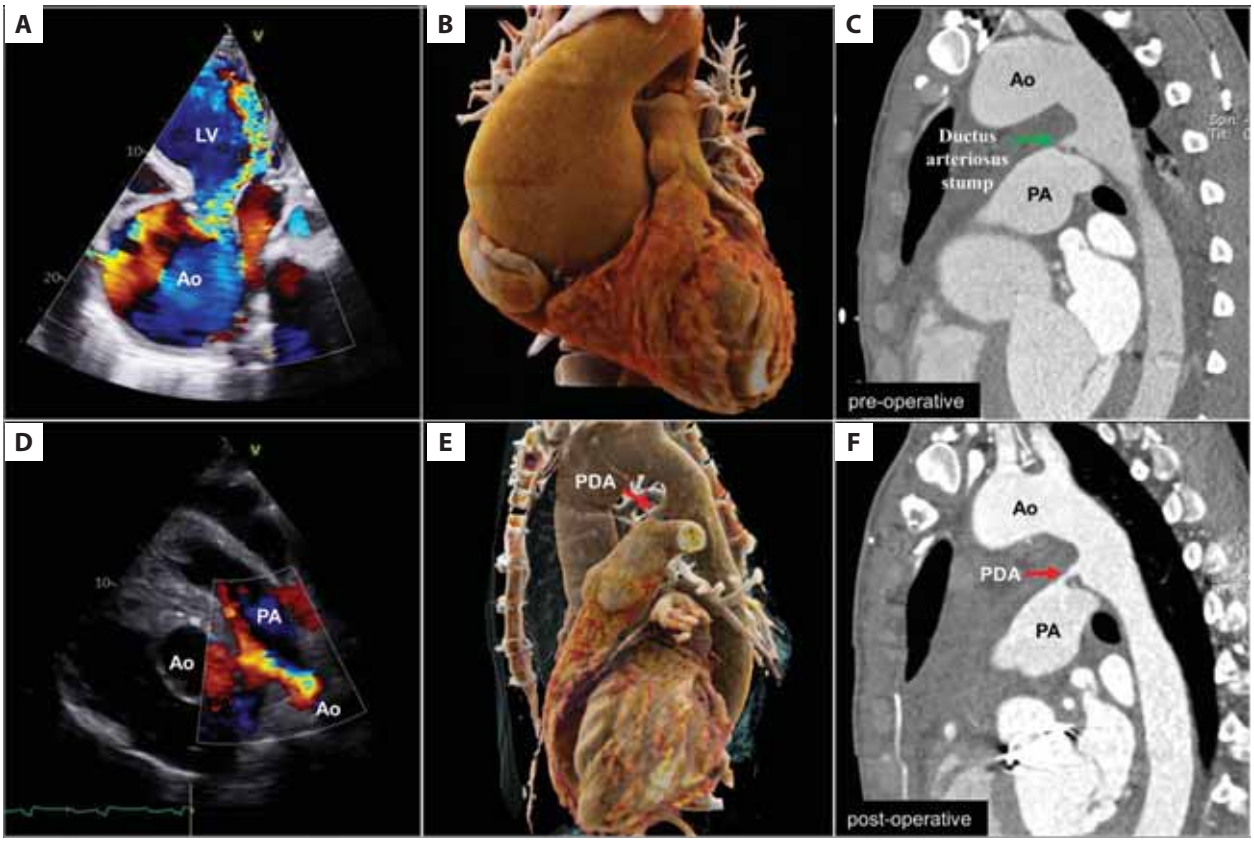

Figure 1A. Transthoracic echocardiogram (TTE), five-chamber view, shows severe aortic regurgitation and ascending aortic aneurysm. **B.** Computed tomography (CT), volume rendering, presents giant aortic aneurysm. **C.** Pre-operative CT angiography shows no connection between the aorta and the pulmonary artery, only ductus arteriosus stump (the green arrow). **D.** Postoperative TTE, parasternal short-axis view, demonstrates flow via patent ductus arteriosus (PDA) between the descending aorta and the left pulmonary artery. **E.** Postoperative CT, volume rendering, presents the aortic graft and PDA (the red arrow). **F.** CT angiography shows PDA (the red arrow)

Abbreviations: Ao, aorta; LV, left ventricle; PA, pulmonary artery; PDA, patent ductus arteriosus

is echocardiography, while CT and magnetic resonance provide a better evaluation of anatomy [1, 2]. However, blood flow via PDA may be diminished in particular circumstances affecting the sensitivity of imaging. In the presented patient, ductus arteriosus was initially visible only in the proximal part, probably as a result of increased pressure in the mediastinum related to the giant aortic aneurysm. Reconstitution of flow occurred after the change in local anatomical and hemodynamic conditions caused by surgery. This emphasizes the role of comprehensive assessment both before and after an operation.

Article information

Conflict of interest: RP received a research grant agreement and honoraria for lectures from Abbott. All other authors declare no conflict of interest.

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Primary neuroendocrine tumor of the heart. Successful management of an extremely rare disease

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A 38-year-old female without medical history was admitted due to severe chest pain. She had no prior symptoms, and this was the first presentation of the disease. Blood pressure was normal. Electrocardiography showed ST depression in inferolateral leads (Figure 1A). High-sensitive troponin I was elevated — 1571.5 ng/l (normal <50 ng/l).

Echocardiography detected a tumor near the right atrium (Figure 1B; Supplementary material, *Video S1*). Additional imaging with computed tomography and magnetic resonance (Figure 1C–E) showed that the tumor was hypervascular, non-invasive, and well-contained mass. It was in close contact and compressing the right atrium and right ventricle but without infiltrating them. It surrounded the right coronary artery. A coronary angiogram revealed no lesions, so coronary artery disease was excluded. Based on radiological features, the neuroendocrine tumor was primarily suspected with a possible differential diagnosis indicating paraganglioma.

Surgical removal was recommended by the heart team. Surgery was performed through median sternotomy using cardiopulmonary bypass (Figure 1F). The tumor was excised *in toto* from the heart walls and the right coronary artery.

The tumor was 55 × 39 × 35 mm in size (Supplementary material, *Figure S1A*). Microscopically, the tissue was composed of uniform polygonal cells with round nuclei, chromatin was fine-grained and diffusely distributed, and cytoplasm was pale eosinophilic. Tumor cells were arranged in organoid, trabecular, and pseudo-glandular formations (Supplementary material, *Figure S1B*). The stroma of the tumor was poor, built of thin connective tissue bands with numerous small blood vessels. Tumor necrosis was absent, and mitoses were rare (<2/10 HPF). The Ki67 proliferative index was <1% (Supplementary material, *Figure S1C*). The immunohistochemical profile was positive for CD56, synaptophysin, and chromogranin (Supplementary material, *Figure S1D–F*). Based on these analyses, the diagnosis of a typical neuroendocrine tumor was made.

The postoperative course was uneventful, and the patient was discharged on the 8th postoperative day. Subsequently, an octreotide scan, computed tomography of the chest, and magnetic resonance of the abdomen and small pelvis were performed in search of other potential tumor localizations. All these studies were negative, so this was a primary tumor of the heart. To the present day, two years after the initial presentation, the patient has been free of symptoms and with no signs of disease recurrence.

Solitary neuroendocrine tumors are rarely found in heart structures. The majority of these are metastatic tumors of the gastrointestinal origin, particularly the small intestine [1]. However, the primary localization of neuroendocrine tumors in the heart is extremely rare [2, 3]. Our case is unique because the tumor was located on the lateral wall of the right heart surrounding the right coronary artery, which contributed to the complexity of surgical management.

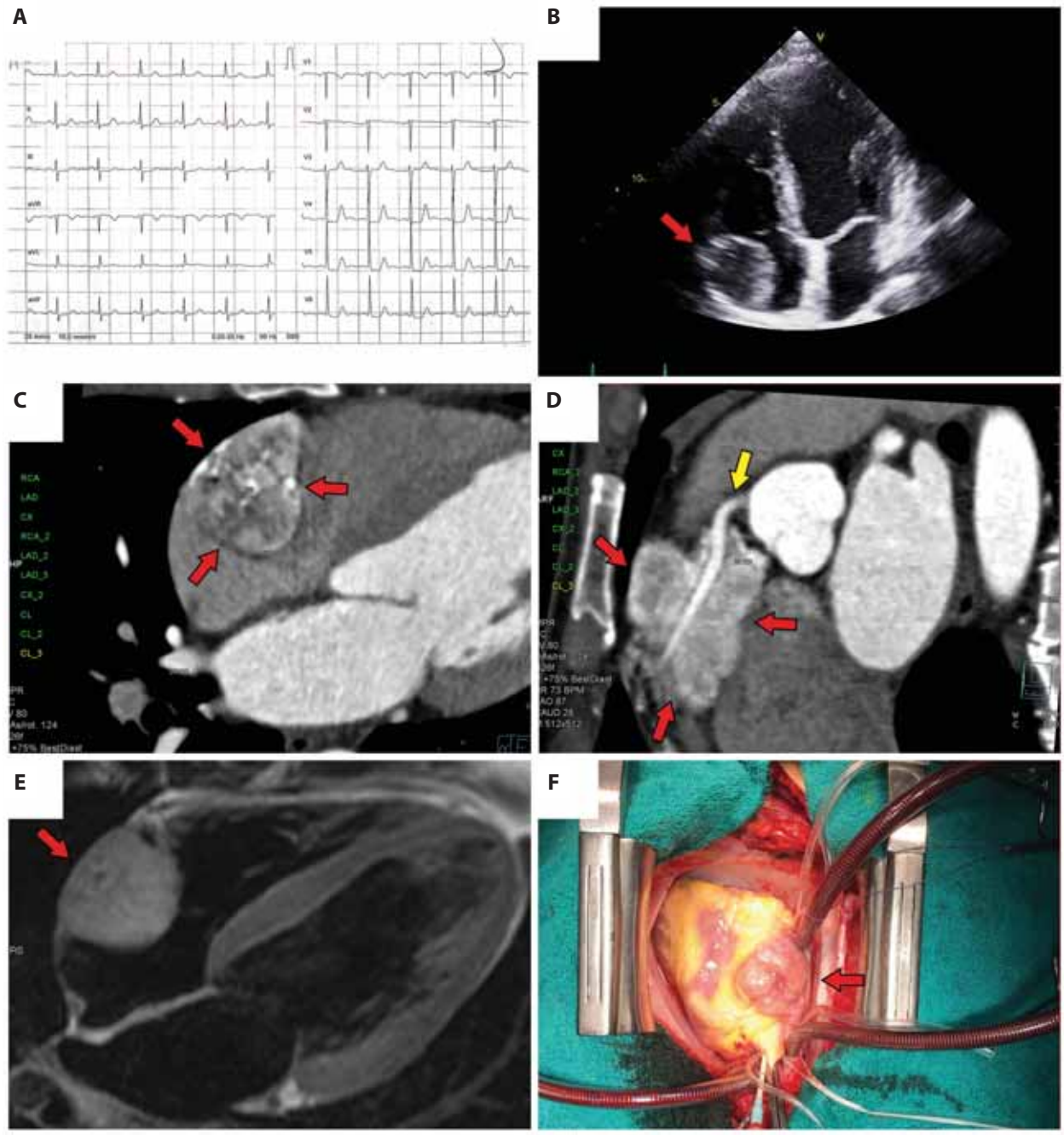

Figure 1. A. Electrocardiography on admission: ST depression in leads II, III, aVF, V4–V6. **B.** Transthoracic echocardiography, apical 4-chamber view: the tumor (red arrow) is located near the right atrium and collapsing it. **C–D.** Cardiac computed tomography: the tumor (the red arrows) is compressing the right atrium and the right ventricle but not infiltrating them and tightly surrounds the right coronary artery (yellow arrow). **E.** Cardiac magnetic resonance: turbo spin-echo (T2)-weighted image shows a hyperintense soft tissue lesion (red arrow). **F.** Intraoperative view: tumor (red arrow) is present on the lateral side of the right atrium and ventricle

The final diagnosis in our patient was a neuroendocrine tumor. Most likely differential diagnosis includes paraganglioma, which is regarded as a sub-family of neuroendocrine neoplasms [4]. This is indicated by the tumor's location, radiological features, the absence of metastatic disease, as well as histology and immunohistochemistry findings. However, the clinical presentation did not suggest any hormonal activity of the tumor, and the patient had a negative family history, while paragangliomas can be hereditary in up to 50% of cases [5].

Supplementary material

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

Article information

Conflict of interest: None declared.

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Infective endocarditis in a 52-year-old male patient with vegetations of all four heart valves and extremely high cardiac operative risk

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A 52-year-old male presenting with weakness, weight loss, and low-grade fever, which had been worsening over the past 6 months, was re-admitted to the district hospital after 6 inconclusive hospitalizations in at least 6 different hospitals and emergency departments.

Transthoracic echocardiography (TTE) showed massive vegetations of the aortic, mitral, and pulmonary valves. Physical examination and medical history revealed highly advanced dental caries as the only significant risk factor of infective endocarditis (IE) in this case. Positive blood culture with *Staphylococcus hominis* and *Streptococcus gallolyticus* was obtained. During hospitalization, the patient got retinal artery occlusion caused by embolic material separated from vegetations. After transferring the patient to our department, laboratory findings revealed moderate anemia, exacerbation of chronic kidney disease, and significantly increased cardiac injury markers. On TTE, the vegetations (Figure 1A–C) were accompanied by severe mitral and tricuspid regurgitation, moderate aortic and pulmonary regurgitation, enlargement of heart cavities, and a high probability of aortic, pulmonary, and mitral cusps perforation (Figure 1D). Despite the standard treatment including acute heart failure management and targeted antibiotic therapy, due to gradual worsening of the patient's clinical condition, the Heart Team decided against transesophageal echocardiography and disqualified the patient from surgery due to an extremely high cardiac operative risk (EuroSCORE II >40%). The patient died on the 4th day of hospitalization.

Infective endocarditis is a rare condition with only 1.7–7.9 cases per 100 000 and occurs most commonly on a single valve [1]. Our case, with the abnormalities of 4 native valves and the initial signs dating back 6 months prior to hospitalization, is exceptionally unique.

Heterogeneous clinical presentation creates significant diagnostic challenges in patients with infective endocarditis. Fever >38°C as an isolated symptom occurs in 83.4% of cases, whereas other symptoms, including new cardiac murmurs, fatigue, or weight loss are not IE-specific, are often correlated to the localization of IE, and occur in less than 40% of patients [1]. Risk factors associated with IE, like prosthetic valves, drugs injection, intracardiac devices, and others, can help to identify a group of patients with a higher probability of IE, which on average has a mortality rate of 20%–25% [2].

Although valvular surgery of patients with IE is associated with lower 1-year mortality [3], sometimes, due to many clinical risk co-factors, the surgical risk is too high. Mitral valve surgery and multiple valve surgery significantly increase mortality [4]. EuroSCORE II helps to predict surgical risk in cardiac surgery. In the presented case the calculated risk of 40% was the result of active endocarditis, renal impairment, the urgency of the procedure, and the extent of the intervention. Such a high score is rarely seen and indicates that the operation is unreasonable.

One of the most crucial steps in managing IE is a quick implementation of antibiotics and surgical treatment, as both of these interventions have a reduced effectiveness with time. The severe medical condition of our patient was the outcome of a late diagnosis and delayed treatment. Close medical supervision

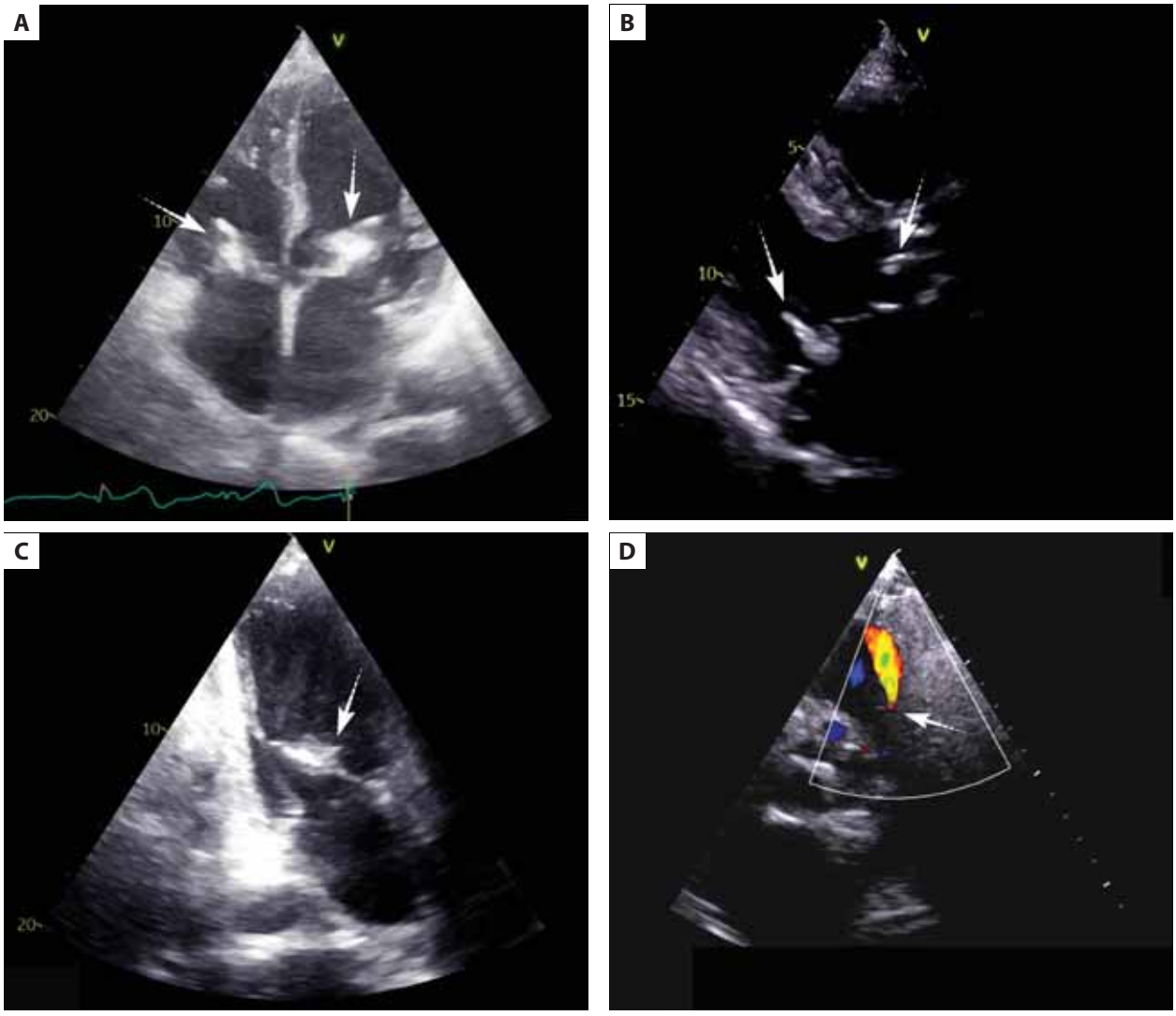

Figure 1. A. Transthoracic echocardiography, apical 4-chamber view. Vegetations of mitral and tricuspid valves have been marked by the arrows. **B.** Transthoracic echocardiography, parasternal long-axis view. Massive vegetations of mitral and aortic valves have been marked by the arrows. **C.** Transthoracic echocardiography, apical 2-chamber view. Massive vegetation of the mitral valve has been marked by the arrow. **D.** Transthoracic echocardiography, parasternal short-axis view with color Doppler. Cusp perforation of the pulmonary valve has been marked by the arrow

can help prevent the development of IE as massive as in the discussed case. The role of the multidisciplinary Heart Team is to make a quick and rational decision, based on the risk assessment, factors not included in common scales (such as EuroSCORE II), and the general condition of the patient.

Article information

Conflict of interest: None declared.

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Large mobile aortic thrombus (MAT) and the role of imaging in urgent selection for invasive treatment

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A 49-year-old female was admitted to the hospital after a loss of consciousness preceded by motor aphasia. Transient cerebral ischemia was diagnosed. She was a hypertensive, heavy smoker, and was taking hormone replacement therapy. The differential diagnosis of systemic embolism was started. The suprasternal view of the echocardiographic examination showed a hyperechoic, mobile structure of 20 mm in length in the ascending aorta (Figure 1B, the blue arrow; Supplementary material, *Video S1*). Computed tomography (CT) angiography confirmed the mobile aortic thrombus (MAT) located proximally to the brachiocephalic trunk (Figure 1A). Computed tomography scan showed neither enlargement of the aortic diameter nor damage to the aortic wall (Figure 1C–E). The CT orthogonal and sagittal projections were used in MAT dimensioning. The irregular-surfaced structure, 18 mm long (Figure 1D, the yellow arrow) and 10 mm wide, was visualized (Figure 1E, the red arrow). The large size and cauliflower shape of the MAT indicated a high potential for embolism. The patient was urgently referred for open aortic surgery. During the procedure, the thrombus moved to the left upper limb, confirming its high embolic potential. An 18 mm-long thrombus was removed from the left brachial artery. The aorta looked healthy without any damage and residual lesions. In the follow-up, no further embolic events were observed. The patient was given a prophylactic dose of aspirin and statins, and she was advised to quit smoking. Hormone replacement therapy was discontinued. Periodic echocardiography was recommended.

The presence of mobile thrombus in a healthy aorta (MAT) is relatively rare. The pathophysiology of MAT is unclear, as thrombotic states are uncommon. In many cases, MAT can be the source of systemic, life-threatening embolisms such as myocardial infarction, cerebral or limb embolization [1]. Although clinical consequences of MAT are serious and may affect a patient's prognosis, there are still no clear guidelines on therapeutic strategies [1–3]. Thus the treatment strategy should be individualized in every case. Three therapeutic goals should be taken under consideration: target anticoagulation therapy, surgical thrombectomy in the treatment of embolic complications, and endovascular/open surgery to remove the primary aortic thrombus [4, 5]. Invasive treatment should be dedicated to patients with high embolic potential and a low risk of surgery complications. In this case, imaging was crucial in assessing the embolic potential of MAT and selecting an urgent invasive treatment strategy.

Supplementary material

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

Article information

Conflict of interest: None declared.

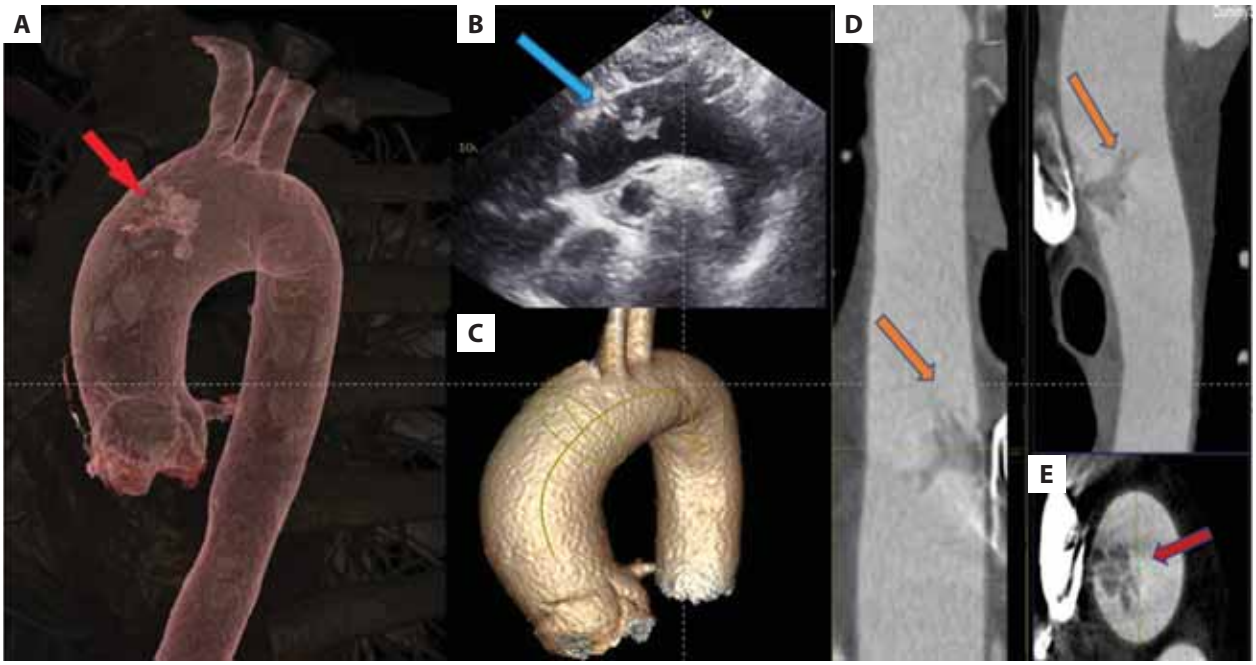

Figure 1. A. A computed tomography 3D scan with visualization of a mobile aortic thrombus (MAT) in the ascending aorta (the red arrow). **B.** Two-dimensional echocardiographic suprasternal long-axis (sagital) view presenting 20 mm MAT within the ascending aorta (the blue arrow). **C.** Computed tomography — a 3D scan showing the size of the aorta, excluding other aortic wall pathologies. **D, E.** Computed angiography, perpendicular and sagittal projections showing the irregular surface structure of the MAT: 18 mm long (**D**, the yellow arrows) and 10 mm wide (**E**, the red arrow)

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The next step in transcatheter aortic valve implantation: Transcatheter aortic valve replacement (TAVR) with BASILICA in a patient with a degenerated self-expanding transcatheter heart valve

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The risk of coronary artery obstruction following transcatheter aortic valve replacement (TAVR) is 4-fold higher for valve-in-valve procedures (i.e., in the presence of a previous bioprosthesis) [1]. However, the highest risk may be associated with TAVR procedures in patients with failing transcatheter heart valves (TAVR-in-TAVR) because of reduced neosinus, tall valve leaflets, and, in some cases, additional supra-annular valve design. Bioprosthetic aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction (BASILICA) is a novel procedure for preventing coronary artery obstruction during TAVR [2]. It involves splitting the leaflet in two so that it cannot block the coronary artery once it has been pushed aside by the new transcatheter heart valve. Since 2018, several hundred BASILICA procedures have been performed worldwide, including in Poland, in patients with native aortic valve or surgical bioprosthesis [2, 3]. However, so far, only a few cases of TAVR-in-TAVR with BASILICA have been described [4].

We report a case of a 63-year-old woman who underwent TAVR with a self-expanding 29 mm CoreValve (Medtronic, Dublin, Ireland) and developed structural valve deterioration with predominant stenosis 7 years later (max/mean gradient, 83/50 mm Hg; aortic valve area, 0.9 cm^2). Because of high surgical risk, redo TAVR was planned. Computed tomography revealed a takeoff of the left main artery 1 mm above the level of the CoreValve cusps (Figure 1A–B).

Considering the high risk of the left main coronary artery obstruction with degenerated CoreValve leaflet, we decided to perform TAVR-in-TAVR with BASILICA. For femoral access, 18-Fr and 7-Fr sheaths were used. A multipurpose catheter was advanced via the 7-Fr introducer to deliver a vascular snare into the left ventricular outflow tract. Under transesophageal echocardiography guidance, an Amplatz Left 2.0 catheter was advanced *via* the 18-Fr sheath and placed above the degenerated valve, near the left main coronary ostium. A Piggyback Wire Converter (Teleflex, Wane, PN, US) microcatheter with an electrified 300 cm Astato X 20 guidewire (Asahi Intecc Co., Seto, Japan) was advanced to puncture the leaflet at 40 W (Figure 1D). Next, the wire was snared into the multipurpose catheter (Figure 1E). The microcatheter was pulled out to create a V shape on the guidewire and scrape off the outer layer to form an "electric knife". The knife was advanced to the leaflet by pulling the snare and pushing the microcatheter, and it was then used to split the leaflet in two while simultaneously pulling both catheters at 70 W (Figure 1F). Before the procedure, a pigtail catheter with a stiff guidewire was advanced via the 18-Fr sheath into the left ventricle in case of hemodynamic instability requiring urgent valve implantation. After BASILICA, we noted signif-

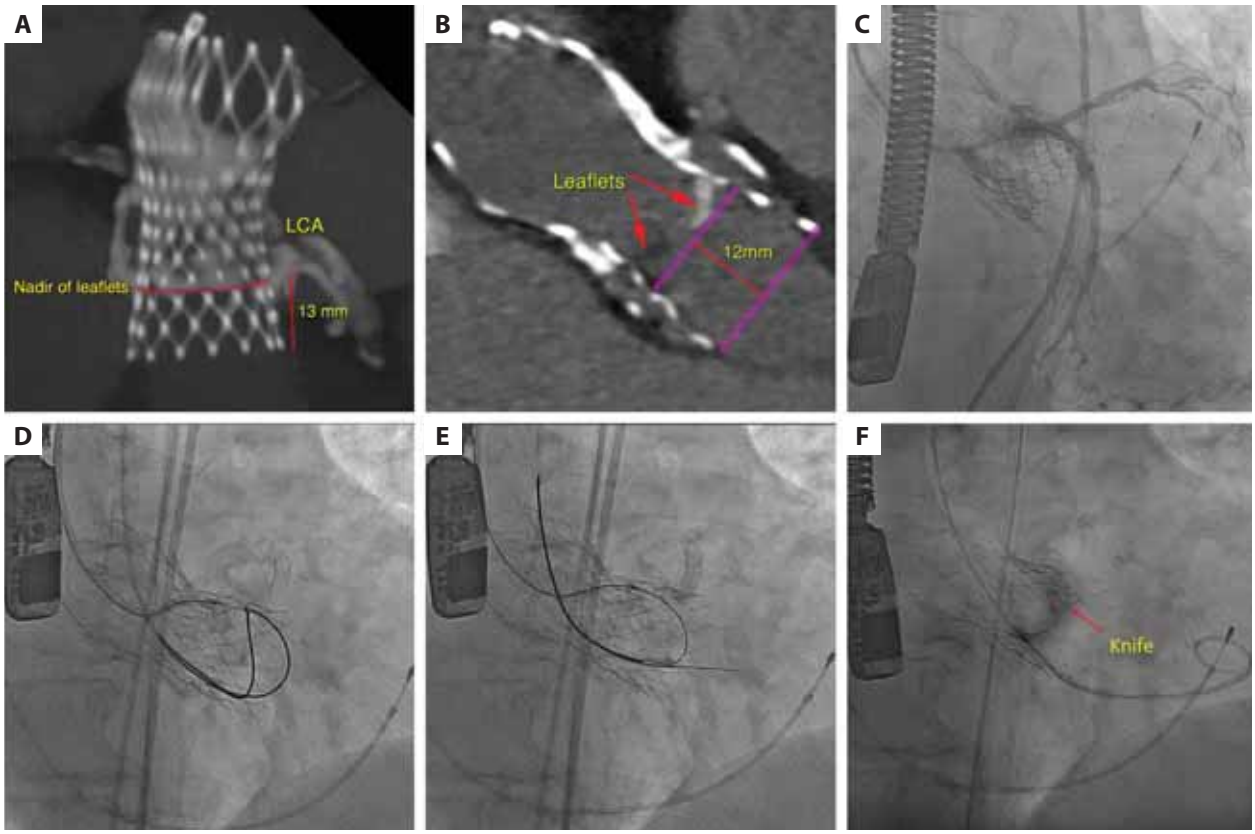

Figure 1. A–B. The coronary artery and CoreValve cusps on computed tomography. **C.** Coronary artery flow after the transcatheter aortic valve replacement (TAVR-in-TAVR). **D**. BASILICA technique: puncture of the leaflet. **E.** BASILICA technique: wire snaring. **F.** BASILICA technique: laceration of the leaflet

Abbreviations: TAVR, transcatheter aortic valve replacement

icant aortic valve regurgitation but without hemodynamic compromise. An Edwards Sapien 3 valve was implanted (Edwards Lifesciences, Irvine, CA, USA). Coronary artery flow was normal, and the procedure was successful (Figure 1C).

The use of BASILICA in TAVR-in-TAVR remains controversial [5]. However, as the number of patients with degenerated aortic valves after TAVR will continue to rise, large-volume centers have to become familiar with this technique in order to reduce the risk of fatal complications in this population, such as coronary artery obstruction.

Article information

Conflict of interest: None declared.

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Staged and primary Yasui repair in infants with interrupted aortic arch

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The techniques and indications for the Yasui operation have evolved from the first procedure performed in 1987 in children with complex heart defects: severe left ventricular outflow tract obstruction (LVOTO), ventricular septal defect (VSD), interrupted aortic arch (IAA), and well developed two ventricles [1]. The operation can be performed as primary correction or staged repair in children with high early mortality risk reaching even 18%–23%, especially in children with low body weight and coexisting organ defects [2–4]. The procedure includes the reconstruction of the IAA with Damus-Stansel-Kaye or Norwood techniques, implantation of the right ventricle (RV) — pulmonary artery (PA) prosthesis, and the closure of VSD rerouting the blood from the left ventricle (LV) to the pulmonary trunk [1–4].

We present cases of two newborns operated on with the staged as well as primary Yasui operation following Kanter's operative techniques [2].

Case 1: A 10-day-old female newborn with D-malposition of the great arteries, double outlet right ventricle (DORV, Taussig-Bing type) (Supplementary material, *Video S1*), subaortic stenosis, subpulmonary VSD (Supplementary material, *Video S2*), IAA (type A), and patent arterial duct (Supplementary material, *Video S3*), was operated on with the primary Yasui correction in cross-clamp circulation and deep hypothermia. The aortic arch was reconstructed with biological CorMatrix Cor™ PATCH (CorMatrix Cardiovascular Inc., GA, USA). RV-PA connection was provided by the 12 mm valved conduit Contegra with a bovine jugular vein (Medtronic Inc, MN, USA). VSD was closed with a patch. In the early postoperative follow-up, the patient required reoperation due to LV-right atrial shunt and finally was discharged home in a good condition.

Case 2: A 14-day-old female newborn with LVOTO (conal septum posterior malalignment), large VSD (Figure 1A, Supplementary material, *Video S4*), atrial septal defect (ASD), IAA (type B) with a retroesophageal right subclavian artery and patent arterial duct (Figure 1B) was operated on with staged repair due to low body weight and severe cardiac compromise.

The first stage included the aortic arch reconstruction with the patch from the left subclavian artery and CorMatrix PATCH with Norwood technique (Figure 1C, Supplementary material, *Video S5*) and Sano modification (5 mm PTFE RV-PA conduit) (Figure 1D, Supplementary material, *Video S6*) without VSD closure. Eight months later, the Yasui correction with the Rastelli-type procedure was performed with VSD closure (Figure 1E, F, Supplementary material, *Video S7*, and *S8*) and 14 mm pulmonary valved conduit Contegra implantation to establish RV-PA continuity. The postoperative follow-up was uncomplicated.

In an 18-month follow-up, the patients were in good condition (the New York Heart Association [NYHA], class I) awaiting the heart catheterization due to RV-PA distal Contegra stenosis.

In both cases, the Yasui operation provided a double-lumen LV outflow tract with aortic arch reconstruction and RV-PA continuity, which was an alternative option for biventricular repair.

A staged approach had a lower risk of reoperation and mortality, although in all children RV-PA prosthesis stenosis, as well as reconstructed aortic arch obstruction or even

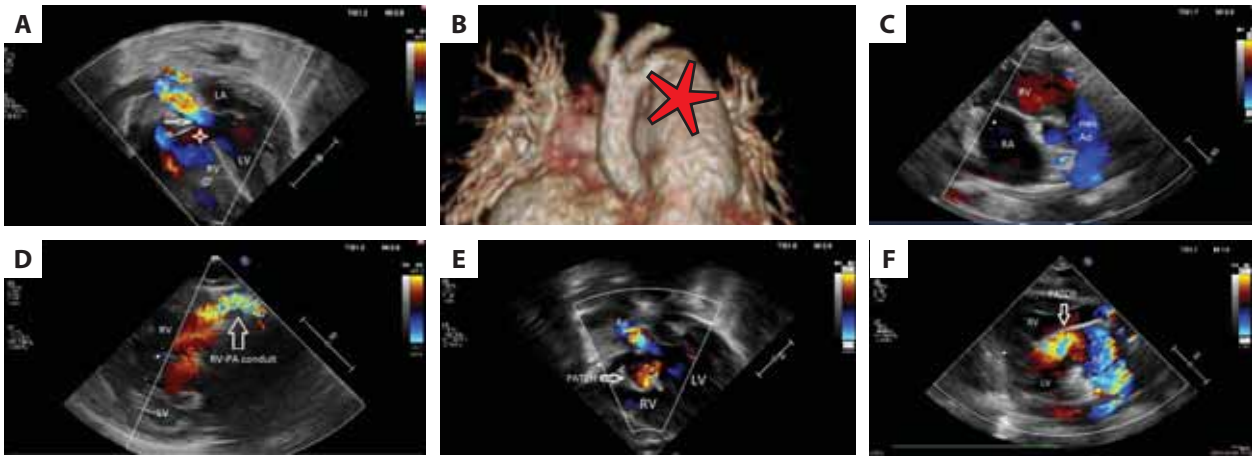

Figure 1. A. Transthoracic echocardiographic. 5-chamber view with well-developed two ventricles, large ventricular septal defect (star), and left ventricular outflow tract obstruction (arrow). **B.** 3D rendered computed tomography — interrupted aortic arch (type B) with large patent arterial duct (red star). **C.** Norwood procedure with aortic arch reconstruction. **D.** Sano modification with the right ventricle — pulmonary artery anastomosis. **E, F.** Large patch (white arrow) providing double-lumen left ventricular outlet tract

Abbreviations: Ao, aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle

dissection, may appear in follow-up with the necessity for surgery or complex endovascular interventions including balloon angioplasty or stent-graft implantations [5].

Supplementary material

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

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The surprising course of multiple sclerosis relapse in a patient after SARS-CoV-2 vaccination

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Multiple sclerosis (MS) is the most common chronic neurological disorder mediated by the excessive immune response with peak morbidity between the ages of 20 and 40 years. MS affects over 2 million people globally. It is characterized by recurrent episodes of inflammation resulting in demyelination and degeneration of neurons, oligodendrocytes, and microglia in the brain and the spinal cord. Patients with MS present a variety of symptoms including fatigue, psychiatric disorders, and more specific alterations determined by the location of the lesion in the nervous system. Some symptoms may be caused by the impact of other diseases on the course of MS, as the burden of some comorbidities in this group of patients is greater than in the general population.

The presented case is a 64-year-old male with a history of MS and no known traditional ischemic heart disease risk factors. The patient, who complained of the feeling of numbness, worsened mobility in the arms, and fatigue, was referred to the Neurology Clinic. He associated his symptoms with the vaccination against SARS-CoV-2 the day before. An initial diagnosis of possible MS relapse or a stroke was made, and the patient was referred to the Emergency Department for further tests. Electrocardiography recorded as a part of standard practice showed changes consistent with ST-elevation myocardial infarction (STEMI) (Figure 1A). Urgent coronary angiography revealed an amputated left anterior descending artery (LAD), significant stenosis of circumflex (Cx) and diagonal artery (Dg), and a chronic total obstruction (CTO) of the right coronary artery (RCA). Intravenous eptifibatide and oral acetylsalicylic acid with ticagrelor were administered. Percutaneous coronary intervention (PCI) on LAD and Dg was performed ad hoc with implantation of 3 drug-eluting stents (DES) (Figure 1B–D). The patient was qualified for further PCI after magnetic resonance imaging with an assessment of the viability of the myocardium. Laboratory tests showed increased troponin I, C-reactive protein, and leukocytosis. Echocardiography revealed decreased left ventricular ejection fraction (40%) and pericardial effusion. Computed tomography of the head revealed a hypodense lesion in the left frontal-parietal area. A relapse of MS was diagnosed and therapy with glucocorticosteroids was initiated. In the following days, the patient's condition continued to improve.

What makes this case particularly interesting is that nothing foreshadowed such a course of events. It is known that patients with MS are at a higher risk of developing coronary artery disease with life expectancy approximately 10 years shorter compared to the general population [1]. It has been proven to increase the risk of death threefold, mostly due to cardiovascular disease, which is clinically manifest as heart failure and ischemic heart disease [2] (Supplementary material). It should be remembered that patients diagnosed with MS may present atypical clinical symptoms or even remain asymptomatic.

What remains unclear in this case is the role of SARS-CoV-2 vaccination. Demonstrating a causal relationship requires longer follow-up, yet there are reports linking immunization with anti-COVID-19 vaccination and episodes of both MS relapse and thrombosis,

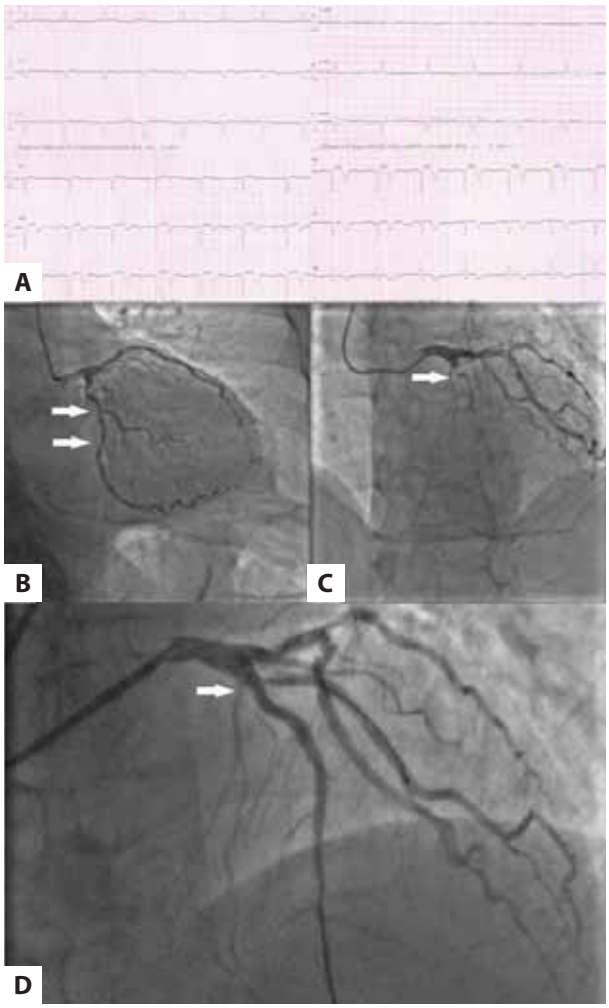

Figure 1. A. The electrocardiograph at admission. Sinus rhythm, left axis deviation, left anterior hemiblock, QS complex in leads II, V1–V4, ST-segment elevation in leads V1–V4, and inverted T waves in leads V1–V6. **B.** Coronary angiography showing stenosis in Cx. **C.** Coronary angiography showing stenosis in LAD and Dg. **D.** Effects of primary PCI on LAD and Dg

Abbreviations: Cx, circumflex artery; Dg, diagonal artery; LAD, left anterior descending artery; PCI, percutaneous coronary intervention

which could be one of the factors leading to STEMI in this case [3, 4]. Recently, articles on post-vaccination myocarditis have been published [5]. Postulated mechanisms that could lead to thrombotic manifestation are immune thrombocytopenia induced by vaccine and Kounis syndrome, which is an allergic reaction to a xenobiotic, resulting in the release of i.a. pro-inflammatory cytokines and platelet-activating factor and, potentially, leading to coronary artery spasm and thrombotic events.

Supplementary material

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

Article information

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An expert opinion of the Heart Failure Association of the Polish Cardiac Society on the 2021 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure: Heart failure guidelines from a national perspective

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ABSTRACT

The Polish expert opinion of the Heart Failure Association of the Polish Cardiac Society on the 2021 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of heart failure points to differences in many aspects related to heart failure in Poland compared with other European countries. These differences include population issues, epidemiology, diagnostic and treatment options, or the organization of healthcare. This expert opinion also includes a review of new results of clinical trials completed after the publication of the ESC guidelines.

Key words: heart failure, diagnosis and therapy, multidisciplinary approach, guidelines

INTRODUCTION

A panel of experts from the Heart Failure Association of the Polish Cardiac Society read with great interest the long-awaited 2021 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic heart failure (HF) [1]. The current update brings into clinical practice numerous novel concepts and diagnostic and therapeutic pathways. Naturally, all the guidelines are prepared in the best interests of patients who are truly **the subject** of the document. On the other hand, every ESC country member has their own unique features, including population structure, geography, gross domestic product, etc. that ultimately is translated into unique healthcare policies. Bearing this in mind, the expert panel

critically revised this document, pointing out its novelty, as well as the reality of Polish patients and physicans who operate within our current healthcare system.

COMMENT ON HF DEFINITION, EPIDEMIOLOGY, AND PROGNOSIS (CHAPTER 3)

A universal definition of HF was published earlier this year. Linking structural and/or functional abnormalities of the heart with typical symptoms remains the mainstay of clinical diagnosis. A unique shift in the classification of HF is the renaming of patients who present with their left ventricular ejection fraction (EF) between 41% and 49%. These patients used to be described as having HF with mid-range; now the term that is proposed is **mildly reduced EF** (notably, the abbreviation does not change — HFmrEF). This emphasizes recently shown similarities between HF with reduced EF (HFrEF) and HFmrEF.

Key information related to the epidemiology and prognosis in HF had no major changes; however, a specific point of interest is how the conditions in Poland compare to general statements found in the guidelines. Like other countries, improvements in therapies are counterbalanced by the increase in HF prevalence due to the aging of the general population. According to the recent national report, in 2018, the prevalence of the disease in the Polish population was 1 240 000 subjects, with an increasing yearly incidence, followed by rising hospitalizations [2]. Notably, Poland is the Organization for Economic Co-operation and Development (OECD) country with the highest rate of HF hospitalizations at 594 for100 000 citizens. This is accompanied by the rise in healthcare system costs related to the imbalanced HF rate in our country. Moreover, the number of deaths hit the record of 142 000 in the HF population (with HF as the direct cause in 41 000 — 9.8% of all deaths) in year 2018. Notably, more recent data encompassing pandemic period is not available as yet.

COMMENT ON HF DIAGNOSIS (CHAPTER 4)

The key diagnostic flowchart does not conceptually differ from the previous edition and in Poland's clinical practice, echocardiography probably still often precedes natriuretic peptides; both tests allow for the rejection of the HF hypothesis when normal (94%–98% negative predictive value for natriuretic peptide tests). The changes in diagnostic recommendations include an increased indication class for coronary computed tomography angiography with less emphasis on invasive coronary angiography. Right heart catheterization is recommended before transplant evaluation. This can also be included in the workup of HF with preserved EF (HFpEF), as well as with the less common HF etiologies, such as constrictive pericarditis, restrictive cardiomyopathy, congenital heart disease or high cardiac output conditions if clinically suspected. Regarding cardiac imaging in healthcare Polish environments, there is extensive expertise in echocardiographic stress testing but a remarkable shortage of dedicated cardiac magnetic resonance (CMR) services, indispensable for the diagnosis of less common myocardial diseases, including amyloidosis, and infiltrative and inflammatory conditions.

COMMENT ON HFrEF (CHAPTER 5)

The current guidelines emphasize that pharmacotherapy is the cornerstone of HFrEF treatment, advising that it be initiated before considering all other interventions, or even used simultaneously [1]. The field of pharmacotherapy is not merely introducing novel groups of drugs but witnessing a paradigm shift in the treatment of patients with HFrEF [1], i.e. the turn towards an individual approach to treatment depending on patients' clinical profiles [3]. The newest expert proposal for the treatment of HFrEF assumes that the 4 groups of recommended drugs should be, if possible, initiated simultaneously or in stages, depending on patients' clinical profiles, in a period not exceeding 4 weeks. After that time, the dosing ought to be optimized [4]. The two algorithms presented in the ESC guidelines are useful in selecting the appropriate treatment options for patients with HFrEF — a very valuable addition, in our view. The first one presents a treatment strategy to reduce mortality, including the indications for using first-class recommendation drugs and devices, in patients with HFrEF while also taking into account the etiology of HF [1]. The second algorithm is a central illustration providing a phenotypic overview of the treatment of HFrEF, including its etiology, patient clinical characteristics, the stage of the disease, and comorbidities. It also emphasizes the need for cardiac rehabilitation for all patients and for enrolling them into multidisciplinary care programs [1].

Presently, four groups of drugs are considered to be pivotal (class I) in the treatment of patients with HFrEF. In addition to the previously recommended angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor-neprilysin inhibitor (ARNI), beta-blockers, and mineralocorticoid-receptor antagonists (MRA), we can see that a new group of drugs has been added: the sodium-glucose co-transporter type 2 inhibitors (SGLT2i), commonly known as flozins.

In addition to the above-mentioned disease-modifying drugs, diuretics are at the top of the algorithm. The effect of this class of drugs on cardiovascular morbidity and mortality has not been studied in randomized controlled trials. However, it should be remembered that every major trial of disease-modifying therapies in HFrEF has been conducted on top of loop diuretic therapy. The current ESC guidelines emphasize that patients should be trained to self-titrate diuretic doses based on self-monitoring for symptoms or signs of congestion and daily body weight measurements [1].

In HFrEF, it took a considerable length of time to replace ACE-I with a more effective class of medication — sacubitril/valsartan, the only representative of the ARNI group. Several studies published in the meantime indicate that

ARNI can be considered a first-line therapy instead of ACE-I. Therefore, the indications for the use of ARNI have been significantly expanded, especially in acute decompensated HFrEF after hemodynamic stabilization [5–7]. In this population, ARNI is safe, and it reduced cardiovascular mortality and HF hospitalizations by 42% when compared to enalapril [7]. The clinical benefit was greater in *de novo* patients who were previously untreated and hospitalized due to HF. Therefore, the initiation of sacubitril/valsartan treatment may be considered in ACE-I naïve patients with HFrEF before discharge (recommendation class IIb, evidence level B). Considering all the available evidence proving the effectiveness of ARNI, in our opinion, ACE-I should be replaced with ARNI in these patients whenever it is possible, and initiation of therapy with this drug should even be considered in *de novo* patients. However, in Poland, unlike in almost all other countries in the EU, sacubitril/valsartan is still not reimbursed. Fortunately, over the recent years, the producer of sacubitril/valsartan significantly decreased the cost of this therapy for individual HFrEF patients. As a result, this therapy became available for an increasing number of patients with HFrEF, but still not for all of them. Angiotensin II receptor blockers (ARBs) are currently on more far position in guidelines (no benefit in reducing mortality) and recommended for patients who are intolerant to ACEIs or ARNIs due to serious adverse events [1].

What undoubtedly constitutes a breakthrough therapy in HFrEF is the arrival of SGLT2i — dapagliflozin and empagliflozin. Adding SGLT2i to standard guideline-based therapy significantly reduces the risk of cardiovascular death and worsening of HF in a short time after treatment initiation (within 1 month). Due to their unique mechanism of action, these drugs can be used at different stages of the metabolic-cardio-renal continuum. Furthermore, these drugs are particularly straightforward to use (1 tablet taken once daily without any need for dose modification) and are well-tolerated and safe (without the requirement for close monitoring of electrolytes or renal parameters). Currently, both dapagliflozin and empagliflozin are recommended for all patients with HFrEF regardless of whether they have type 2 diabetes or not [1]. In some patients with a *de novo* diagnosis of HFrEF, and especially patients with a profile including low arterial pressure and impaired renal function — flozins may be, next to beta-blockers, the first drug of choice, which will then enable the use of other recommended I class medications.

The new 2021 ESC guidelines also included vericiguat — the first-in-class guanylate cyclase receptor stimulator — which was assessed in patients with HFrEF and a recent decompensation of HF [1]. Unfortunately, vericiguat is not currently available in Poland.

COMMENTS ON CARDIAC RHYTHM MANAGEMENT IN HFrEF (CHAPTER 6)

According to the new document, the indication for cardioverter-defibrillator implantation (ICD) in secondary prevention remains unchanged; it is a class I recommendation if there is an expected >1-year survival in good functional status, with no reversible causes of cardiac arrest and when there has been no early ventricular arrhythmia (<48 hours) following the onset of acute myocardial infarction. Mainly, as a consequence of the DANISH study, the new document makes distinctions in the strength of its recommendations for the ICD in primary prevention (EF ≤35%) based on HF etiology: ICD has become class I for ischemic HF and class IIa for non-ischemic etiology. The guidelines highlight the need to re-evaluate the indications for continuing ICD therapy by an experienced cardiologist at the time of generator elective replacement (class IIa). They also note no indications for ICD (class III) in NYHA class IV patients with severe recurrent symptoms despite pharmacotherapy, unless they are candidates for cardiac resynchronization therapy (CRT), a left ventricular assist device (LVAD), or heart transplantation (HTX). The guidelines also mention a wearable cardioverted-defibrillator (WCD) as a therapy to prevent sudden death in a shorter period or as a bridge to the implantation of an ICD (class IIb). Although WCD is becoming increasingly popular in a subset of patients in Poland, there is still room for improvement of WCD availability, including unlimited reimbursement for those in need. The indications for a subcutaneous cardioverter-defibrillator are comparable to those for transvenous devices with a preference for patients with expected long-term survival and at increased risk of infectious and vascular complications. Subcutaneous devices are not recommended in patients with indications for cardiac pacing, antiarrhythmic pacing, or CRT. The main recommendations for CRT are a wide QRS (≥150 ms) with a morphology of the left bundle branch block type (LBBB) (class I). The class I recommendation for CRT to reduce mortality also applies, irrespective of the NYHA class and the QRS width, in patients with indicated ventricular pacing due to a high-grade AV block, including patients with atrial fibrillation. In the new guidelines, on the one hand, the recommendation class was reduced (from I to IIa) for CRT in symptomatic patients with sinus rhythm, EF ≤35%, and the QRS width 130–149 ms with LBBB morphology. On the other hand, the recommendation was increased (from IIb to IIa) for upgrading to CRT in patients with a previously implanted ICD or conventional pacemaker, who have a high percentage of ventricular pacing.

The guidelines also mention other devices currently under investigation, such as systems that modify the activity of the autonomic nervous system or cardiac contractility modulation (CCM). CCM was evaluated in NYHA III–IV patients with EF 25%–45% and the QRS width <130 ms, which may reduce symptoms of exercise intolerance and improve the quality of life. The guidelines do not specify any differences in indications for CRT-P (CRT-pacemaker) alone or CRT with the cardioverter-defibrillator option (CRT-D). According to the simultaneously published ESC guidelines on cardiac pacing and resynchronization, CRT-P may be preferred over CRT-D in patients with non-ischemic

cardiomyopathy, with shorter expected survival, multiple comorbidities, impaired renal function, or patient preference [8]. Summarizing the guidelines for cardiac electrotherapy, from the perspective of our practice, it is clear that the guidelines place an emphasis on the patient obtaining full, optimal pharmacotherapy (including sacubitril-valsartan and SGLT2i) used over a sufficiently long period before qualifying for electrotherapy.

In the treatment of coexisting atrial fibrillation, the position of non-vitamin K antagonist oral anticoagulants (NOACs) over vitamin K antagonists (VKAs), and the role of catheter ablation (for heart rate control in symptomatic patients despite optimal pharmacotherapy) have been strengthened by being made class I and IIa recommendations, respectively. It is important to underscore the increased role of NOACs here, which should be preferred over VKAs (class I), with the limitation of their use in patients with artificial mechanical valves, and moderate/severe mitral stenosis. In the cases where there is a clear association between paroxysmal or persistent atrial fibrillation and worsening of HF symptoms, catheter ablation should be considered for the prevention or treatment of atrial fibrillation. The role of beta-blockers has been reduced (downgraded from class I to IIa). In patients with atrial fibrillation and poor ventricular rate control despite pharmacotherapy, simultaneous AV node ablation and CRT implantation can be considered.

COMMENT ON HFmrEF (CHAPTER 7)

For the first time in the ESC guidelines for HF, therapy dedicated to HFmrEF has been described. There have been no specific randomized controlled trials in HFmrEF; however, some trials in HFpEF included patients with EF >40%, and from the sub-analyses, some data have emerged. Four groups of pharmacological therapies are described in the guidelines with class IIb and C levels for HFmrEF: ACE-Is, ARBs, β-blockers, MRAs, and ARNIs. However, sacubitril/valsartan (ARNI) is only approved to treat patients in a broad spectrum of HF (both HFrEF and HFpEF) by the FDA but not in Europe by the EMA (in Europe only in HFrEF).

COMMENT ON HF WITH PRESERVED EF (HFpEF) (CHAPTER 8)

The identification of patients with HFpEF remains challenging. In our country, no data exists on the number of patients with HFpEF. The diagnostic approach to HFpEF includes natriuretic peptides; however, general practitioners in Poland have no means of measuring this biomarker. So, the diagnosis of HFpEF is usually made by cardiologists or at the hospital during HF hospitalization. In the 2021 ESC guidelines, no specific treatment for HFpEF is given; nonetheless, ESC guidelines still recommend the screening and treatment of risk factors and comorbidities. Despite the positive results of EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction), there are no recommendations in the present guidelines regarding empagliflozin for the treatment of HFpEF due to the parallel timelines of the publication of this document and the EMPEROR-Preserved results [9].

COMMENT ON MULTIDISCIPLINARY TEAM MANAGEMENT FOR THE PREVENTION AND TREATMENT OF CHRONIC HF (CHAPTER 9)

For the first time, a special chapter is dedicated to patient education, self-care, and lifestyle advice. New recommendations are described for a self-management approach, and either home-based and/or clinic-based programs to reduce the risk of HF hospitalization and mortality (class I). Unfortunately, in our country, HF management programs are still unavailable.

COMMENT ON ADVANCED HEART FAILURE (CHAPTER 10)

In the new 2021 guidelines, also for the first time, there is a separate chapter centered on advanced HF, in which its epidemiology, diagnostics, prognosis, and management are discussed. With the recent progress in HF treatment, the prolongation of survival among HF patients, the decrease in the risk of sudden cardiac death, the number of advanced HF patients is growing. It is estimated that 1%–10% of patients with HF are at an advanced stage of HF, and this highlights the importance of the proper and early diagnosis of advanced HF and the referral of these patients to tertiary centers. The updated HFA-ESC 2018 definition of advanced HF is underlined. What is new in these guidelines is that starting the use of continuous inotropes and/or vasopressors may be considered a bridge to mechanical circulatory support (MCS) or HTX.

The INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) classification, which characterizes advanced HF patients under consideration for MCS implantation, an elegant algorithm for the treatment of patients with advanced HF is clearly described, and crucially, applied. The current guidelines stress the proper referral of suitable candidates at the right time for LVAD implantation. Unfortunately, MCS is still underused in Poland, and awareness-raising about this treatment type should be urgently initiated among Polish cardiologists. Encouragingly, new generations of these devices offer an 80% chance of 1-year survival and a 70% chance of 2-year survival.

However, the gold standard of treatment for advanced HF remains HTX, which is linked to an approx. 90% rate of 1-year survival, and 12.5 years of median survival. In Poland, there are still too few HTX procedures. In principle, indications and contraindications for HTX have not changed for several years. Advanced age (>65 years) is no longer an absolute contraindication, and in some centers, patients of up to 70 years are accepted while taking into account their biological age.

The decision pathway to HTX or LVAD is a complex process and is quite individual for each patient. What must

be considered is not just indications but also a long list of contraindications and limitations. In addition, the care of the patients following HTX and LVAD is of utmost importance, and it requires good cooperation and motivation from patients and their relatives and a readiness on the part of the center to assist the patients round the clock. While a patient post-HTX has a healthy heart, a patient with an LVAD is still an HF patient, taking HF medications and at risk of decompensation, e.g. worsening of the right ventricle (not mechanically assisted). In Poland, in the period 2019–2020, 290 HTXs were performed, and since then, up to November 2021, more than 160 procedures were carried out.

End-of-life care and key components of palliative care in advanced HF are also described. The management of advanced HF is based mainly on expert experience and opinions. Urgent research dedicated to advanced HF is required, necessitating the development of novel inotropes and myotropes, as well as the development of new treatment algorithms which could have a positive impact on survival, quality of life, and hospitalization rates.

COMMENT ON ACUTE HF (CHAPTER 11)

In a new section, the authors clearly distinguish individual phenotypic forms of acute HF (AHF) while also combining phenotypes with treatment tactics, all presented in a very straightforward scheme. So, although there has been no breakthrough in the drugs available for AHF treatment, the tactics have been clarified, which makes this part helpful for the physician treating a patient with AHF.

The authors drew attention to the fact that clinical severity and patient outcomes are determined by a complex interplay between precipitants, the underlying cardiac substrate, and the patients' comorbidities. The management of AHF patients is presented with due consideration of all these factors. Among the initial AHF diagnostic tests, apart from the classical ones, new recommendations for tests have appeared:

- LUS (lung ultrasound) for congestion assessment and monitoring;
- Iron status (transferrin, ferritin) for iron deficiency assessment;
- Lactate for perfusion status assessment.

Based mainly on the presence of signs of congestion and/or peripheral hypoperfusion, AHF clinical presentations were described as 4 major clinical phenotypes:

- Acutely decompensated heart failure — distinct from pulmonary edema — this phenotype is the most common form of AHF (50%–70%);
- Acute pulmonary edema;
- RV failure;
- Cardiogenic shock.

For the in-hospital management of AHF, a new acronym was established — CHAMPIT — extended with I for infection and T for tamponade. In pre-discharge and post-discharge management, for the first time, the recommendations for the management of patients after HF hospitalization are described with careful evaluation of any signs of congestion. The administration before the discharge of evidence-based oral medical treatment and the treatment of comorbidities (with iron deficiency making its first appearance in the guidelines) are presented as well. There is a recommendation made to schedule one follow-up visit within 1 to 2 weeks after discharge, which in Poland, but perhaps in other countries as well, is hard to execute. The guidelines do not specify who exactly should make this follow-up visit — general practitioners, cardiologists, or HF nurses. To date, there are no HF nurses in Poland; however, a newly-developed educational platform now exists for the certification of HF nurses (*www.edu.slabeserce.pl*).

The selected treatment recommendations used for AHF were refined:

- Diuretics (class I/level of evidence C) treatment should be started intravenously and, based on the diuretic response, related to spot urine sodium content and/or the hourly urine output measurement after 2 or 6 hours. If the diuretic response is insufficient, the loop diuretic i.v. dose should be doubled, with a later assessment of diuretic response. Concomitant administration with diuretics acting at different sites, namely thiazides or acetazolamide, may be considered (IIa B). In Poland, the measurement of urine sodium content is rarely performed despite its low cost;
- Vasodilators may be considered intravenously as initial therapy in patients with systolic blood pressure >110 mm Hg with a lower class/level IIb/B than in the 2016 guidelines.
- From Inotropes (class/level IIb/C), Levosimendan (non-adrenergic mechanisms) still holds a position that is too low, in our opinion. Even though the current guidelines recommend Levosimendan over dobutamine for patients on β-blockers, Polish physicians still underuse this drug, apart from centers specialized for HF, where the situation is more satisfactory [10];
- Opiates (class/level III/C), the routine use of opiates in AHF is now not recommended, although they may be considered in selected patients, particularly in the case of severe/intractable pain or anxiety, or in the setting of palliation.

It is worth noting that the results of the EMPULSE study (Empagliflozin Compared to Placebo Initiated in Patients Hospitalized for Acute Heart Failure Who Have Been Stabilized) were presented on November 14, 2021, at the American Heart Association Congress. The benefits of empagliflozin initiation in patients hospitalized for AHF resulted 36% more likely (stratified win ratio, 1.36; 95% CI, 1.09–1.68; $P = 0.0054$) to experience a clinical benefit, including reduced all-cause mortality, HF events, and an improvement in HF symptoms versus placebo during a 90-day follow-up, regardless of EF and diabetes status.

COMMENT ON CARDIOVASCULAR COMORBIDITIES (CHAPTER 12)

The management of cardiovascular comorbidities remains a key component of proper HF care. In HFrEF patients with concomitant chronic coronary syndromes, myocardial revascularization should be considered when angina persists despite the use of beta-blockers supplemented by other antianginal drugs. Medical therapy should also facilitate the control of hypertension, with at least standard treatment targets; mild asymptomatic hypotension may be acceptable in HFrEF if caused by target doses of prognosis-related drugs. All ACE-I, HF-approved beta-blockers, and diuretics are advisable as pillars of blood pressure control, whereas other classes remain a second choice. Correcting advanced valve disease contributing to or causing HF is beyond debate in patients with limited comorbidities, and percutaneous techniques (TAVI, MitraClip) play an increasingly important role in these high-risk patients. We were surprised to read a caution against beta-blockers in aortic regurgitation — there is neither clinical nor evidence-based data to support such a concern. In secondary mitral regurgitation (MR), the readership should pay much attention to the current concept of the actively defined patient subgroup with disproportional MR [11]. Patients with a high regurgitant volume-to-LV end-diastolic volume ratio and with an absence of any significant right-sided disease component or terminal LV disease are optimal candidates for targeting MR with Mitraclip (COAPT-like population). Wider access to percutaneous mitral and tricuspid interventions is necessary but poses a critical challenge for the Polish healthcare system due to the restrictive policy of the National Health Fund.

COMMENT ON NON-CARDIOVASCULAR COMORBIDITIES (CHAPTER 13)

In real clinical day-to-day experience, HF is rarely the only clinical problem. According to different registries, each HF patient suffers from 3 to 5 other chronic diseases, usually regarded as comorbidities. In the recent ESC guidelines, this issue has attracted a great deal of attention. Here, we would like to provide a subjective commentary. All chronic pathologies accompanying HF can be grouped into different categories. The authors of the guidelines divided them into the categories of cardiovascular (chapter 12), and non-cardiovascular (chapter 13). All of the comorbidities mentioned in the guidelines may either facilitate the development of *de novo* HF or may precipitate acute decompensations. However, their coexistence with HF may vary over different timescales. Given that chronic disease may either precede HF (working as an etiologic or co-etiologic factor, i.e. diabetes, chronic kidney disease, sarcopenia) or develop during its course, any knowledge obtained concerning the chronology of the diseases may be of importance to clinicians. By design, based on the guidelines' development, each chronic disease is described as a sole companion of HF. However, in real life, certain comorbidities aggregate in HF, based mostly on the pathophysiology shared with the HF condition. Such specific clusters of chronic diseases produce characteristic clinical phenotypes and — critically — may differ in terms of prognosis.

Chronic obstructive pulmonary disease (COPD) and HF share numerous risk factors and their clinical presentation may be similar. Careful examination in the congestion-free phase is a key issue because clinical and even spirometry testing may show significant reductions in bronchial flow in incompletely decongested patients. The difference between forced expiratory volume in one second expressed as % (FEV_1%) before and after the resolution of congestion may be as high as 15%–20% [12]. Current guidelines suggest that the use of inhaled broncho-dilators in AHF presenting with a reduction of FEV_1% may be beneficial. The basis for this suggestion stems from a single study in which patients with COPD and documented hyperinflation received indacaterol/glycopyrronium or placebo, in a cross-over design. The study showed a slight decrease in end-diastolic volume in patients receiving active treatment, which was interpreted as an improvement in cardiac function [13]. This finding requires special comment. It is worth noting that the patients in this study were free from HF, and one should be extremely cautious about expecting similar effects in HF patients, especially in those with extremely dilated ventricles. Such patients may not be able to increase their contractility force in response to further dilation as the gain of Starling's law may be exhausted, leading to the opposite effect and the reduction of stroke volume.

Worsening of kidney function arising from chronic and acute kidney disease in HF are both important comorbidities. There is no doubt that chronic kidney disease aggravates HF course and negatively impacts prognosis. However, deteriorating kidney function may be associated with both worse and better prognoses. The key issue is the clinical context because poor kidney function in patients who are responding positively to treatment (for example by decreasing natriuretic peptide levels) is associated with better outcomes, while the opposite is true when the clinical response is absent, or merely marginal.

New in the current guidelines is the extensive discussion on abnormalities such as hyponatremia, hypochloremia, metabolic alkalosis, and hyperkalemia, as important comorbidities. Apart from their possible iatrogenic genesis, we believe that they reflect other aspects of kidney dysfunction, namely the exhaustion of kidney homeostatic regulatory potential in each patient-specific pathophysiological and HF treatment environment. Their occurrence should prompt careful examination in an effort to tailor therapy to the specific clinical situation.

Also for the first time, there are recommendations for the management of patients with HF and iron deficiency (ID), which is related to the results of the AFFIRM-HF study [14]. In HF, it is now recommended that all patients undergo periodic screening for ID and anemia (class I), and intravenous iron supplementation with ferric car-

boxymaltose in symptomatic patients, either recently hospitalized for HF with EF ≤50% or with EF <45% (class IIa). Unfortunately, ID is still underdiagnosed in Poland and thus, there is a need to increase awareness of this deficiency among physicians.

COMMENT ON CARDIOMYOPATHIES AND MYOCARDITIS (CHAPTER 14)

Uniquely, and for the first time, in the current HF guidelines, there is a separate section entitled "Special Conditions" (section 14), which includes topics devoted exclusively to pregnancy, cardiomyopathies, left ventricular non-compaction, atrial disease, myocarditis, amyloidosis, iron overload cardiomyopathy, and adult congenital heart disease [1]. This inclusion highlights the rapid development of this critically important field within the whole HF spectrum. All the information contained in this section is beyond the scope of this concise commentary; nonetheless, the most essential items and novel features are briefly presented below:

- New guidelines underline various direct causes of cardiomyopathies, and conditions classified as disease modifiers. The guidelines urge that specific causes of cardiomyopathies should be sought out;
- For each main cardiomyopathy type, there is a detailed section on genetic testing with a minimal set of genes deemed mandatory. Clear recommendations are given on genetic counseling in index patients and relatives;
- Interestingly, above and beyond the well-known main cardiomyopathy types, such as dilated (DCM) and hypertrophic (HCM) cardiomyopathy, the current guidelines also introduce the novel concept of arrhythmogenic cardiomyopathy (AC) [15]. This is a much broader term than the "classic" arrhythmogenic right ventricular cardiomyopathy (ARVC), typically restricted to the RV and, instead, acknowledges that left ventricular (LV) involvement occurs in approximately one-third of cases;
- Given that beneficial LV reverse remodeling (LVRR) occurs in approximately 50% of DCM patients, the question arises as to whether to continue HF-modifying treatment in those with LVRR [16]. This issue was tackled by the authors of the TRED-HF study, where it was shown that withdrawal of treatment resulted in HF relapse in up to 44% of DCM patients [17];
- The guidelines spotlight a possible first-of-its-kind disease-specific treatment in HCM. The EXPLORER-HCM study reported that Mavacamten, which reduces cardiac muscle contractility by inhibiting excessive myosin-actin cross-bridge formation, improved exercise tolerance and NYHA class and reduced LV outflow tract gradient in obstructive HCM;
- The guidelines address the controversy concerning LV non-compaction cardiomyopathy (LVNC). Although several echocardiographic and magnetic resonance criteria exist, they lack much specificity and their diagnostic accuracy is thought to be somewhat limited. Therefore, the guidelines propose not treating LVNC as separate cardiomyopathy but rather as a rare presentation of DCM or HCM.

The document also briefly comments on iron overload cardiomyopathy (IOCM). The examination of choice to confirm myocardial iron deposition is a special magnetic resonance technique — T2*.

A special sub-section (14.6) explores a hot topic in HF — amyloid cardiomyopathy. A rapid non-invasive diagnostic algorithm, based on the exclusion of light chain amyloidosis (AL) and the utilization of technetium-labeled ^{99m}Tc-PYP or DPD or HMDP scintigraphy, has a very high specificity and yields positive predictive values for the diagnosis of transthyretin (TTR) cardiomyopathy (TTR-CM) [18]. Unfortunately, TTR amyloidosis is still underdiagnosed in Poland, and a "rising awareness" campaign should be initiated among Polish physicians. The document briefly introduces two types of TTR-CA — a wild one (>90% of cases) and a hereditary one — and draws attention to typical "red flags" for both TTR-CM and AL-CM, as well as a clear diagrammatic presentation of workup. Current treatment of AL-CM is based on chemotherapy and/or autologous stem-cell transplant and is normally managed by hematologists. The fruitful results of the recently published ATTR-ACT trial have paved the way for the incorporation of Tafamidis, a stabilizer of TTR tetramers into the standard treatment regime for TTR-CM and now has class Ib recommendation [19]. The dedicated drug program (with Tafamidis) for TTR-CM has been prepared and is currently under review.

The 2021 ESC guidelines in the chapter "Special conditions" also for the first time provide information on the epidemiology, etiology, diagnostics, and treatment of patients with acute myocarditis. For etiology, only three groups of causes are listed (infectious with a focus on viral agents, systemic diseases, and finally toxic), which, on balance, seems to be justified. In these groups, it is possible to determine the diagnosis and make therapeutic decisions. The diagnostic workup involves many diagnostic tests, but only three are considered methods of high or intermediate sensitivity and specificity: CMR, coronary angiography, and endomyocardial biopsy (EMB). What is new is the discussion on EMB indications is the number and sites of the biopsy specimens and the methods to be used when analyzing the biopsy material. In addition to the histological and immunohistochemical analyses, the assessment should also refer to the determination of the etiology. If viral etiology is suspected, the EMB, in addition to quantifying the viral genome (rt-PCR) for the most common cardiotropic viruses (parvovirus B19, HHV4, HHV6, enteroviruses, adenovirus and coxsackievirus, SARS-CoV-2), should also provide data on active viral replication via the evaluation of viral mRNA. A thorough analysis of the EMB specimens should lead to the right therapeutic decisions. At the present stage of knowledge, immunosuppression has been considered for the treatment of patients with chronic cardiac inflammation at EMB and with no evidence of ac-

tive viral infection. To date, the diagnosis of myocarditis in Poland is based on CMR. It is well known that while CMR brings many advantages, it cannot establish the etiology of myocarditis. Qualitative and quantitative typing of viruses in the myocardial tissue has only been made possible thanks to research grants in individual centers in Poland. Currently, in Poland, we lack procedures financed by the National Health Fund that would allow us to conduct comprehensive diagnostic evaluation in relation to myocarditis, carry out staff training or establish professionally equipped pathology departments in referral centers. These guidelines reveal the enormous work that we must undertake in Poland to reach a more refined diagnosis of myocarditis.

CONCLUSIONS

The 2021 ESC guidelines for the diagnosis and treatment of acute and chronic HF propose and summarize the best management strategies for HF patients, including the new diagnostic and therapeutic options. However, the final decision about an individual patient is related to the capacity of the healthcare system and is taken by health professionals considering the patient's preferences. A panel of experts from the Heart Failure Association of the Polish Cardiac Society commented on the 2021 ESC guidelines based on the reality of the Polish healthcare system.

Article information

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Professor Robert H Jones (1940–2022)

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It is with great regret that we received the news of the death of Professor Robert H Jones, MD (1940–2022).

Professor Robert H Jones was one of the most distinguished figures of cardiac surgery and was renowned as a leader of clinical research in the field of cardiology and cardiac surgery. Professor Jones graduated from the Johns Hopkins University School of Medicine in 1965. He completed his surgical residency at the Duke University Medical Center (DUMC) in 1968–1974. Then he worked at DUMC, obtaining scientific and professional positions, such as Professor of Surgery, DUMC 1982–1987, Mary and Deryl Hart Professor of Surgery 1987–2014, Associate Professor of Radiology 1982–2014, Faculty Duke Clinical Research Institute 1992–2014, Mary and Deryl Hart Professor of Surgery Emeritus 2014–2022.

He was an active member of several scientific societies and has received many awards and honors including the Master of the American College of Cardiology Award in 2011.

He published nearly 300 articles as an author/co-author in leading scientific journals; his papers have been cited 16 429 times and his H-Index is 61.

Professor Jones greatly contributed the development and promotion of Polish cardiology and cardiac surgery on the global forum. He supported our scientific community since his first visit in Poland as a lecturer at the American College of Cardiology Circuit Course in May 1984. He was a great friend of Poland and Polish people, gladly accepting the changes taking place over the years in all areas of life in our country. Inviting Polish cardiology and cardiac surgery centers to participate in the NHLBI non-commercial clinical study Surgical Treatment for Ischemic Heart Failure (STICH) was a privilege and a challenge at the same time. This research program initiated a new treatment strategy for complications of ischemic heart disease and impacted guideline changes. We can proudly say that Polish participation in this study was

Figure 1. A meeting from the early period of the STICH trial at the Institute of Cardiology in Warsaw 2005. From the left: Professor Zbigniew Religa, Director of the Institute, Professor Robert H Jones, Principal Investigator in the STICH trial, Professor Zygmunt Sadowski, a member of the steering committee and a national coordinator of the STICH trial

Figure 2. A meeting of the STICH Family, Tarnowskie Góry, 2011. Our guests from the Duke University responsible for the STICH trial: first row from the left: second — Thomas C Barfield, MBA, project leader; third — Kerry L Lee, MD, PhD, biostatistician; fifth — Professor Robert H Jones; eighth — Professor Eric J Velazuez, MD,the principal investigator in the STICHES trial (continuation of STICH), and a group of Polish cardiac surgeons and cardiologists at the meeting organized on the initiative of Professor Marian Zembala

important due to high numbers of randomized patients, the quality of patient care, as well as high scientific activity during meetings of committees and working groups. Participation in the STICH created an additional important platform for cooperation between cardiac surgeons and cardiologists from various Polish centers. Professor Jones brought us together, participating in this study, into a great international community, called the STICH-Family. We had a great privilege to get to know Professor Jones better (Figures 1 and 2). He was a great leader who made sure that each member of the team genuinely felt a part of it and made a real contribution to the success of the project. He taught us a lot, especially how to work as a team. During the long-lasting cooperation (2003–2018), an original STICH mode of action has been developed under the leadership of Professor Jones. As a result of the STICH/STICHES study, more than 50 original articles in high-impact journals were published, of which 37 were attended and supervised by authors from Polish cardiac centers. Polish authors also had an opportunity to present the STICH trial results during ESC and AHA/ACC meetings. In recognition of his activities for the benefit of Polish cardiology, he was awarded the title of the Honorary Member of the Polish Cardiac Society in 1990. He was also awarded Doctor Honoris Causa at the Medical University of Lodz, 2008. Many of us owe a lot to Professor Robert H Jones and he will remain our Mentor. We will always remember him with respect and gratitude.

Cardiologists and cardiac surgeons forming
the STICH trial team in Poland

Supplementary material

The list of the STICH trial publications coauthored by Polish authors is available in Supplementary material at https://journals.viamedica.pl/kardiologia_polska.

Article information

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VII Konferencja *online* czasopisma

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The conference is intended only for persons authorized to prescribe drugs or pharmacists and for persons trading in medicinal products — legal basis. Act of 6 September 2001. Pharmaceutical Law (Journal of Laws from 2019, item 499, as amended).

Od teraz Entresto jeszcze bardziej dostępne dla pacjenta

Entresto®
sakubitryl/walsartan

Postać i skład: Tabletki powlekane. Jedna tabletka zawiera 24,3 mg sakubitrylu i 25,7 mg walsartanu lub 48,6 mg sakubitrylu i 51,4 mg walsartanu, lub 97,2 mg sakubitrylu i 102,8 mg walsartanu (w postaci kompleksu soli sodowych sakubitrylu i walsartanu). **Wskazania:** Lek Entresto jest wskazany do stosowania u dorosłych pacjentów w leczeniu objawowej, przewlekłej niewydolności serca ze zmniejszoną frakcją wyrzutową. **Dawkowanie:** Zalecana dawka początkowa to jedna tabletka 49 mg/51 mg podawana dwa razy na dobę, z wyjątkiem opisanych niżej sytuacji. Po 2-4 tygodniach dawkę tę należy podwoić do dawki docelowej, czyli jednej tabletki 97 mg/103 mg podawanej dwa razy na dobę, w zależności od tolerancji pacjenta. Jeśli u pacjenta wystąpią problemy z tolerancją leku [skurczowe ciśnienie krwi (SBP) ≤ 95 mm Hg, objawy niedociśnienia, hiperkaliemia, zaburzenia czynności nerek], zaleca się dostosowanie jednocześnie podawanych leków, czasowe obniżenie dawki lub przerwanie podawania leku Entresto. W badaniu PARADIGM-HF lek Entresto był podawany w połączeniu z innymi lekami stosowanymi w niewydolności serca, zamiast inhibitora ACE lub innego antagonisty receptora angiotensyny II (ARB). Doświadczenie u pacjentów nieprzyjmujących obecnie inhibitora ACE lub ARB lub przyjmujących małe dawki tych leków jest ograniczone, dlatego u tych pacjentów zaleca się dawkę początkową 24 mg/26 mg dwa razy na dobę i powolne zwiększanie dawki (podwajanie dawki co 3-4 tygodnie). Nie należy rozpoczynać leczenia u pacjentów ze stężeniem potasu w surowicy > 5,4 mmol/l lub z SBP < 100 mm Hg. U pacjentów z SBP ≥ 100 do 110 mm Hg należy rozważyć podanie dawki początkowej 24 mg/26 mg dwa razy na dobę. Nie należy podawać leku Entresto jednocześnie z inhibitorem ACE lub z ARB. Nie wolno rozpoczynać podawania leku Entresto przez co najmniej 36 godzin od przerwania leczenia inhibitorem ACE ze względu na potencjalne ryzyko obrzęku naczynioruchowego podczas jednoczesnego leczenia inhibitorem ACE. Walsartan zawarty w leku Entresto ma większą biodostępność niż walsartan zawarty w innych lekach dostępnych na rynku w postaci tabletek. W przypadku pominięcia dawki pacjent powinien przyjąć kolejną dawkę o wyznaczonej porze. Nie zaleca się dzielenia lub rozkruszania tabletek. *Szczególne populacje pacjentów: Pacjenci w podeszłym wieku:* U pacjentów w podeszłym wieku dawka leku powinna być dostosowana do stanu czynnościowego nerek. *Zaburzenia czynności nerek:* Nie ma konieczności dostosowania dawki u pacjentów z łagodnymi [wyliczony wskaźnik przesączania kłębuszkowego (eGFR) 60-90 ml/min/1,73 m^2] zaburzeniami czynności nerek. U pacjentów z umiarkowanymi zaburzeniami czynności nerek (eGFR 30-60 ml/min/1,73 m^2) należy rozważyć dawkę początkową 24 mg/26 mg dwa razy na dobę. Ponieważ doświadczenie kliniczne u pacjentów z ciężkimi zaburzeniami czynności nerek (eGFR < 30 ml/min/1,73 m^2) jest ograniczone, lek należy stosować z zachowaniem ostrożności i zaleca się stosowanie dawki początkowej 24 mg/26 mg dwa razy na dobę. Brak jest doświadczenia ze stosowaniem leku Entresto u pacjentów ze schyłkową niewydolnością nerek, dlatego stosowanie leku w tej grupie pacjentów nie jest zalecane. *Zaburzenia czynności wątroby:* Nie ma konieczności dostosowania dawki, gdy lek jest podawany pacjentom z łagodnymi zaburzeniami czynności wątroby (stopnia A w skali Child-Pugh). Doświadczenie kliniczne u pacjentów z umiarkowanymi zaburzeniami czynności wątroby (stopnia B w skali Child-Pugh) lub z wartościami AST/ALT powyżej dwukrotności górnej granicy normy jest ograniczone. Należy zachować ostrożność, stosując lek u tych pacjentów, a zalecana dawka początkowa wynosi 24 mg/26 mg dwa razy na dobę. Lek Entresto jest przeciwwskazany u pacjentów z ciężkimi zaburzeniami czynności wątroby, marskością żółciową lub cholestazą (stopnia C w skali Child-Pugh). *Dzieci i młodzież:* Nie określono bezpieczeństwa stosowania ani skuteczności leku u dzieci i młodzieży w wieku poniżej 18 lat. Dane nie są dostępne. Sposób podawania: Podanie doustne. Lek może być podawany z pokarmem lub bez. Tabletki należy połykać, popijając szklanką wody. **Przeciwwskazania:** Nadwrażliwość na substancje czynne lub na którąkolwiek substancję pomocniczą, jednoczesne stosowanie inhibitorów ACE (leku Entresto nie wolno stosować do 36 godzin od zakończenia terapii inhibitorem ACE), obrzęk naczynioruchowy w wywiadzie związany z wcześniejszym leczeniem inhibitorem ACE lub ARB, dziedziczny lub idiopatyczny obrzęk naczynioruchowy, jednoczesne stosowanie produktów leczniczych zawierających aliskiren u pacjentów z cukrzycą lub u pacjentów z zaburzeniami czynności nerek (eGFR < 60 ml/min/1,73 m^2), ciężkie zaburzenia czynności wątroby, marskość żółciowa i cholestaza, drugi lub trzeci trymestr ciąży (patrz ChPL). **Środki ostrożności/ostrzeżenia:** Podwójna blokada układu renina-angiotensyna-aldosteron (RAAS): Leczenie skojarzone sakubitrylem/walsartanem z inhibitorem ACE jest przeciwwskazane ze względu na ryzyko obrzęku naczynioruchowego. Nie wolno rozpoczynać leczenia sakubitrylem/walsartanem do 36 godzin od przyjęcia ostatniej dawki inhibitora ACE. Po przerwaniu stosowania sakubitrylu/walsartanu nie wolno rozpoczynać leczenia inhibitorem ACE do 36 godzin od zażycia ostatniej dawki sakubitrylu/walsartanu. Nie zaleca się leczenia skojarzonego sakubitrylem/walsartanem z bezpośrednimi inhibitorami reniny, takimi jak aliskiren. Leczenie skojarzone sakubitrylem/walsartanem z produktami zawierającymi aliskiren jest przeciwwskazane u pacjentów z cukrzycą lub pacjentom z zaburzeniami czynności nerek (eGFR < 60 ml/min/1,73 m^2). Lek Entresto zawiera walsartan i dlatego nie należy go stosować jednocześnie z innym produktem zawierającym ARB. Niedociśnienie: Nie należy rozpoczynać leczenia do chwili, gdy SBP wyniesie ≥ 100 mm Hg. Nie przeprowadzono badań u pacjentów z SBP < 100 mm Hg. U pacjentów leczonych sakubitrylem/walsartanem podczas badań klinicznych zgłaszano przypadki objawowego niedociśnienia, zwłaszcza u pacjentów w wieku ≥ 65 lat, pacjentów z chorobami nerek i pacjentów z małym SBP (< 112 mm Hg). Rozpoczynając leczenie lub podczas zwiększania dawki sakubitrylu/walsartanu, należy rutynowo monitorować ciśnienie krwi. Jeśli wystąpi niedociśnienie, zaleca się tymczasowe stopniowe zmniejszenie dawki lub przerwanie stosowania sakubitrylu/walsartanu. Należy rozważyć dostosowanie dawki leków moczopędnych, jednocześnie podawanych leków przeciwnadciśnieniowych oraz leczenie innych przyczyn niedociśnienia (np. hipowolemii). Wystąpienie objawowego niedociśnienia jest bardziej prawdopodobne u pacjentów odwodnionych, np. w wyniku leczenia moczopędnego, diety z ograniczoną podażą soli, biegunki lub wymiotów. Przed rozpoczęciem leczenia sakubitrylem/walsartanem należy skorygować niedobór sodu i (lub) płynów, jednak podejmując działania korygujące, należy wziąć pod uwagę ryzyko przewodnienia. Zaburzenia czynności nerek: Ocena stanu pacjentów z niewydolnością serca powinna zawsze obejmować ocenę czynności nerek. U pacjentów z łagodnymi i umiarkowanymi zaburzeniami czynności nerek ryzyko wystąpienia niedociśnienia jest większe. Doświadczenie u pacjentów z ciężkimi zaburzeniami czynności nerek (wyliczony GFR < 30 ml/min/1,73 m^2) jest bardzo ograniczone i ci pacjenci mogą podlegać największemu ryzyku niedociśnienia. Brak jest doświadczenia u pacjentów ze schyłkową niewydolnością nerek i stosowanie sakubitrylu/walsartanu w tej grupie pacjentów nie jest zalecane. Pogorszenie czynności nerek: Stosowanie sakubitrylu/walsartanu może być związane z pogorszeniem czynności nerek. Ryzyko to może być dodatkowo zwiększone w przypadku odwodnienia lub jednoczesnego stosowania niesteroidowych leków przeciwzapalnych (NLPZ). Należy rozważyć stopniowe zmniejszenie dawki u pacjentów, u których wystąpi klinicznie istotne pogorszenie czynności nerek. Hiperkaliemia: Nie należy rozpoczynać leczenia, jeśli stężenie potasu w surowicy jest > 5,4 mmol/l. Stosowanie sakubitrylu/walsartanu może być związane ze zwiększonym ryzykiem hiperkaliemii, chociaż może również wystąpić hipokaliemia. Zaleca się monitorowanie stężenia potasu w surowicy, szczególnie u pacjentów z takimi czynnikami ryzyka, jak zaburzenia czynności nerek, cukrzyca lub hipoaldosteronizm oraz u pacjentów stosujących dietę bogatą w potas lub u pacjentów przyjmujących antagonistów receptora mineralokortykoidowego. Jeśli u pacjentów wystąpi klinicznie istotna hiperkaliemia, zaleca się dostosowanie jednocześnie przyjmowanych produktów leczniczych lub tymczasowe stopniowe zmniejszenie dawek bądź przerwanie podawania. Jeśli stężenie potasu w surowicy wyniesie > 5,4 mmol/l, należy rozważyć przerwanie leczenia. Obrzęk naczynioruchowy: U pacjentów leczonych sakubitrylem/walsartanem zgłaszano występowanie obrzęku naczynioruchowego. Jeśli wystąpi obrzęk naczynioruchowy, należy natychmiast przerwać stosowanie sakubitrylu/walsartanu i rozpocząć odpowiednie leczenie oraz monitorowanie pacjenta aż do całkowitego i trwałego ustąpienia objawów przedmiotowych i podmiotowych. Nie wolno wznawiać leczenia. W przypadkach potwierdzonego obrzęku naczynioruchowego z obrzmieniem ograniczonym do twarzy i warg stan ten na ogół ustępował bez leczenia, chociaż podanie leków antyhistaminowych łagodziło objawy. Obrzęk naczynioruchowy przebiegający z obrzękiem krtani może zagrażać życiu. Gdy obrzęk dotyczy języka, głośni lub krtani, które mogą spowodować niedrożność dróg oddechowych, należy szybko zastosować odpowiednie leczenie, np. podanie roztworu adrenaliny w stężeniu 1 mg/1 ml (0,3-0,5 ml), i (lub) odpowiednie postępowanie udrażniające drogi oddechowe. Pacjenci z obrzękiem naczynioruchowym w wywiadzie nie uczestniczyli w badaniach. Z uwagi na możliwość zwiększonego ryzyka obrzęku naczynioruchowego zaleca się zachowanie ostrożności podczas stosowania sakubitrylu/walsartanu u tych pacjentów. Sakubitryl/walsartan jest przeciwwskazany u pacjentów z obrzękiem naczynioruchowym w wywiadzie związanym z wcześniejszym stosowaniem inhibitora ACE lub ARB bądź u pacjentów z dziedzicznym lub idiopatycznym obrzękiem naczynioworuchowym. Pacjenci rasy czarnej są bardziej podatni na wystąpienie obrzęku naczynioruchowego. Pacjenci ze zwężeniem tętnicy nerkowej: Sakubitryl/walsartan mogą zwiększać stężenie mocznika we krwi i stężenie kreatyniny w surowicy u pacjentów z obustronnym lub jednostronnym zwężeniem tętnicy nerkowej. Należy zachować ostrożność u pacjentów ze zwężeniem tętnicy nerkowej i zaleca się monitorowanie czynności nerek. Pacjenci w IV klasie czynnościowej wg NYHA: Należy zachować ostrożność, rozpoczynając leczenie sakubitrylem/walsartanem u pacjentów w IV klasie czynnościowej wg NYHA ze względu na ograniczone doświadczenie kliniczne w tej populacji. Peptyd natriuretyczny typu B (BNP): BNP nie jest właściwym biomarkerem niewydolności serca u pacjentów leczonych sakubitrylem/walsartanem, ponieważ jest on substratem neprylizyny. Pacjenci z zaburzeniami czynności wątroby: Doświadczenie kliniczne u pacjentów z umiarkowanymi zaburzeniami czynności wątroby (stopnia B w skali Child-Pugh) lub z wartościami AST/ALT powyżej dwukrotności górnej granicy normy jest ograniczone. U tych pacjentów ekspozycja na lek może być zwiększona, a bezpieczeństwo stosowania nie zostało ustalone. Dlatego zaleca się ostrożność, podając lek tym pacjentom. Sakubitryl/walsartan są przeciwwskazane u pacjentów z ciężkimi zaburzeniami czynności wątroby, marskością żółciową lub cholestazą (stopnia C w skali Child-Pugh). Zaburzenia psychiczne: Ze stosowaniem sakubitrylu/walsartanu wiązało się występowanie zdarzeń niepożądanych ze strony OUN, takich jak omamy, paranoja i zaburzenia snu, które występowały w kontekście zaburzeń psychotycznych. Jeśli u pacjenta wystąpią takie zdarzenia, należy rozważyć zakończenie leczenia sakubitrylem/walsartanem. **Działania niepożądane:** Podsumowanie profilu bezpieczeństwa: Najczęściej zgłaszanymi działaniami niepożądanymi podczas leczenia sakubitrylem/walsartanem było niedociśnienie (17,6%), hiperkaliemia (11,6%) i zaburzenia czynności nerek (10,1%). U pacjentów leczonych sakubitrylem/walsartanem zgłaszano występowanie obrzęku naczynioruchowego (patrz opis wybranych działań niepożądanych). Działania niepożądane zostały przedstawione według klasyfikacji układów i narządów oraz według częstości występowania, poczynając od najczęstszych, zgodnie z następującą konwencją: bardzo często (≥ 1/10); często (≥ 1/100 do < 1/10); niezbyt często (≥ 1/1000 do < 1/100); rzadko (≥ 1/10 000 do < 1/1000); bardzo rzadko (< 1/10 000). W obrębie każdej grupy o określonej częstotliwości objawy niepożądane uszeregowano według zmniejszającego się nasilenia. Bardzo często: hiperkaliemia, niedociśnienie, zaburzenia czynności nerek. Często: niedokrwistość, hipokaliemia, hipoglikemia, zawroty głowy, ból głowy, omdlenia, zawroty głowy, hipotonia ortostatyczna, kaszel, biegunka, nudności, zapalenie żołądka, niewydolność nerek (niewydolność nerek, ostra niewydolność nerek), uczucie zmęczenia, słabienie. Niezbyt często: nadwrażliwość, ortostatyczne zawroty głowy, świąd, wysypka, obrzęk naczynioruchowy. Rzadko: omamy, zaburzenia snu. Bardzo rzadko: paranoja. Opis wybranych działań niepożądanych: *Obrzęk naczynioruchowy:* U pacjentów leczonych sakubitrylem/walsartanem zgłaszano występowanie obrzęku naczynioruchowego. W badaniu PARADIGM-HF obrzęk naczynioruchowy zgłaszano u 0,5% pacjentów leczonych sakubitrylem/walsartanem w porównaniu z 0,2% pacjentów leczonych enalaprylem. Większą częstość występowania obrzęku naczynioruchowego zgłaszano u pacjentów rasy czarnej leczonych sakubitrylem/walsartanem (2,4%) i enalaprylem (0,5%). *Hiperkaliemia i stężenie potasu w surowicy:* W badaniu PARADIGM-HF hiperkaliemię i stężenia potasu w surowicy > 5,4 mmol/l zgłaszano odpowiednio u 11,6% i 19,7% pacjentów leczonych sakubitrylem/walsartanem oraz u 14,0% i 21,1% pacjentów leczonych enalaprylem. *Ciśnienie krwi:* W badaniu PARADIGM-HF niedociśnienie i klinicznie istotne niskie skurczowe ciśnienie krwi (< 90 mm Hg oraz spadek o > 20 mm Hg względem wartości wyjściowych) zgłaszano odpowiednio u 17,6% i 4,76% pacjentów leczonych sakubitrylem/walsartanem w porównaniu z 11,9% i 2,67% pacjentów leczonych enalaprylem. *Zaburzenia czynności nerek:* W badaniu PARADIGM-HF zaburzenia czynności nerek były zgłaszane u 10,1% pacjentów leczonych sakubitrylem/walsartanem i 11,5% pacjentów leczonych enalaprylem. Zgłaszanie podejrzewanych działań niepożądanych: Po dopuszczeniu produktu leczniczego do obrotu istotne jest zgłaszanie podejrzewanych działań niepożądanych. Umożliwia to nieprzerwane monitorowanie stosunku korzyści do ryzyka stosowania produktu leczniczego. Osoby należące do fachowego personelu medycznego powinny zgłaszać wszelkie podejrzewane działania niepożądane za pośrednictwem Departamentu Monitorowania Niepożądanych Działań Produktów Leczniczych Urzędu Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych (patrz ChPL). **Pozwolenia Komisji Europejskiej na dopuszczenie do obrotu nr:** Tabletka powlekana 24 mg/26 mg: EU/1/15/1058/001, EU/1/15/1058/008-010, EU/1/15/1058/017-018. Tabletka powlekana 49 mg/51 mg: EU/1/15/1058/002-004, EU/1/15/1058/011-013, EU/1/15/1058/019-020. Tabletka powlekana 97 mg/103 mg: EU/1/15/1058/005-007, EU/1/15/1058/014-016, EU/1/15/1058/021-022. **Kategoria dostępności:** Produkt leczniczy wydawany na receptę (Rp). **Podmiot odpowiedzialny:** Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Irlandia. **Uwaga:** Przed przepisaniem leku należy zapoznać się z pełną informacją o leku. Pełna informacja o leku jest dostępna w Novartis Poland Sp. z o.o., ul. Marynarska 15, 02-674 Warszawa, tel. (22) 375 4 888. **Opracowano:** 06/2021.

1. Aktualna Charakterystyka Produktu Leczniczego Entresto®. **2.** Claggett B. i wsp. Estimating the long-term treatment benefits of sacubitril-valsartan. N Engl J Med 2015; 373(23): 2289-2290. **3.** Niewydolność serca w Polsce. Realia, koszty, sugestie poprawy sytuacji. Podsumowanie raportu 2020, dostęp: https://ptkardio.pl/resources/data/pliki/42/2020_12_07_raport_niewydolnosci_serca_w_polsce.pdf?download=true. **4.** McDonagh T.A., Metra M. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021; 00: 1-128, doi:10.1093/eurheartj/ehab368. **5.** Maddox T.M. i wsp. J Am Coll Cardiol 2021; 77(6): 772-810. **6.** McDonald M. i wsp. CCS/CHFS heart failure guidelines update: defining a new pharmacologic standard of care for heart failure with reduced ejection fraction. Can J Cardiol 2021; 37(4): 531-546. **7.** https://www.nice.org.uk/guidance/ng106. **8.** McMurray J.J. i wsp. N Engl J Med 2014; 371(11): 993-1004. **9.** Velazquez E.J. i wsp. N Engl J Med 2019; 380(6): 539-548.

NOVARTIS

HFrEF – niewydolność serca z obniżoną frakcją wyrzutową.
* Dorośli pacjenci z przewlekłą niewydolnością serca (klasy II, III lub IV wg NYHA) i zredukowaną frakcją wyrzutową (LVEF ≤ 40%)[2].
1. Charakterystyka produktu leczniczego JARDIANCE® z dnia 22.10.2021 r. 2. Packer M. i wsp. N Engl J Med. 2020; 383 (15): 1413-1424. (Wyniki badania EMPEROR-Reduced® oraz dodatek uzupełniający do publikacji). 3. McDonagh T, Metra M, Adamo M, Gardner R, Baumbach A, Bohm M, Burri H, Butler J, Celutkiene J, Chioncel O, Cleland J, Coats A, Crespo-Leiro M, Farmakis D, Gilard M, Heymans S. Hoes W, Jaarsma T, Jankowska E, Lainscak M, Lam C, Lyon A, McMurray, Mebazaa A, Mindham R, Muneretto C, Piepoli M, Price S, Rosano G, Ruschitzka F, Skibelund A. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2021; 00, 1-128. doi:10.1093/eurheartj/ehab368.

Skrócona informacja o leku JARDIANCE®

Nazwa produktu leczniczego, dawka i postać farmaceutyczna: Jardiance® 10 mg, 25 mg tabletki powlekane. Każda tabletka zawiera 10 mg empagliflozyny lub 25 mg empagliflozyny. Jardiance® 10 mg okrągła tabletka powlekana barwy bladożółtej, obustronnie wypukła, o średnicy 9,1 mm ze ściętą ostro krawędzią, z wytłoczonym symbolem „S10" na jednej stronie oraz logo Boehringer Ingelheim na drugiej. Każda tabletka zawiera ilość laktozy jednowodnej odpowiadającą 154,3 mg laktozy bezwodnej. Każda tabletka zawiera mniej niż 1 mmol (23 mg) sodu, to znaczy lek uznaje się za „wolny od sodu". Jardiance® 25 mg owalna, bladożółta, obustronnie wypukła tabletka powlekana z wytłoczonym symbolem „S25" na jednej stronie oraz logo Boehringer Ingelheim na drugiej (długość tabletki: 11,1 mm, szerokość: 5,6 mm). Każda tabletka zawiera ilość laktozy jednowodnej odpowiadającą 107,4 mg laktozy bezwodnej. Każda tabletka zawiera mniej niż 1 mmol (23 mg) sodu, to znaczy lek uznaje się za „wolny od sodu". **Wskazania do stosowania:** Cukrzyca typu 2 Produkt leczniczy Jardiance® jest wskazany do stosowania w leczeniu dorosłych z niewystarczająco kontrolowaną cukrzycą typu 2 łącznie z dietą i aktywnością fizyczną: w monoterapii, kiedy nie można stosować metforminy z powodu jej nietolerancji, w skojarzeniu z innymi produktami leczniczymi stosowanymi w leczeniu cukrzycy. Wyniki badań dotyczące różnych skojarzeń, wpływu na kontrolę glikemii i zdarzenia sercowo-naczyniowe oraz badane populacje, patrz punkt Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania. Niewydolność serca Produkt leczniczy Jardiance® jest wskazany do stosowania u dorosłych w leczeniu objawowej przewlekłej niewydolności serca ze zredukowaną frakcją wyrzutową. **Dawkowanie i sposób podawania:** Dawkowanie Cukrzyca typu 2 Zalecana dawka początkowa wynosi 10 mg empagliflozyny raz na dobę w monoterapii oraz w terapii skojarzonej z innymi produktami leczniczymi stosowanymi w leczeniu cukrzycy. U pacjentów tolerujących dawkę 10 mg empagliflozyny raz na dobę z wartością eGFR ≥ 60 ml/min/1,73 m^2 i wymagających ściślejszej kontroli glikemii, dawkę można zwiększyć do 25 mg raz na dobę. Maksymalna dawka dobowa wynosi 25 mg. Niewydolność serca Zalecana dawka to 10 mg empagliflozyny raz na dobę. Wszystkie wskazania Podczas stosowania empagliflozyny w skojarzeniu z pochodną sulfonylomocznika lub z insuliną, konieczne może być zmniejszenie dawki pochodnej sulfonylomocznika lub insuliny, aby zmniejszyć ryzyko wystąpienia hipoglikemii. W razie pominięcia dawki pacjent powinien ją zażyć niezwłocznie po przypomnieniu sobie o tym; nie należy jednak przyjmować podwójnej dawki tego samego dnia. *Szczególne grupy pacjentów Upośledzenie czynności nerek* U pacjentów z cukrzycą typu 2 skuteczność empagliflozyny w kontrolowaniu glikemii zależy od czynności nerek. Aby zmniejszyć ryzyko sercowo-naczyniowe, u pacjentów z wartością eGFR poniżej 60 ml/min/1,73 m^2 dodatkowo do standardowego leczenia należy stosować 10 mg empagliflozyny raz na dobę (patrz Tabela 1). Ze względu na to, że skuteczność empagliflozyny w zmniejszaniu glikemii jest mniejsza u pacjentów z umiarkowanym uszkodzeniem nerek i prawdopodobnie nieobecna u pacjentów z ciężkim uszkodzeniem nerek, jeśli konieczna jest dalsza kontrola glikemii, należy rozważyć zastosowanie innych produktów leczniczych obniżających stężenie glukozy. Patrz tabela 1, aby uzyskać informacje dotyczące dostosowywania dawki w zależności od wartości eGFR lub CrCl. Tabela 1: Zalecenia dotyczące dostosowywania dawki[a]

Wskazanie	eGFR [ml/min/1,73 m^2] lub CrCL [ml/min]	Całkowita dawka dobowa
Cukrzyca typu 2	≥60	Rozpocząć od dawki 10 mg empagliflozyny. U pacjentów tolerujących dawkę 10 mg empagliflozyny i wymagających dodatkowej kontroli glikemii dawkę można zwiększyć do 25 mg empagliflozyny.
	45 do <60	Rozpocząć od dawki 10 mg empagliflozyny.[b] Kontynuować stosowanie dawki 10 mg empagliflozyny u pacjentów, którzy już przyjmują produkt leczniczy Jardiance®.
	30 do <45[b]	Rozpocząć od dawki 10 mg empagliflozyny. Kontynuować stosowanie dawki 10 mg empagliflozyny u pacjentów, którzy już przyjmują produkt leczniczy Jardiance.
	<30	Nie zaleca się stosowania empagliflozyny.
Niewydolność serca (z cukrzycą typu 2 lub bez cukrzycy typu 2)	≥20	Zalecana dawka dobowa to 10 mg empagliflozyny.
	<20	Nie zaleca się stosowania empagliflozyny.

[a] Patrz punkty Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania, Działania niepożądane [b] Pacjenci z cukrzycą typu 2 i z potwierdzoną chorobą sercowo-naczyniową

W przypadku leczenia niewydolności serca u pacjentów z cukrzycą typu 2 lub bez cukrzycy typu 2 stosowanie dawki 10 mg empagliflozyny można rozpocząć lub kontynuować leczenie do wartości eGFR równej 20 ml/min/1,73 m^2 lub wartości CrCl równej 20 ml/min. Nie należy stosować empagliflozyny u pacjentów ze schyłkową niewydolnością nerek (SNN), ani u pacjentów dializowanych. Nie ma wystarczających danych, aby uzasadnić stosowanie w tej grupie pacjentów. *Upośledzenie czynności wątroby* Nie ma konieczności dostosowania dawki u pacjentów z upośledzeniem czynności wątroby. U pacjentów z ciężkim upośledzeniem czynności wątroby ekspozycja na empagliflozynę jest zwiększona. Doświadczenie w leczeniu pacjentów z ciężkim upośledzeniem czynności wątroby jest ograniczone, w związku z czym nie zaleca się stosowania empagliflozyny w tej populacji pacjentów. *Pacjenci w podeszłym wieku* Nie ma konieczności dostosowania dawki w zależności od wieku pacjenta. U pacjentów w wieku 75 lat i starszych należy wziąć pod uwagę zwiększone ryzyko zmniejszenia objętości płynów. Z uwagi na ograniczone doświadczenie w leczeniu pacjentów w wieku 85 lat i starszych, nie zaleca się rozpoczynania leczenia empagliflozyną w tej grupie wiekowej. *Dzieci i młodzież* Nie określono dotychczas bezpieczeństwa stosowania ani skuteczności empagliflozyny u dzieci i młodzieży. Dane nie są dostępne. Sposób podawania Tabletki mogą być przyjmowane jednocześnie z posiłkiem lub niezależnie od niego. Tabletki należy połykać w całości popijając wodą. **Przeciwwskazania:** Nadwrażliwość na substancję czynną lub na którąkolwiek substancję pomocniczą wymienioną w punkcie Wykaz substancji pomocniczych ChPL. **Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania:** Kwasica ketonowa U pacjentów z cukrzycą leczonych inhibitorami SGLT2, w tym empagliflozyną, zgłaszano rzadkie przypadki kwasicy ketonowej, w tym przypadki zagrażające życiu i zakończone zgonem. W niektórych przypadkach obraz kliniczny był nietypowy, tylko z umiarkowanym zwiększeniem stężenia glukozy we krwi, poniżej 14 mmol/l (250 mg/dl). Nie wiadomo, czy zastosowanie większych dawek empagliflozyny zwiększa ryzyko kwasicy ketonowej. Należy uwzględnić ryzyko kwasicy ketonowej w razie wystąpienia niespecyficznych objawów, takich jak: nudności, wymioty, jadłowstręt, ból brzucha, silne pragnienie, zaburzenia oddychania, splątanie, niezwykłe zmęczenie lub senność. W razie wystąpienia takich objawów należy niezwłocznie zbadać pacjentów, czy nie występuje u nich kwasica ketonowa, niezależnie od stężenia glukozy we krwi. Należy natychmiast przerwać leczenie empagliflozyną u pacjentów z podejrzeniem lub rozpoznaniem kwasicy ketonowej. Należy przerwać leczenie u pacjentów hospitalizowanych z powodu dużych zabiegów chirurgicznych lub ostrych ciężkich chorób. U tych pacjentów zaleca się monitorowanie stężeń ciał ketonowych. Preferowane jest oznaczanie stężenia ciał ketonowych we krwi, niż w moczu. Leczenie empagliflozyną można wznowić, gdy stężenie ciał ketonowych będzie prawidłowe, a stan pacjenta ustabilizuje się. Przed rozpoczęciem leczenia empagliflozyną należy rozważyć czynniki w wywiadzie predysponujące pacjenta do kwasicy ketonowej. Do pacjentów ze zwiększonym ryzykiem kwasicy ketonowej zalicza się osoby z małą rezerwą czynnościową komórek beta (np. pacjenci z cukrzycą typu 2 i małym stężeniem peptydu C lub późno ujawniającą się cukrzycą autoimmunologiczną dorosłych - ang. latent autoimmune diabetes in adults - LADA lub pacjenci z zapaleniem trzustki w wywiadzie), pacjentów ze stanami prowadzącymi do ograniczenia przyjmowania pożywienia lub z ciężkim odwodnieniem pacjentów, którym zmniejszono dawkę insuliny oraz pacjentów ze zwiększonym zapotrzebowaniem na insulinę z powodu ostrej choroby, zabiegu chirurgicznego lub nadużywania alkoholu. U tych pacjentów należy ostrożnie stosować inhibitory SGLT2. Nie zaleca się wznawiania leczenia inhibitorem SGLT2 u pacjentów, u których wcześniej wystąpiła kwasica ketonowa podczas stosowania inhibitora SGLT2, chyba że zidentyfikowano i usunięto inną wyraźną przyczynę. Produktu leczniczego Jardiance® nie należy stosować w leczeniu pacjentów z cukrzycą typu 1. Dane z programu badań klinicznych u pacjentów z cukrzycą typu 1 wykazały zwiększone, częste występowanie kwasicy ketonowej u pacjentów leczonych empagliflozyną w dawce 10 mg i 25 mg jako uzupełnienie insuliny w porównaniu z placebo. Niewydolność nerek We wskazaniu cukrzyca typu 2 u pacjentów z wartością eGFR poniżej 60 ml/min/1,73 m^2 lub CrCl <60 ml/min dawka dobowa empagliflozyny jest ograniczona do 10 mg. Nie zaleca się stosowania empagliflozyny w przypadku wartości eGFR poniżej 30 ml/min/1,73 m^2 lub CrCl poniżej 30 ml/min. We wskazaniu niewydolność serca nie zaleca się stosowania produktu leczniczego Jardiance u pacjentów z wartością eGFR <20 ml/min/1,73 m^2. Nie należy stosować empagliflozyny u pacjentów ze schyłkową niewydolnością nerek (SNN) ani u pacjentów dializowanych. Nie ma wystarczających danych, aby uzasadnić stosowanie w tej grupie pacjentów. Monitorowanie czynności nerek Zaleca się ocenę czynności nerek w następujący sposób: przed rozpoczęciem leczenia empagliflozyną i okresowo podczas leczenia, tzn. co najmniej raz na rok; przed rozpoczęciem leczenia jakimkolwiek innym jednocześnie stosowanym produktem leczniczym, który może mieć niekorzystny wpływ na czynność nerek. Ryzyko zmniejszenia objętości płynów Z uwagi na mechanizm działania inhibitorów SGLT-2, diureza osmotyczna towarzysząca glukozurii może spowodować nieznaczne zmniejszenie ciśnienia krwi. W związku z tym należy zachować ostrożność u pacjentów, dla których taki spadek ciśnienia krwi spowodowany przez empagliflozynę mógłby stanowić zagrożenie, takich jak pacjenci z rozpoznaną chorobą układu krążenia, pacjenci stosujący leczenie przeciwnadciśnieniowe z epizodami niedociśnienia w wywiadzie lub pacjenci w wieku 75 i więcej lat. W przypadku stanów, które mogą prowadzić do utraty płynów przez organizm (np. choroba przewodu pokarmowego) zaleca się dokładne monitorowanie stanu nawodnienia (np. badanie przedmiotowe, pomiar ciśnienia krwi, testy laboratoryjne włącznie z oznaczeniem hematokrytu) i stężenia elektrolitów u pacjentów przyjmujących empagliflozynę. Należy rozważyć tymczasowe wstrzymanie leczenia empagliflozyną do czasu wyrównania utraty płynów. Pacjenci w podeszłym wieku Wpływ empagliflozyny na wydalanie glukozy z moczem związany jest z diurezą osmotyczną, co może mieć wpływ na stan nawodnienia. Pacjenci w wieku 75 i więcej lat mogą być w większym stopniu zagrożeni wystąpieniem zmniejszenia objętości płynów. Większa liczba takich pacjentów leczonych empagliflozyną miała działania niepożądane związane ze zmniejszeniem objętości płynów w porównaniu z pacjentami otrzymującymi placebo. W związku z tym należy zwracać szczególną uwagę na przyjmowaną objętość płynów w razie jednoczesnego podawania z produktami leczniczymi mogącymi prowadzić do zmniejszenia objętości płynów (np. leki moczopędne, inhibitory ACE). Doświadczenie dotyczące leczenia pacjentów w wieku 85 i więcej lat jest ograniczone. Nie zaleca się rozpoczynania leczenia empagliflozyną w tej grupie wiekowej. Powiklane zakażenia dróg moczowych U pacjentów otrzymujących empagliflozynę zgłaszano przypadki powikłanych zakażeń dróg moczowych, w tym odmiedniczkowe zapalenie nerek i posocznicę moczopochodną. Należy rozważyć tymczasowe wstrzymanie leczenia empagliflozyną u pacjentów z powikłanym zakażeniem dróg moczowych. Martwicze zapalenie powięzi krocza (zgorzel Fourniera) Zgłaszano przypadki martwiczego zapalenia powięzi krocza (znanego także jako zgorzel Fourniera) u pacjentów płci żeńskiej i męskiej z cukrzycą przyjmujących inhibitory SGLT2. Jest to rzadkie, ale ciężkie i mogące zagrażać życiu zdarzenie, które wymaga pilnej interwencji chirurgicznej i antybiotykoterapii. Pacjentom należy zalecić, aby zgłosili się do lekarza, jeśli wystąpi u nich zespół objawów, takich jak ból, wrażliwość na dotyk, rumień lub obrzęk w okolicy zewnętrznych narządów płciowych lub krocza, z jednoczesną gorączką lub uczuciem rozbicia. Należy pamiętać o tym, że martwicze zapalenie powięzi może być poprzedzone zakażeniem narządów układu moczowo-płciowego lub ropniem krocza. Jeśli podejrzewa się wystąpienie zgorzeli Fourniera, należy przerwać stosowanie produktu Jardiance® i niezwłocznie rozpocząć leczenie (w tym antybiotykoterapię oraz chirurgiczne opracowanie zmian chorobowych). Amputacje w obrębie kończyn dolnych W długoterminowych badaniach klinicznych innego inhibitora SGLT2 zaobserwowano zwiększoną częstość przypadków amputacji w obrębie kończyn dolnych (szczególnie palucha). Nie wiadomo, czy jest to „efekt klasy leków". Podobnie jak w przypadku wszystkich chorych na cukrzycę, ważna jest edukacja pacjentów dotycząca profilaktycznej pielęgnacji stóp. Uszkodzenie wątroby W badaniach klinicznych obejmujących empagliflozynę zgłaszano przypadki uszkodzenia wątroby. Nie ustalono związku przyczynowo-skutkowego pomiędzy empagliflozyną a uszkodzeniem wątroby. Zwiększenie wartości hematokrytu Obserwowano zwiększenie wartości hematokrytu podczas leczenia empagliflozyną. Przewlekła choroba nerek Istnieje doświadczenie dotyczące stosowania empagliflozyny w leczeniu cukrzycy u pacjentów z przewlekłą chorobą nerek (eGFR ≥30 ml/min/1,73 m^2) z albuminurią i bez albuminurii. Leczenie empagliflozyną może być bardziej skuteczne u pacjentów z albuminurią. Laboratoryjna analiza moczu Z uwagi na mechanizm działania produktu Jardiance®, pacjenci przyjmujący go będą mieć dodatni wynik testu na zawartość glukozy w moczu. Wpływ na badanie stężenia 1,5-anhydroglucitolu (1,5-AG) Nie zaleca się monitorowania kontroli glikemii za pośrednictwem badania stężenia 1,5-AG, ponieważ oznaczanie stężenia 1,5-AG nie jest miarodajne w ocenie kontroli glikemii u pacjentów przyjmujących inhibitory SGLT2. Zaleca się stosowanie innych metod monitorowania kontroli glikemii. Laktoza Tabletki produktu leczniczego zawierają laktozę. Produkt leczniczy nie powinien być stosowany u pacjentów z rzadko występującą dziedziczną nietolerancją galaktozy, brakiem laktazy lub zespołem złego wchłaniania glukozy-galaktozy. **Działania niepożądane:** Podsumowanie profilu bezpieczeństwa *Cukrzyca typu 2* Łącznie 15 582 pacjentów z cukrzycą typu 2 wzięło udział w badaniach klinicznych oceniających bezpieczeństwo stosowania empagliflozyny, z czego 10 004 pacjentów otrzymywało empagliflozynę w monoterapii lub w skojarzeniu z metforminą, pochodną sulfonylomocznika, pioglitazonem, inhibitorami DPP-4 lub insuliną. W 6 badaniach przeprowadzonych z kontrolą placebo trwających od 18 do 24 tygodni wzięło udział 3534 pacjentów, z których 1183 otrzymywało placebo, a 2351 - empagliflozynę. Ogólna częstość występowania zdarzeń niepożądanych u pacjentów leczonych empagliflozyną była podobna do częstości w grupie otrzymującej placebo. Najczęściej obserwowanym działaniem niepożądanym była hipoglikemia przy stosowaniu w skojarzeniu z pochodną sulfonylomocznika lub insuliną. *Niewydolność serca* Do badania EMPEROR-Reduced włączono 3 730 pacjentów z niewydolnością serca i zmniejszoną frakcją wyrzutową, którzy otrzymywali leczenie 10 mg empagliflozyny lub placebo. U około połowy pacjentów występowała cukrzyca typu 2. Najczęściej zgłaszanym działaniem niepożądanym było zmniejszenie objętości płynów (10 mg empagliflozyny: 10,6%; placebo: 9,9%). Ciężką hipoglikemię (zdarzenia wymagające interwencji) obserwowano wyłącznie u pacjentów z cukrzycą. Ogólny profil bezpieczeństwa stosowania empagliflozyny był zasadniczo spójny w badanych wskazaniach. W badaniu niewydolności serca EMPEROR-Reduced nie zidentyfikowano żadnych nowych działań niepożądanych. Wykaz działań niepożądanych w postaci tabeli W poniższej tabeli przedstawiono działania niepożądane - sklasyfikowane według grup układowo-narządowych oraz według preferowanych terminów MedDRA – zgłaszane u pacjentów, którzy otrzymali empagliflozynę w badaniach prowadzonych z kontrolą placebo (Tabela 2). Działania niepożądane są wymienione według bezwzględnej częstości występowania. Częstość występowania zdefiniowana jest następująco: bardzo często (≥ 1/10); często (≥ 1/100 do < 1/10); niezbyt często (≥ 1/1000 do < 1/100); rzadko (≥ 1/10 000 do < 1/1000), bardzo rzadko (< 1/10 000), nieznana (częstość nie może być określona na podstawie dostępnych danych). Tabela 2: Wykaz działań niepożądanych (MedDRA) obserwowanych w badaniach prowadzonych z kontrolą placebo i zgłoszonych po wprowadzeniu produktu do obrotu, w postaci tabeli

Klasyfikacja układów i narządów	Bardzo często	Często	Niezbyt często	Rzadko
Zakażenia i zarażenia pasożytnicze		kandydoza pochwy, zapalenie pochwy i sromu, zapalenie żołędzi i inne zakażenia narządów płciowych[a] zakażenie dróg moczowych (w tym odmiedniczkowe zapalenie nerek i posocznica moczopochodna)[a]		martwicze zapalenie powięzi krocza (zgorzel Fourniera)[a,*]
Zaburzenia metabolizmu i odżywiania	hipoglikemia (przy stosowaniu w skojarzeniu z pochodną sulfonylomocznika lub insuliną)[a]	pragnienie		cukrzycowa kwasica ketonowa[*]
Zaburzenia żołądka i jelit		zaparcie		
Zaburzenia skóry i tkanki podskórnej		świąd (uogólniony) wysypka	pokrzywka obrzęk naczynioruchowy	
Zaburzenia naczyniowe	zmniejszenie objętości płynów[a]			
Zaburzenia nerek i dróg moczowych		zwiększone oddawanie moczu[a]	dyzuria	
Badania diagnostyczne		zwiększenie stężenia lipidów w surowicy[a]	zwiększenie stężenia kreatyniny we krwi i (lub) zmniejszenie współczynnika filtracji kłębuszkowej[a] zwiększenie hematokrytu[a]	

[a] patrz dodatkowe informacje podane poniżej [*] W badaniu niewydolności serca EMPEROR-Reduced obserwowano jeden przypadek (<0,1%) martwiczego zapalenia powięzi krocza (zgorzeli Fourniera) u pacjenta z niewydolnością serca i cukrzycą leczonego empagliflozyną. [*] patrz punkt Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania

Opis wybranych działań niepożądanych *Hipoglikemia* Częstość występowania hipoglikemii zależała od leczenia podstawowego stosowanego w poszczególnych badaniach i była podobna jak po zastosowaniu placebo u pacjentów stosujących empagliflozynę w monoterapii, jako leczenie skojarzone z metforminą, jako leczenie skojarzone z pioglitazonem w skojarzeniu z metforminą lub bez niej, jako leczenie skojarzone z linagliptyną i metforminą, jako leczenie dodane do terapii standardowej oraz w razie stosowania skojarzenia empagliflozyny z metforminą u nieleczonych uprzednio pacjentów w porównaniu z pacjentami leczonymi osobnymi lekami empagliflozyną i metforminą. Zwiększoną częstość zaobserwowano w przypadku stosowania jako leczenie skojarzone z metforminą i pochodnymi sulfonylomocznika (10 mg empagliflozyny: 16,1%; 25 mg empagliflozyny: 11,5%; placebo: 8,4%), jako leczenie skojarzone z insuliną podstawową w skojarzeniu z metforminą lub bez niej oraz w skojarzeniu z pochodną sulfonylomocznika lub bez niego (10 mg empagliflozyny: 19,5%; 25 mg empagliflozyny: 28,4%; placebo: 20,6% w ciągu pierwszych 18 tygodni leczenia, gdy nie można było dostosowywać dawki insuliny; 10 mg i 25 mg empagliflozyny: 36,1%; placebo: 35,3% w ciągu 78 tygodni badania) i jako leczenie skojarzone z insuliną MDI w skojarzeniu z metforminą lub bez niej (empagliflozyna 10 mg: 39,8%, empagliflozyna 25 mg: 41,3%, placebo: 37,2% podczas pierwszych 18 tygodni leczenia, gdy nie można było dostosować dawki insuliny; empagliflozyna 10 mg: 51,1%, empagliflozyna 25 mg: 57,7%, placebo: 58% w ciągu 52 tygodni badania). W badaniu niewydolności serca EMPEROR-Reduced obserwowano podobną częstość występowania hipoglikemii podczas stosowania w skojarzeniu z sulfonylomocznikiem lub insuliną (10 mg empagliflozyny: 4,2%; placebo: 4,6%). *Ciężka hipoglikemia (zdarzenia wymagające interwencji)* Nie zaobserwowano zwiększenia częstości występowania ciężkiej hipoglikemii przy stosowaniu empagliflozyny w porównaniu do placebo, w monoterapii, w leczeniu skojarzonym z metforminą, w leczeniu skojarzonym z metforminą i pochodną sulfonylomocznika, w leczeniu skojarzonym z pioglitazonem w skojarzeniu z metforminą lub bez niej, w leczeniu skojarzonym z linagliptyną i metforminą, jako leczenie dodane do terapii standardowej oraz w razie stosowania skojarzenia empagliflozyny z metforminą u nieleczonych uprzednio pacjentów w porównaniu z pacjentami leczonymi osobnymi lekami empagliflozyną i metforminą. Zwiększoną częstość zaobserwowano w przypadku stosowania jako leczenie skojarzone z insuliną podstawową w skojarzeniu z metforminą lub bez niej oraz w skojarzeniu z pochodną sulfonylomocznika lub bez niego (10 mg empagliflozyny: 0%; 25 mg empagliflozyny: 1,3%; placebo: 0% w ciągu pierwszych 18 tygodni leczenia, gdy nie można było dostosowywać dawki insuliny; 10 mg empagliflozyny: 0%; 25 mg empagliflozyny: 1,3%; placebo: 0% w ciągu 78 tygodni badania) i jako leczenie skojarzone z insuliną MDI w skojarzeniu z metforminą lub bez niej (empagliflozyna 10 mg: 0,5%, empagliflozyna 25 mg: 0,5%, placebo: 0,5% podczas pierwszych 18 tygodni leczenia, gdy nie można było dostosować dawki insuliny; empagliflozyna 10 mg: 1,6%, empagliflozyna 25 mg: 0,5%, placebo: 1,6% w ciągu 52 tygodni badania). W badaniu dotyczącym niewydolności serca EMPEROR-Reduced ciężką hipoglikemię obserwowano tylko u jednego pacjenta z cukrzycą podczas stosowania w skojarzeniu z sulfonylomocznikiem lub insuliną (10 mg empagliflozyny: 1,2%, placebo: 1,5%). *Kandydoza pochwy, zapalenie pochwy i sromu, zapalenie żołędzi i inne zakażenia narządów płciowych* Kandydoza pochwy, zapalenie pochwy i sromu, zapalenie żołędzi i inne zakażenia narządów płciowych były obserwowane częściej u pacjentów leczonych empagliflozyną (10 mg empagliflozyny: 4,0%; 25 mg empagliflozyny: 3,9%) w porównaniu z pacjentami otrzymującymi placebo (1,0%). Zakażenia takie obserwowano częściej u kobiet leczonych empagliflozyną w porównaniu z placebo. Różnica ta była mniej wyraźna w przypadku mężczyzn. Zakażenia narządów płciowych miały nasilenie łagodne lub umiarkowane. W badaniu dotyczącym niewydolności serca EMPEROR-Reduced częstość występowania tego typu zakażeń była większa u pacjentów z cukrzycą (10 mg empagliflozyny: 1,9%; placebo: 0,4%) niż u pacjentów bez cukrzycy (10 mg empagliflozyny: 1,4%; placebo: 0,9%) w trakcie leczenia empagliflozyną w porównaniu z placebo. *Zwiększone oddawanie moczu* Zwiększone oddawanie moczu (obejmujące określone wcześniej takie terminy jak częstomocz, wielomocz i oddawanie moczu w nocy) były obserwowane częściej u pacjentów leczonych empagliflozyną (10 mg empagliflozyny: 3,5%; 25 mg empagliflozyny: 3,3%) w porównaniu z pacjentami otrzymującymi placebo (1,4%). Zwiększone oddawanie moczu miało przeważnie nasilenie łagodne lub umiarkowane. Obserwowana częstość oddawania moczu w nocy była podobna dla empagliflozyny i dla placebo (< 1%). W badaniu niewydolności serca EMPEROR-Reduced zwiększone oddawanie moczu obserwowano z podobną częstością występowania u pacjentów leczonych empagliflozyną i placebo (10 mg empagliflozyny: 0,7%, placebo 0,4%). *Zakażenie dróg moczowych* Ogólna częstość występowania zakażeń dróg moczowych zgłaszanych jako zdarzenie niepożądane była podobna u pacjentów otrzymujących 25 mg empagliflozyny i placebo (7,0% i 7,2%), i wyższa u pacjentów otrzymujących 10 mg empagliflozyny (8,8%). Podobnie jak w przypadku placebo, zakażenia dróg moczowych były zgłaszane częściej u pacjentów leczonych empagliflozyną z przewlekłymi lub nawracającymi zakażeniami dróg moczowych w wywiadzie. Nasilenie (łagodne, umiarkowane, ciężkie) zakażenia dróg moczowych było podobne u pacjentów otrzymujących empagliflozynę i placebo. Zakażenia dróg moczowych były zgłaszane częściej u kobiet leczonych empagliflozyną w porównaniu z placebo; nie było takiej różnicy w przypadku mężczyzn. *Zmniejszenie objętości płynów* Ogólna częstość występowania zmniejszenia objętości płynów (obejmującego określone wcześniej takie terminy jak spadek ciśnienia krwi (określony ambulatoryjnie), spadek skurczowego ciśnienia krwi, odwodnienie, niedociśnienie, hipowolemia, hipotonia ortostatyczna oraz omdlenie) była podobna u pacjentów otrzymujących empagliflozynę (10 mg empagliflozyny: 0,6%; 25 mg empagliflozyny: 0,4%) i placebo (0,3%). Częstość występowania zmniejszenia objętości płynów była zwiększona u pacjentów w wieku 75 lat i starszych leczonych empagliflozyną (10 mg empagliflozyny: 2,3%; 25 mg empagliflozyny: 4,3%) w porównaniu z pacjentami otrzymującymi placebo (2,1%). *Zwiększenie stężenia kreatyniny we krwi i (lub) obniżenie współczynnika filtracji kłębuszkowej* Ogólna częstość występowania przypadków zwiększenia stężenia kreatyniny we krwi i obniżenie współczynnika filtracji kłębuszkowej była podobna u pacjentów otrzymujących empagliflozynę lub placebo (zwiększenie stężenia kreatyniny: empagliflozyna 10 mg 0,6%, empagliflozyna 25 mg 0,1%, placebo 0,5%; zmniejszenie szybkości filtracji kłębuszkowej; empagliflozyna 10 mg 0,1%, empagliflozyna 25 mg 0%, placebo 0,3%). Występujące początkowo zwiększenie stężenia kreatyniny we krwi i (lub) obniżenie współczynnika filtracji kłębuszkowej u pacjentów leczonych empagliflozyną jako terapią uzupełniającą leczenie metforminą zwykle ustępowało w trakcie ciągłego leczenia lub było odwracalne po zakończeniu leczenia tym lekiem. Konsekwentnie w badaniu EMPA-REG OUTCOME u pacjentów leczonych empagliflozyną obserwowano występujący początkowo spadek eGFR (średnia: 3 ml/min/1,73 m^2). Następnie wartość eGFR utrzymywała się w czasie trwania leczenia. Średnia wartość eGFR powracała do wartości początkowej po zakończeniu leczenia, co sugeruje, że w patogenezie tych zmian czynnościowych nerek mogą odgrywać rolę ostre zmiany hemodynamiczne. *Zwiększenie stężenia lipidów w surowicy* Średnie zwiększenie procentowe od punktu początkowego dla 10 mg i 25 mg empagliflozyny w porównaniu z placebo wynosiło odpowiednio dla cholesterolu całkowitego 4,9% i 5,7% w porównaniu z 3,5%; dla cholesterolu HDL 3,3% i 3,6% w porównaniu z 0,4 %; dla cholesterolu LDL 9,5% i 10,0% w porównaniu z 7,5%; dla trójglicerydów 9,2% i 9,9% w porównaniu z 10,5%. *Zwiększenie wartości hematokrytu* Średnia zmiana wartości hematokrytu od punktu początkowego wynosiła odpowiednio 3,4% i 3,6% dla 10 mg i 25 mg empagliflozyny w porównaniu z 0,1% dla placebo. W badaniu EMPA-REG Outcome wartości hematokrytu powróciły do wartości wyjściowych po 30-dniowym okresie kontroli po zakończeniu leczenia. Zgłaszanie podejrzewanych działań niepożądanych Po dopuszczeniu produktu leczniczego do obrotu istotne jest zgłaszanie podejrzewanych działań niepożądanych. Umożliwia to nieprzerwane monitorowanie stosunku korzyści do ryzyka stosowania produktu leczniczego. Osoby należące do fachowego personelu medycznego powinny zgłaszać wszelkie podejrzewane działania niepożądane za pośrednictwem Departamentu Monitorowania Niepożądanych Działań Produktów Leczniczych Urzędu Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych: Al. Jerozolimskie 181C, 02-222 Warszawa, tel.: +48 22 49-21-301, faks: +48 22 49-21-309, strona internetowa: https://smz.ezdrowie.gov.pl. Działania niepożądane można zgłaszać również podmiotowi odpowiedzialnemu. **Podmiot odpowiedzialny:** Boehringer Ingelheim International GmbH, Binger Str. 173, 55216 Ingelheim am Rhein, Niemcy. **Numery pozwoleń na dopuszczenie do obrotu:** Jardiance® 10 mg tabletki powlekane: EU/1/14/930/013 (28 tabletek), Jardiance® 10 mg tabletki powlekane: EU/1/14/930/014 (30 tabletek) wydane przez Komisję Wspólnot Europejskich. **Data zatwierdzenia lub częściowej zmiany tekstu ChPL:** 22.10.2021. **Kategoria dostępności:** Produkt leczniczy wydawany na receptę - Rp. **Cena urzędowa detaliczna:** Jardiance® 10 mg x 28 tabl. – 170,38 zł. Wysokość dopłaty pacjenta: 54,00 zł we wskazaniu: Cukrzyca typu 2, u pacjentów przed włączeniem insuliny, leczonych co najmniej dwoma doustnymi lekami hipoglikemizującymi od co najmniej 6 miesięcy, z HbA1c ≥ 8 % oraz bardzo wysokim ryzykiem sercowo-naczyniowym rozumianym jako: 1) otwierdzona choroba sercowo-naczyniowa, lub 2) uszkodzenie innych narządów objawiające się poprzez: białkomocz lub przerost lewej komory lub retinopatię, lub 3) obecność 3 lub więcej głównych czynników ryzyka spośród wymienionych poniżej: -wiek ≥ 55 lat dla mężczyzn, ≥ 60 lat dla kobiet, -dyslipidemia, -nadciśnienie tętnicze, -palenie tytoniu, -otyłość – na podstawie obwieszczenia Ministra Zdrowia z dnia 21 października 2021 r. w sprawie wykazu refundowanych leków, środków spożywczych specjalnego przeznaczenia żywieniowego oraz wyrobów medycznych na 1 listopada 2021 r. (DZ. URZ. Min. Zdr. 2021.82).

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Repetytorium z Kardiologii i Hipertensjologii 2022

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